II JORNADA DE ACTUALIZACIÓN EN
URO-ONCOLOGÍA:
UPDATE 2025
Madrid, 25 de febrero de 2025

MESA 3. CÁNCER DE VEJIGA METASTÁSICO

FGFR, nectina-4, trop-2, Her-2… ¿qué biomarcadores debemos determinar en nuestros pacientes?

Pilar González-Peramato

Servicio de Anatomía Patológica, Hospital Universitario La Paz, UAM, IdiPAZ, Madrid

PD-L1

Tratamiento:
- Nivolumab: >1% CT (28-8)

Ensayos
- NIAGARA: Durvalumab (SP263)
- AMBASSADOR: Pembrolizumab (22C3) CPS>10
- EV-302: EV+ Pembro (22C3) CPS>10

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2024
Bladder Cancer

NCCN Guidelines Inde
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Discussio

PRINCIPLES OF SYSTEMIC THERAPY

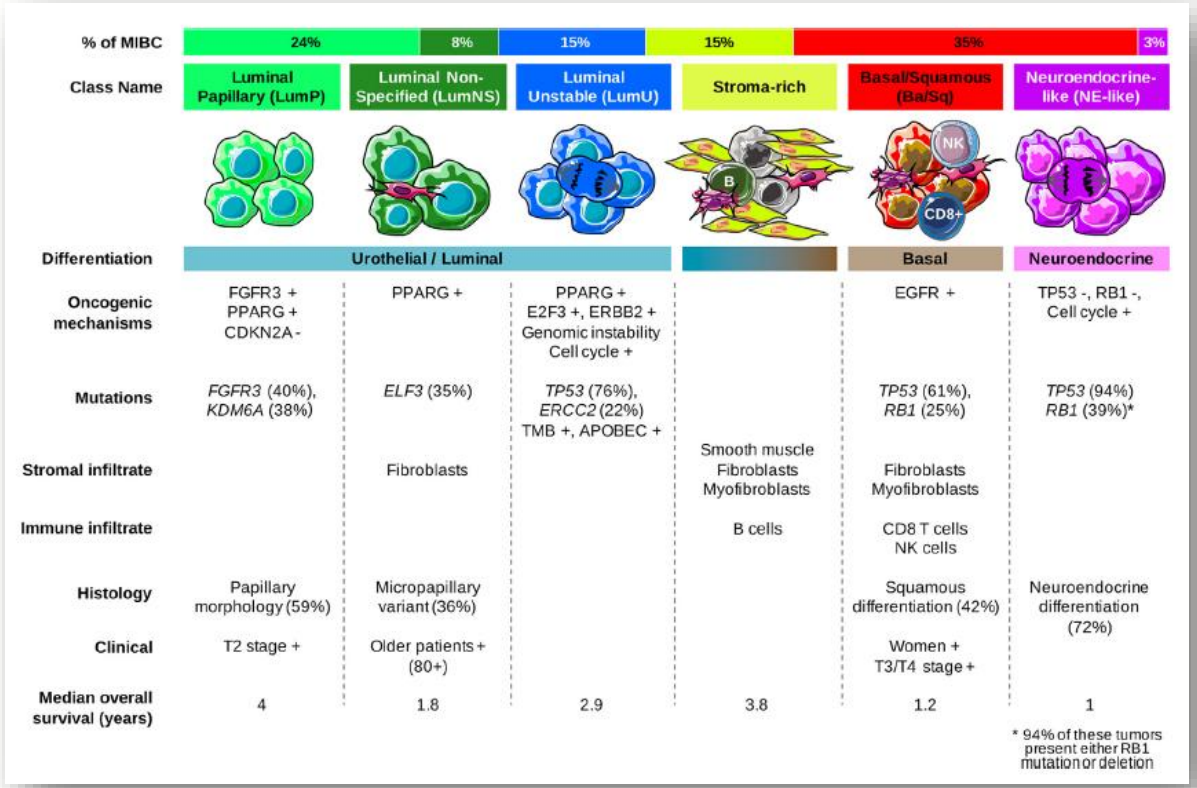
First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	Preferred regimens • Pembrolizumab and enfortumab vedotin-ejfv[15] (category 1) Other recommended regimens • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,13] • Nivolumab, gemcitabine, and cisplatin (category 1) followed by nivolumab maintenance therapy[14] (category 1) Useful under certain circumstances • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,13]
Cisplatin ineligible	Preferred regimens • Pembrolizumab and enfortumab vedotin-ejfv[15,17] (category 1) Other recommended regimens • Gemcitabine and carboplatin[16] followed by avelumab maintenance therapy (category 1)[a,13] Useful under certain circumstances • Gemcitabine[18] • Gemcitabine and paclitaxel[19] • Ifosfamide, doxorubicin, and gemcitabine[21] (for patients with good kidney function and good performance status) • Pembrolizumab[22] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab[20] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-platinum or other chemotherapy)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1 post-platinum)[24]	Other recommended regimens • Paclitaxel[30] or docetaxel[31] • Gemcitabine[18] • Pembrolizumab and enfortumab vedotin-ejfv (category 2B)[17]
Alternative preferred regimens • Immune checkpoint inhibitor ‣ Nivolumab[25] ‣ Avelumab[26,27] • Erdafitinib[d,28] • Enfortumab vedotin-ejfv[e,29]	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine[22] • Gemcitabine and paclitaxel[19] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimens for cisplatin ineligible, chemotherapy naïve • Enfortumab vedotin-ejfv[29] • Gemcitabine and carboplatin • Erdafitinib[d,28]	Other recommended regimens • Paclitaxel or docetaxel[31] • Gemcitabine[18]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2] • Erdafitinib[d,28]	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine[22] • Gemcitabine and paclitaxel[19]

