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REUNIÓN POST CONGRESO DE
LA SOCIEDAD AMERICANA
DE ONCOLOGÍA CLÍNICA

Presentaciones más destacadas en cáncer urotelial ASCO 2024

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Servicio Oncología Médica

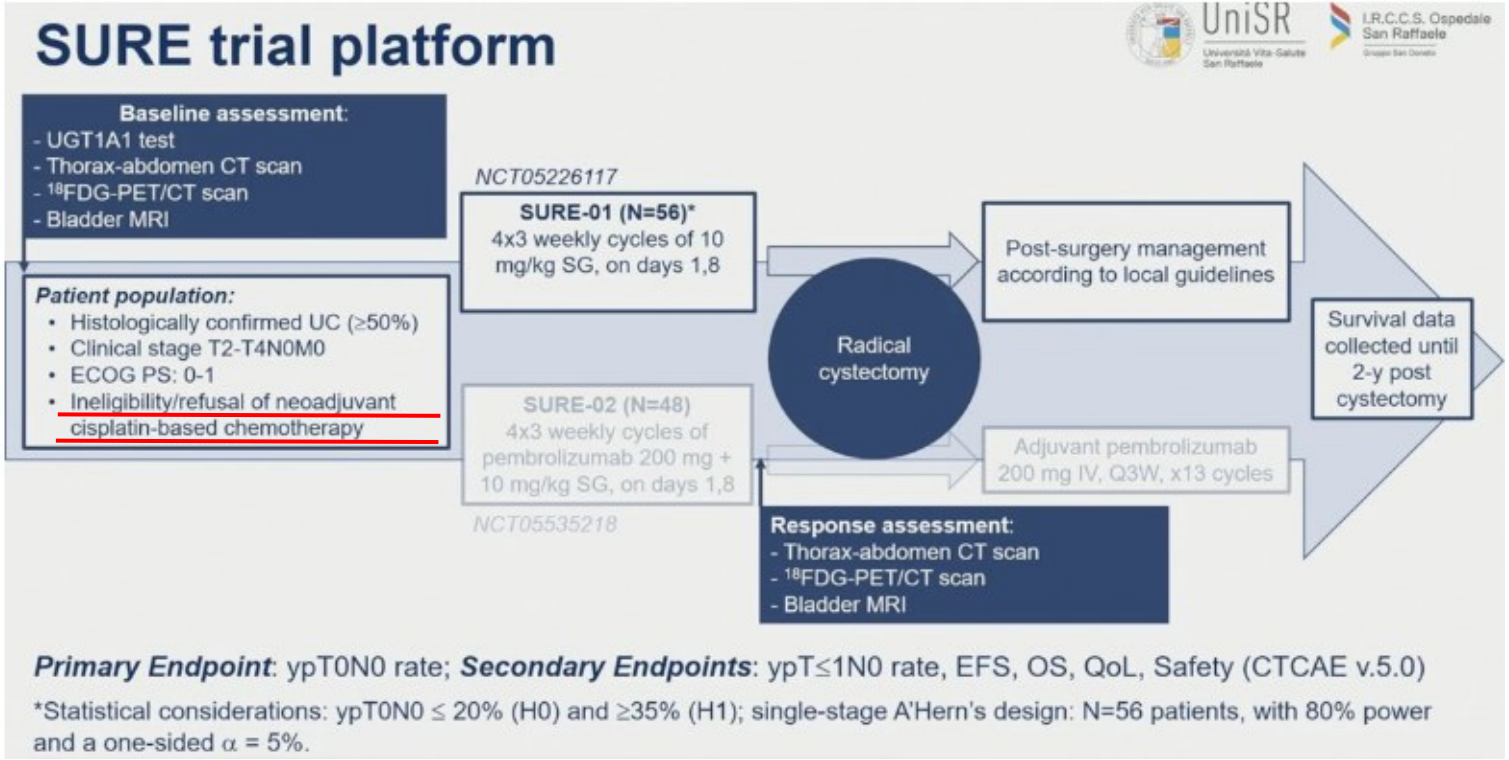
Hospital Universitario Donostia - Onkologikoa

San Sebastián

17 Junio 2024

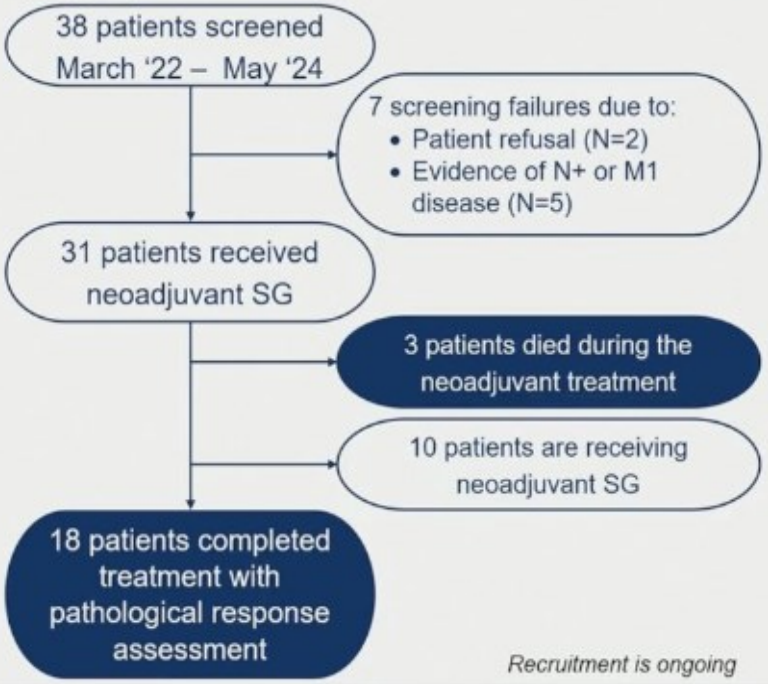
Presentaciones más destacadas en cáncer urotelial

- VEJIGA:
  - **TRATAMIENTO PERIOPERATORIO**
  - AVANZADO/METASTÁSICO
    - VARIANTES HISTOLÓGICAS.
    - HER 2.
    - Biología molecular
- CA UROTELIAL NO VESICAL
  - URACO
- CONCLUSIONES



Antonio Cigliola, MD, Medical Oncology Department, IRCCS San Raffaele Hospital, Milan, Italy

SURE-01: Patient disposition (as of May 2024) and baseline characteristics of the interim analysis population



	Patients (N=21) N (%)
Male gender	16 (76.2)
Median age (IQR), years	70 (62-75)
White race	21 (100)
Current or former smoker	12 (57.1)
ECOG performance status	
• 0	17 (81.0)
• 1	4 (19.0)
Cisplatin ineligible	5 (23.8)
Cisplatin refusing	16 (76.2)
Clinical stage	
• cT2N0	14 (66.7)
• cT3N0	5 (23.8)
• cT4aN0	2 (9.5)
Histology	
• Pure urothelial carcinoma (UC)	11 (52.4)
• UC with other variant histologies:	10 (47.6)
○ Squamous cell carcinoma	5 (23.8)
○ Plasmacytoid	1 (4.8)
○ Trophoblastic tumor	1 (4.8)
○ Micropapillary variant	3 (14.2)

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RESULTADOS

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- 18/21: 4 CICLOS + CIRUGÍA.
- 11/18 CISTECTOMÍA RADICAL
  - **ypT0 4/11 (36.4%)**
  - **ypT≤1N0 response was observed in patients 5/11 (45%).**

7 RECHAZARON CIRUGÍA

Gene	ypT0N0-x response N=8; N (%)	Non-ypT0N0-x response N=7 ; N (%)
TERT	8 (100)	4 (57.1)
RB1	3 (37.5)	1 (14.3)
TP53	3 (37.5)	5 (71.4)
BRCA1	1 (12.5)	2 (28.6)
BRCA2	**2 (25.0)**	0
ARID1A	**4 (50.0)**	0
CDKN1A	2 (25.0)	0
CDKN2A/B	4 (50.0)	2 (28.6)
ERBB2	1 (12.5)	**3 (42.8)**
ERBB3	0	1 (14.3)
PIK3CA	0	2 (28.6)
FBXW7	2 (25.0)	2 (28.6)
KMD6A	0	3 (42.8)
NF2	1 (12.5)	1 (14.3)
KMT2D	0	2 (28.6)
MTAP	2 (25.0)	1 (14.3)
FGF3	0	2 (28.6)
FGF4	0	2 (28.6)

Responses assessed with reTURBT

Our definition of cCR

UniSR Università Vita-Salute San Raffaele — I.R.C.C.S. Ospedale San Raffaele

Patient ID	VI-RADS post-therapy[1]	Cystoscopy	ctDNA post-therapy	Pathological findings (reTURBT)	Clinical CR	
11	0	Neg	Neg	ypT0Nx	✓	Observation
13	0	Neg	Neg	ypT0Nx	✓	
16	0	Neg	Neg	ypT0Nx	✓	
17	0	Neg	Neg	ypT0Nx	✓	
19	0	Neg	Neg	ypT0Nx	✓	
20	0	Neg	Neg	ypT0Nx	✓	
21	5	Pos	Pos (MTM/mL: 0.32)	ypT2Nx	✗	ChemoRT

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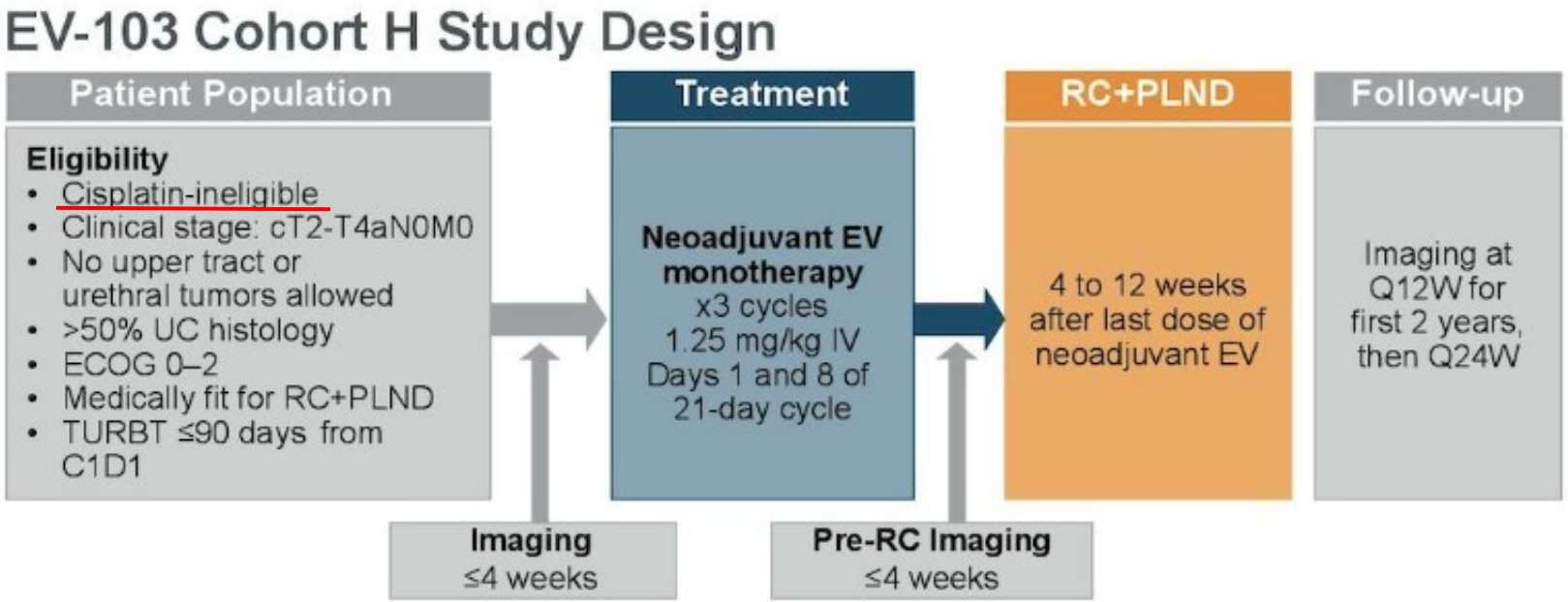
TOXICIDAD