Subsequent-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)[f,g] Participation in clinical trials of new agents is recommended.		
Preferred regimens • Enfortumab vedotin-ejfv (category 1)[32,33] • Erdafitinib[d,28] (category 1)	Other recommended regimens • Sacituzumab govitecan-hziy[34] • Gemcitabine[18] • Paclitaxel[30] or docetaxel[31] • Ifosfamide, doxorubicin, and gemcitabine[22] • Gemcitabine and paclitaxel[19] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	Useful in Certain Cirumstances regimens • Fam-trastuzumab deruxtecan-nxki (HER2-positive, IHC 3+)[43]

Carcinoma urotelial: gran heterogeneidad molecular



Vías oncogénicas diferentes

↓

Terapias diana

↓

Biomarcadores predictivos

Kamoun A et al. Eur Urol 2020; 77: 420-423.

Terapias dirigidas por alteración molecular

Table 3. Targeted therapy approved in bladder cancer.

Molecular Target	Targeted Therapy	Clinical Trial [Ref.]	Patient Eligibility	Study Arms	Results	Comments
FGFR	Erdafitinib	BLC2001 [17,184]	Advanced UC and progression on prior platinum-based chemotherapy, with or without prior immunotherapy and with *FGFR* alterations (mutations/fusions)	Phase II single-arm study	ORR: 40% Median PFS: 5.5 months Median OS: 13.8 months Adverse events: stomatitis, hyponatremia, hyperphosphatemia	Accelerated FDA approval based on ORR. First gene-targeted therapy approved in UC.
Nectin-4 (a cell adhesion molecule)	**Enfortumumab vedotin** (an antibody targeting Nectin-4 linked to a microtubule inhibitor conjugate (monomethyl auristatin E)	EV 201 [192]	Locally advanced or metastatic disease ineligible for cisplatin, not having received prior platinum-based chemotherapy, and previously treated with either a PD-1 or a PD-L1 inhibitor; no biomarker assay needed	Phase II single-arm study	ORR: 52% Adverse events: Neutropenia Rash Pneumonitis	Nectin-4 levels on tumor tissue are assessed with IHC. An H score is assigned with a range of 0–300, where 0 means no expression and 300 means maximal IHC staining.
		EV301 [187]	Locally advanced unresectable or metastatic UC (including those with squamous differentiation or mixed cell types) previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitor; no biomarker assay needed	Enfortumab vedotin or investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine)	Significant improvement in Median OS: 13 vs. 9 months, Median PFS: 6 vs. 4 months ORR: 41% vs. 18% Adverse events: Rash Peripheral neuropathy Hyperglycemia	FDA-approved for locally advanced or metastatic UC progressed on both platinum-based chemotherapy and immunotherapy.
Trop-2 (a transmembrane glycoprotein highly expressed in most UC)	**Sacituzumab govitecan** (antibody–drug conjugate that targets Trop-2, and is coupled with SN-38, an active metabolite ofirinotecan)	TROPHY-U-01 [191]	Advanced UC previously treated with platinum-based chemotherapy or immunotherapy; no biomarker assay needed.	Single-arm phase II study	ORR: 27% Median PFS: 5 months Median OS: 11 months Adverse events: Neutropenia Anemia Thrombocytopenia	Advanced UC previously treated with platinum-based chemotherapy or immunotherapy.