- ENMIENDA AL PROTOCOLO TRAS VALORACIÓN TOXICIDAD 8 PRIMEROS PACIENTES → **75% NTG3/4; 50% DIARREA G3/4.**
- TIMING: TRAS C1D8
- 6/8 pts REDUCCIÓN DOSIS SG.
- 2/8 STOP TTO.
- 2 MUERTES (1 MUERTE TÓXICA)

- REDUCCIÓN DOSIS SG DE 10 A 7,5mg/kg.
- G - CSF tras C1D9.
- EXCLUÍDOS ≥3 FACTORES RIESGO NT FEBRIL

- ITT: EA **Grade 3 33,3%** G4 19,1%
- EA más frecuente: neutropenia (33%) and diarrhea (24%).
- EA más frecuentes en homocigotos/heterocigotos para polimorfismo **UGT1A1*28 (62,5% vs 20%.**



Mediana edad: 74a. **cT2 (68.2%), cT3 (27.3%),** or cT4 (4.5%) disease.

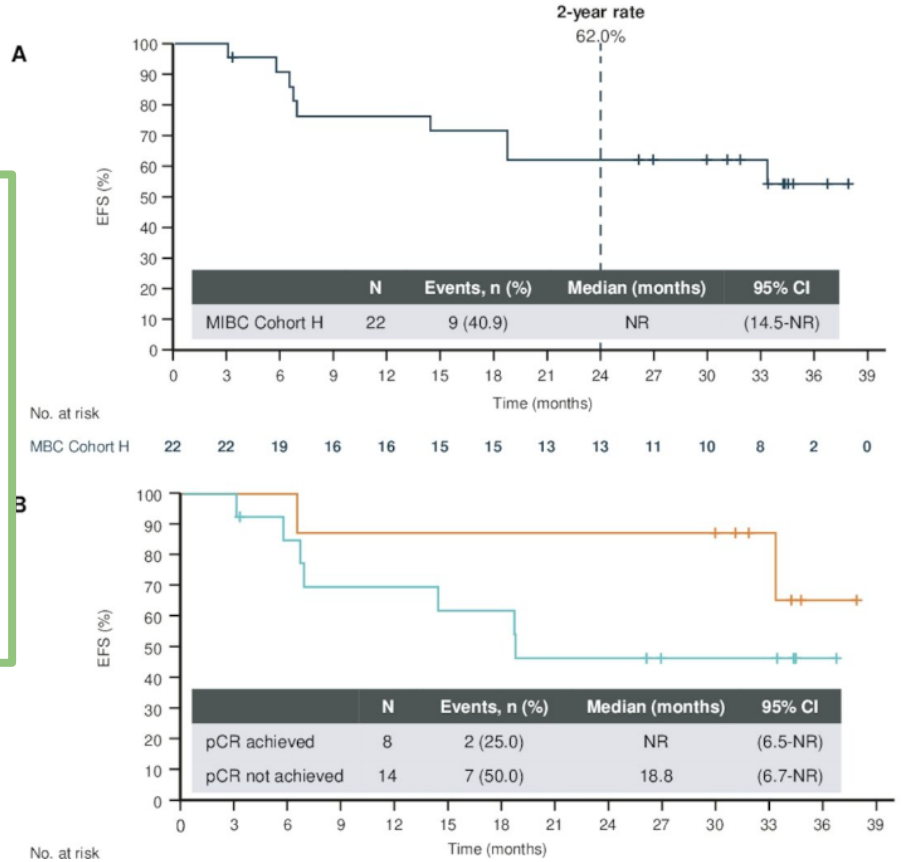
68% urothelial carcinoma only; 31.8% had a mixed histology.

Peter H. O'Donnell, MD, Medical Oncologist at the University of Chicago, Chicago, IL.

RESULTADOS

- pCR: 8 pts (36,4%).
- pDS (<pT2 y N0) 11pts (50%)
- 2yEFS 62%
  - pCR NR
  - no pCR mediana 18m.

Figure 2. EFS (A) by investigator regardless of pCR and (B) by pCR



TOXICIDAD

- EAs + FRECUENTES: **FATIGA 45,5%, DISGEUSIA 36,4% Y ALOPECIA 31,8%**
- **18,2% EAs ≧ 3 RELACIONADOS CON EV.**
- 32% EAs ≧ 3 RELACIONADOS CON LA CIRUGÍA
- 3 MUERTES RELACIONADAS CON EA NO RELACIONADOS CON EV: IRA, IAM, TEP.

Table 6. EV-related TEAEs[a]

EV-related TEAEs, n (%)	Patients (N=22)
Any-grade EV-related TEAE	22 (100.0)
Any-grade EV-related TEAEs in ≥20% of patients	
Fatigue	10 (45.5)
Dysgeusia	8 (36.4)
Alopecia	7 (31.8)
Diarrhea	6 (27.3)
Nausea	6 (27.3)
Peripheral sensory neuropathy	6 (27.3)
Dry eye	5 (22.7)
Rash maculopapular	5 (22.7)
Grade ≥3 EV-related TEAEs	4 (18.2)
Dehydration	1 (4.5)
Erythema multiforme	1 (4.5)
Hyperglycemia	1 (4.5)
Post-procedural urine leak	1 (4.5)
Rash maculopapular	1 (4.5)
Small intestinal obstruction	1 (4.5)
Any serious EV-related TEAE	4 (18.2)
EV-related TEAEs leading to EV discontinuation	3 (13.6)
Dehydration	1 (4.5)
Erythema multiforme	1 (4.5)
Rash maculo-papular	1 (4.5)
EV-related TEAE leading to death	0

[a]Treatment relatedness determined by investigator.

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AURA (Avelumab)

AURA : a multi-centric non comparative randomized phase II trial investigating neoadjuvant avelumab alone or in combination with chemotherapy

Key eligibility
- Pathological confirmation of muscle-invasive urothelial bladder carcinoma
- Planned radical cystectomy and lymphadenectomy

Tumor tissue and blood samples are taken at baseline, during treatment and at surgery for exploratory analysis

R 1:1

Cohort 1 : Cisplatin-eligible

Gemcitabine – cisplatin + avelumab
Cisplatin 70 mg/m² D1, gemcitabine 1g/m² D1 & D8 Q3W (x4) + avelumab 10mg/kg Q2W (x6)

Dose-dense MVAC + avelumab
Methotrexate 30mg/m² D1, vinblastine 3mg/m² D2, doxorubicin 30mg/m² D2, cisplatin 70mg/m² D2 Q2W (x4) + avelumab 10mg/kg Q2W (x4)

R 1:1

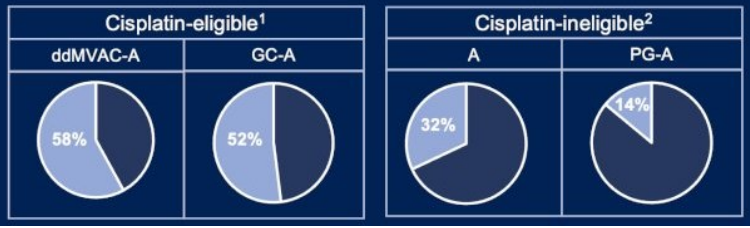
Cohort 2 : Cisplatin-ineligible

Paclitaxel – gemcitabine + avelumab
Paclitaxel 80mg/m² D1 & D15, gemcitabine 1g/m² D1 & D15 Q4W (x2) + avelumab 10mg/kg Q2W (x4)

Avelumab
Avelumab 10mg/kg Q2W (x4)

Radical cystectomy

Primary Endpoint:
- Proportion of patients achieving a pathological complete response (pCR) ypT0/TisN0



ypT0/TisN0

54%

58%

14%

33%

Jeremy Blanc, MD, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles, Brussels, Belgium

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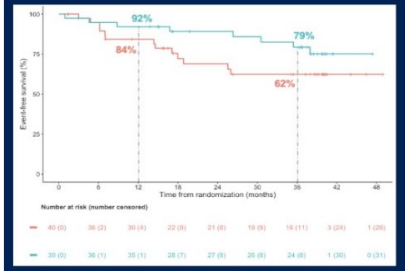
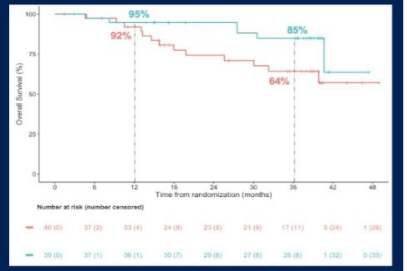
Survival in the **cisplatin-eligible** cohort

Event-free survival



Overall survival

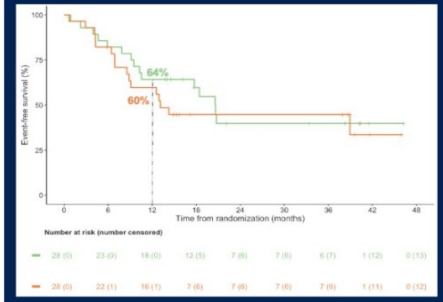


12-month EFS	92% ddMVAC-A 84% GC-A
Preliminary 36-month EFS	79% ddMVAC-A 62% GC-A

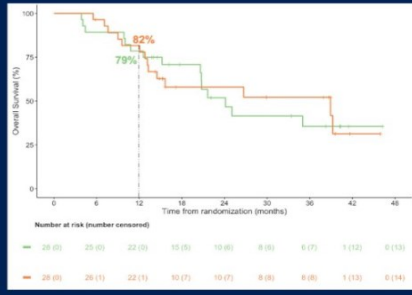
12-month OS	95% ddMVAC-A 92% GC-A
Preliminary 36-month OS	85% ddMVAC-A 64% GC-A

Survival in the **cisplatin-ineligible** cohort

Event-free survival



Overall survival

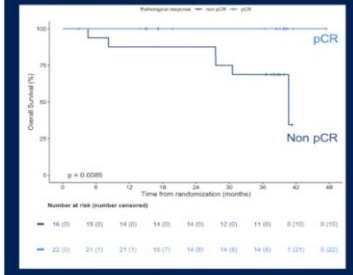


12-month EFS	64% A 60% PG-A

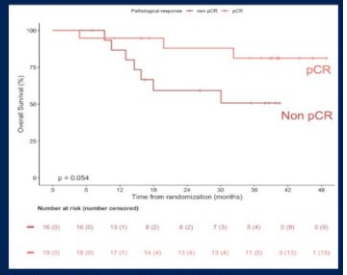
12-month OS	79% A 82% PG-A

Overall survival in the **cisplatin-eligible** cohort according to pCR

ddMVAC-A arm



GC-A arm

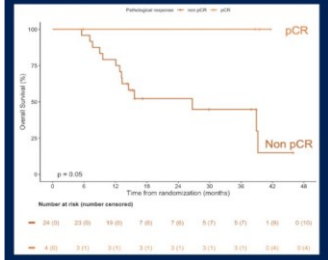


Achieving a **pCR** is associated with **longer overall survival**

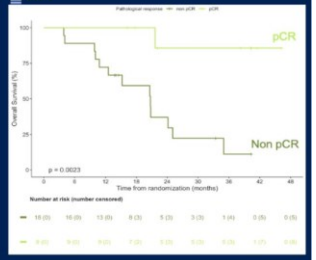
pCR → SUPERVIVENCIA GLOBAL

Overall survival in the **cisplatin-ineligible** cohort according to pCR

PG-A arm



A arm



Achieving a **pCR** is associated with **longer overall survival**

Presentaciones más destacadas en cáncer urotelial

- VEJIGA:
  - TRATAMIENTO PERIOPERATORIO
  - AVANZADO/METASTÁSICO
    - VARIANTES HISTOLÓGICAS.
    - HER 2.
    - Biología molecular
- CA UROTELIAL NO VESICAL
  - URACO
- CONCLUSIONES

VARIANTES HISTOLÓGICAS

- Son muy diferentes entre sí.
- Distribución (Koehner et al, 2024) → Tratamiento:
  - 31% escamoso → paclitaxel, ifosfamida, CDDP. Peor rta a EV +- Pembrolizumab.
  - 17% neuroendocrino → platino - etopósido +- Avelumab (QTNA, 1L); Lurbinectedina +- Avelumab (LASER trial, 2L).
  - 16% adenocarcinoma
  - 16% variantes sarcomatoides → gemcitabina, docetaxel, cisplatino. PD - L1, buena rta a ICI.
  - 3% plasmocitoide
  - micropapilar → HER2.
  - Pendientes resultados CheckMate901.

Jean H. Hoffman-Censits, MD, Genitourinary medical oncologist at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, and The Greenberg Bladder Cancer Institute at Johns Hopkins.

What Is Variant Histology Urothelial Cancer and What Are the Available Treatment Options? Dr Jean Hoffman - Censits; ASCO, 2024

Updated Outcomes of EV in VH - UNITE

- N= 566 total, 200 with VH[1]
- UC predominant (n=151), ≥50% VH (n=35), and pure VH (n=14)

Variant	UC predominant ORR	Variant Predominant ORR
Squamous n=94	55%	33%
Micropapillary n=41	38%	20%
Plasmacytoid n=23	64%	NE
Sarcomatoid n=21	38%	100%
Adeno/glandular n=9	63%	0%

- Pure Variant ORR 0% (0/5 scc, 0/3 PC, 0/1 Sarc, 0/2 Small Cell)
- ORR 0% with any small cell component regardless of %
  - Corroborated by low or no NECTIN-4 expression by IHC and mRNA measures[2-4]

1. Jindal T, et al J Clin Oncol 2024 abstr 652
2. Hoffman-Censits JH et al Appl Im Mol Morphol. 202
3. Fan Y et al Front Oncol. 2022

Outcomes of Sactiuzumab Govitecan in VH - UNITE

- N= 116 pts treated with SG, 44 with VH

Variant	ORR
All pts	24%
Any VH	23%
Pure UC	24%
Squamous n=19	21%
Micropapillary n=9	25%
Plasmacytoid n=8	0%
AdenoCa n=3	67%
Small Cell n=2	50%

SMART: A phase II study of sacituzumab govitecan (SG) with or without atezolizumab immunotherapy in rare genitourinary (GU) tumors such as small cell, adenocarcinoma, and squamous cell bladder/urinary tract cancer, renal medullary carcinoma (RMC) and penile cancer.
NCT06161532

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JAVELIN 100

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SE MANTIENE BENEFICIO DE AVELUMAB

	Patients with UC mixed with histological subtypes		Overall population	
	Avelumab + BSC (n=44)	BSC alone (n=57)	Avelumab + BSC (n=350)	BSC alone (n=350)
Age, median (range), years	68 (45-85)	68 (32-89)	68 (37-90)	69 (32-89)
Sex, n (%)				
Male	31 (70.5)	38 (66.7)	266 (76.0)	275 (78.6)
Female	13 (29.5)	19 (33.3)	84 (24.0)	75 (21.4)
Pooled geographic region, n (%)				
Europe	26 (59.1)	39 (68.4)	214 (61.1)	203 (58.0)
North America	1 (2.3)	3 (5.3)	12 (3.4)	22 (6.3)
Asia	8 (18.2)	6 (10.5)	73 (20.9)	74 (21.1)
Australasia	5 (11.4)	7 (12.3)	34 (9.7)	37 (10.6)
Rest of the world	4 (9.1)	2 (3.5)	17 (4.9)	14 (4.0)
ECOG PS, n (%)				
0	24 (54.5)	33 (57.9)	213 (60.9)	211 (60.3)
≥1	20 (45.5)	24 (42.1)	137 (39.1)	139 (39.7)
PD-L1 status, n (%)				
Positive	26 (59.1)	32 (56.1)	189 (54.0)	169 (48.3)
Negative	15 (34.1)	16 (28.1)	139 (39.7)	131 (37.4)
Unknown	3 (6.8)	9 (15.8)	22 (6.3)	50 (14.3)
Best response to 1L chemotherapy, n (%)				
CR or PR	35 (79.5)	36 (63.2)	253 (72.3)	252 (72.0)
SD	9 (20.5)	21 (36.8)	97 (27.7)	98 (28.0)
Site of metastasis at start of 1L chemotherapy, n (%)				
Visceral	25 (56.8)	22 (38.6)	191 (54.6)	191 (54.6)
Nonvisceral	19 (43.2)	35 (61.4)	159 (45.4)	159 (45.4)
Histological classification, n (%)				
UC	0	0	306 (87.4)	292 (83.4)
UC with squamous differentiation	16 (36.4)	26 (45.6)	16 (4.6)	26 (7.4)
UC with glandular differentiation	6 (13.6)	9 (15.8)	6 (1.7)	9 (2.6)
UC with variant differentiation	22 (50.0)	22 (38.6)	22 (6.3)	22 (6.3)
Other	0	0	0	1 (0.3)

Figure 3. Investigator-assessed PFS in patients with UC mixed with histological subtypes

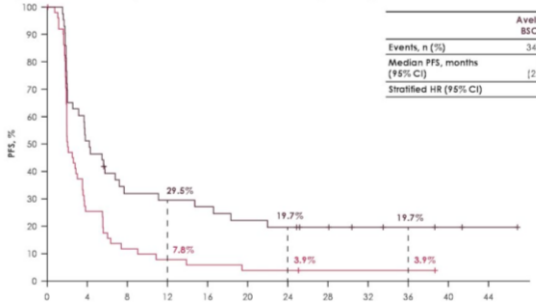
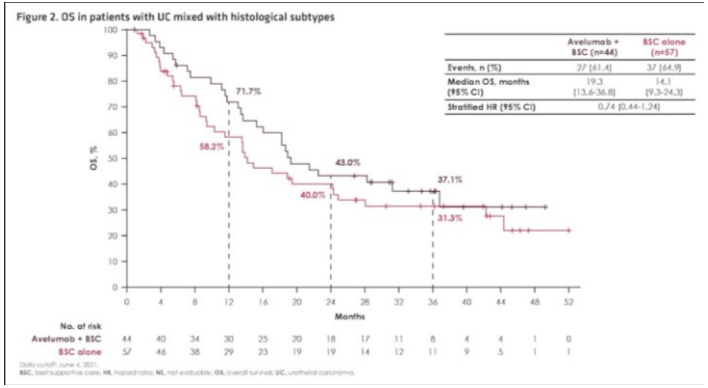


Figure 2. OS in patients with UC mixed with histological subtypes



Yohann Loriot, MD, PhD. Physician Scientist; Director of Bladder Cancer Program, Gustave Roussy, Université Paris-Saclay, Villieuf, France

En marcha…

- SMART: A phase II study of **sacituzumab govitecan (SG) with or without atezolizumab** immunotherapy in rare genitourinary (GU) tumors such as small cell, adenocarcinoma, and squamous cell bladder/urinary tract cancer, renal medullary carcinoma (RMC) and penile cancer.
- A phase II multicenter study of **enfortumab vedotin with or without pembrolizumab** in rare genitourinary tumors (E-VIRTUE).
- **Enfortumab vedotin plus pembrolizumab** in the treatment of locally advanced or metastatic bladder cancer of variant histology: A phase II study.

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HER – 2

REUNIÓN POST CONGRESO DE LA SOCIEDAD AMERICANA DE ONCOLOGÍA CLÍNICA

Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: Results from the bladder cohort of the DESTINY-PanTumor02 (DP-02) study.

Piotr Jan Wysocki
Jagiellonian University Medical College Hospital, Kraków, Poland

	All Pts	HER2 IHC 3+	HER2 IHC 2+	HER2 IHC 1+	HER2 IHC 0
n	41	16	20	2	2
Pts with OR, n	16	9	7	0	0
ORR, % (95% CI)	39.0 (24.2, 55.5)	56.3 (29.9, 80.2)	35.0 (15.4, 59.2)	0	0
mDOR, months (95% CI)	8.7 (4.3, 11.8)	8.7 (2.8, 10.6)	10.3 (4.3, 17.8)	-	-
mPFS, months (95% CI)	7.0 (4.2, 9.7)	7.4 (3.0, 11.9)	7.8 (2.6, 11.6)	5.5 (4.0, NE)	2.6 (1.0, NE)
DCR at 12 weeks, % (95% CI)	70.7 (54.5, 83.9)	75.0 (47.6, 92.7)	70.0 (45.7, 88.1)	100 (15.8, 100)	50.0 (1.3, 98.7)

By INV. Local HER2 status confirmed by central testing; upon reanalysis, some pts were IHC 1+/0/unknown. 1 pt: central IHC unknown. DOR was assessed in pts with an OR. CIs omitted: 0%. NE, not evaluable.

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This open-label, Phase 2 study (NCT04482309) evaluated T-DXd (5.4 mg/kg Q3W) in pts with HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing) locally advanced/metastatic disease after ≥1 systemic treatment (Tx), or without Tx options. The primary endpoint was confirmed ORR by INV. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and safety. Exploratory endpoints included efficacy outcomes according to HER2 expression.

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HER – 2

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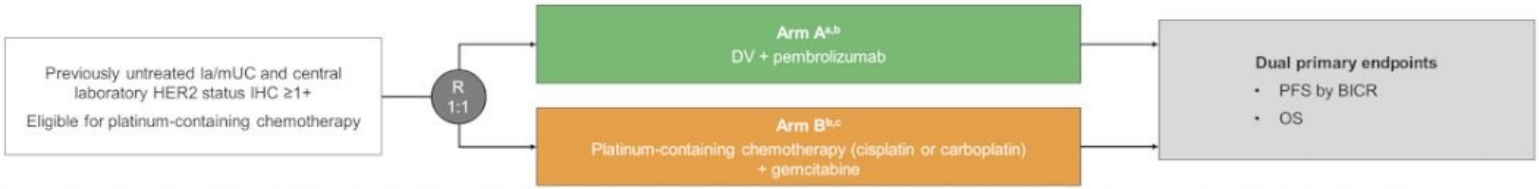
Figure 2. DV-001 Phase 3 Trial Design



[a]Pembrolizumab is to be administered for a maximum of 18 six-weekly infusions (approximately 2 years). [b]Treatment with DV or chemotherapy will continue until disease progression, intolerable toxicity, withdrawal from the study, or a maximum of 6 cycles (Arm B only). [c]Maintenance therapy (ie, avelumab), where approved and appropriate, after 4 to 6 cycles of platinum chemotherapy.

Stratification factors include cisplatin eligibility, presence of liver metastases, HER2 status ("high" defined as IHC 3+ or 2+ and ISH positive, or "low" defined as IHC 1+ or 2+ and ISH negative), and intent of avelumab maintenance use. Tumor assessments will occur every 8 weeks (±7 days) during the treatment period, irrespective of treatment delays or interim tumor assessments.

Eligibility Criteria

Key inclusion criteria:

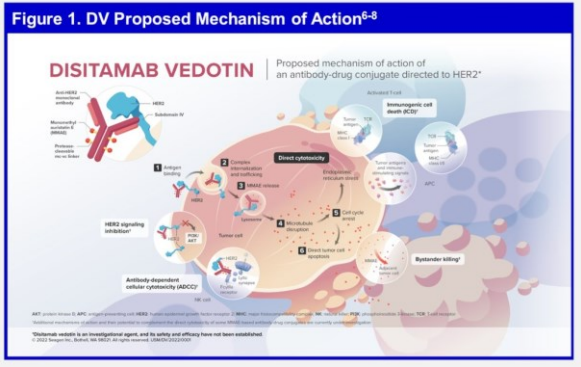
- Previously untreated Ia/mUC
- Measurable disease per RECIST 1.1
- ECOG performance status score of 0-2
- No prior systemic therapy except for:
  - Neoadjuvant or adjuvant therapy, including PD-(L)1 inhibitors, if disease recurrence/progression occurred more than 12 months after last dose
- Eligible for platinum-containing chemotherapy
- HER2 expression of 1+ or greater on IHC determined using the VENTANA 4B5 HER2 IHC assay at a central laboratory and using the most recent archival or fresh tumor sample

Key exclusion criteria:

- Known hypersensitivity to DV, cisplatin, carboplatin, gemcitabine or pembrolizumab
- Toxicity from previous treatment that has not returned to grades 0 or 1, except grade 2 alopecia
- Prior MMAE-based or HER2-directed therapy
- Peripheral sensory or motor neuropathy ≥ grade 2
- History of another invasive malignancy within 3 years before the first dose of study intervention, or any evidence of residual disease from a previously diagnosed malignancy

Figure 3. Enrollment Sites

Figure 1. DV Proposed Mechanism of Action[6-8]



Matt Galsky, MD, Professor of Medicine, Hematology and Medical Oncology, Director of Genitourinary Medical Oncology, Co-Director of the Center of Excellence for Bladder Cancer at The Tisch Cancer Institute, and Associate Director for Translational Research at The Tisch Cancer Institute, New York, NY

Presentaciones más destacadas en cáncer urotelial

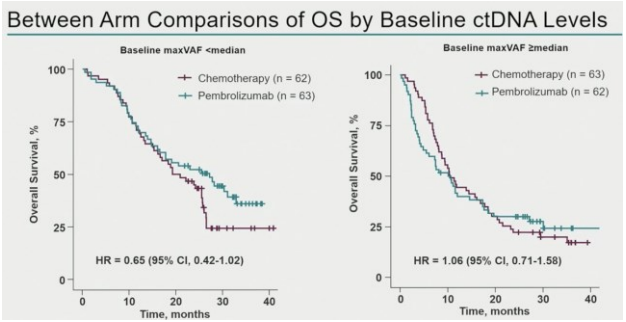
- VEJIGA:
  - TRATAMIENTO PERIOPERATORIO
  - AVANZADO/METASTÁSICO
    - VARIANTES HISTOLÓGICAS.
    - HER 2.
    - **Biología molecular**
- CA UROTELIAL NO VESICAL
  - URACO
- CONCLUSIONES

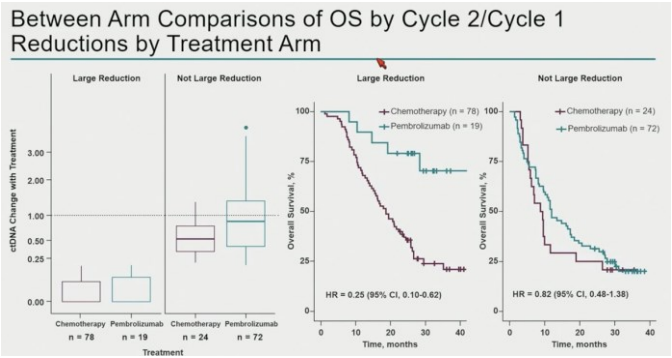
GONORTE
Grupo Oncológico

REUNIÓN POST CONGRESO DE LA SOCIEDAD AMERICANA DE ONCOLOGÍA CLÍNICA

Quantitative Circulating Tumor DNA (ctDNA) Assessment in Patients with Advanced Urothelial Carcinoma Treated with Pembrolizumab or Platinum-Based Chemotherapy from the Phase 3 KEYNOTE-361 Trial

- Most patients were positive for ctDNA at baseline.
- Baseline ctDNA levels were associated with clinical outcomes for pembrolizumab but not for chemotherapy.
- Chemotherapy induced larger ctDNA decreases from baseline to treatment cycle 2 than pembrolizumab (including cDNA clearance)
- Changes with pembrolizumab were more strongly associated with long-term outcomes and were enriched with higher tTMB and PD-L1 levels.
- Short-term ctDNA reductions were not treatment-independent surrogates for clinical outcomes.
- Patients with larger ctDNA reductions in the pembrolizumab arm had a much more favorable overall survival relative to patients with larger ctDNA reductions in the chemotherapy arm.



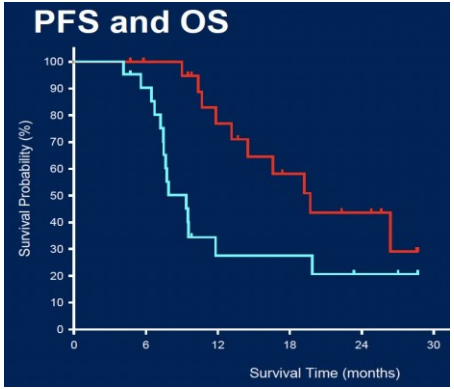


Thomas Powles, MBBS, MRCP, MD, Professor of Genitourinary Oncology, Director, Barts Cancer Centre at St. Bartholomew's Hospital, London, UK

A Multicenter Phase II Study of Modified FOLFIRINOX for First-Line Treatment for Advanced Urachal Cancer (ULTMA; KCSG GU20-03)

	No. of pts/percentage
Complete Response (CR)	2(9.5%)
Partial Response (PR)	11(52.4%)
Stable Disease (SD)	8(38.1%)
Progressive Disease (PD)	0

Overall response rate was 61.9% (95% CI, 41.1-82.7)



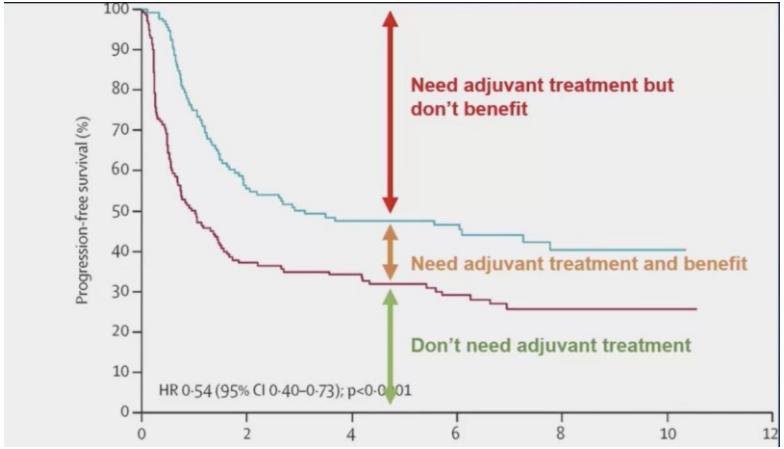
- The ULTIMA study, the first prospective study in advanced urachal cancer, showed that a modified FOLFIRINOX showed an encouraging objective response rate (62%) and progression-free survival (9.3 months).
- This regimen is well tolerated with no febrile neutropenic events using prophylactic long-acting G-CSF
- Modified FOLFIRINOX should be considered for the 1st line treatment of advanced urachal cancer

Jae-Lyun Lee, MD, PhD, Professor, Asan Medical Center and University College of Medicine, Seoul, South Korea

Conclusiones → Necesidades

- Irrupción de nuevos fármacos en tratamiento perioperatorio.
- Necesidad de más investigación en tumores poco frecuentes (variantes histológicas; uraco; UTUC).
- Necesidad de más estudio molecular que guíe el tratamiento sistémico.
- …

Using Molecular Testing to Guide Perioperative Systemic Therapy for Urothelial Cancer



Matt D. Galsky, MD, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

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