HER2

Otros

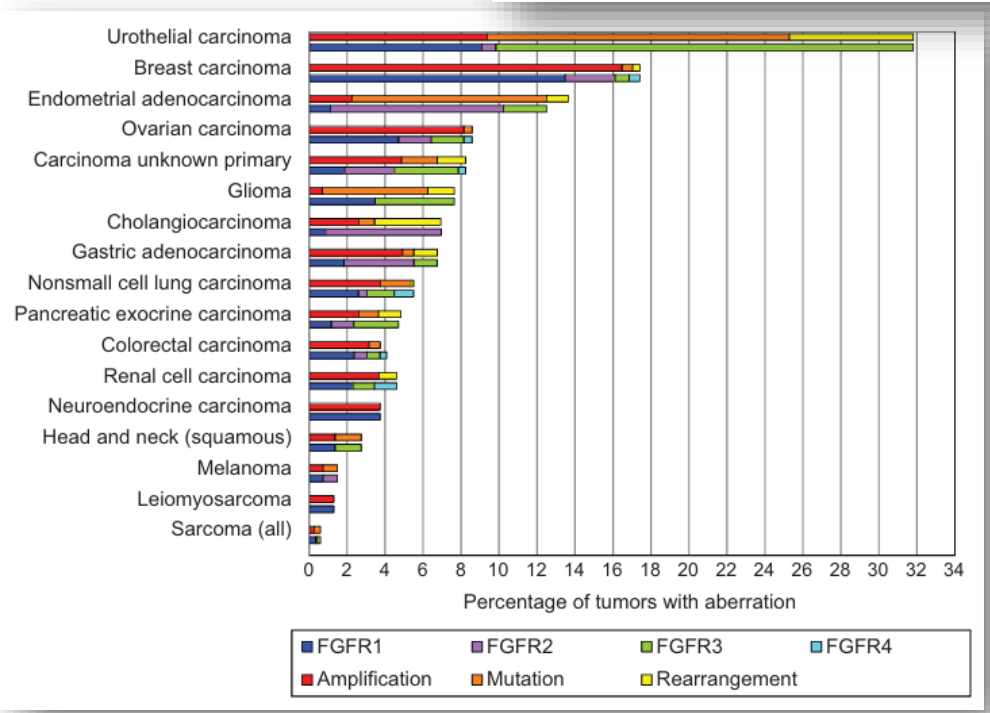
Mohanty SK et al. Precision Medicine in Bladder Cancer: Present Challenges and Future Directions. J. Pers. Med. 2023; 13: 756.

FGFR3

The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing

Teresa Helsten[1], Sheryl Elkin[2], Elisa Arthur[1], Brett N. Tomson[2], Jennifer Carter[2], and Razelle Kurzrock[1]

Clin Cancer Res; 2016: 259–267.



Mayor capacidad proliferativa

Mayor agresividad

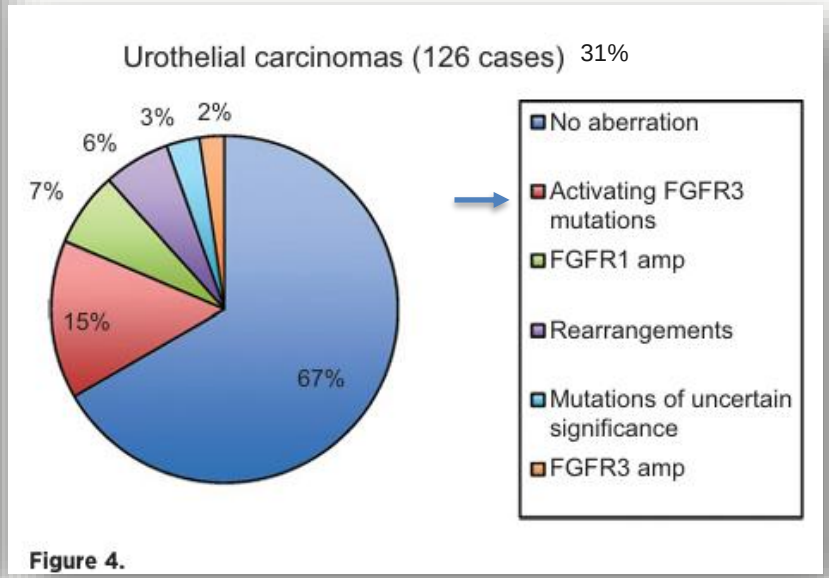


Figure 4.

FGFR3

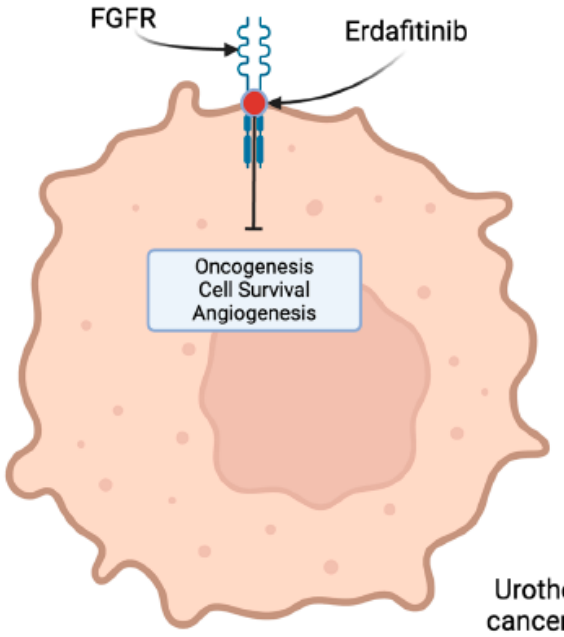


Figure 2. FGFR as a therapeutic target for pan-FGFR-sensitive inhibitor Erdafitinib inhibiting oncogenesis, survival and angiogenesis resulting in increased cell death.

Factor de crecimiento de fibroblastos

Familia de receptores de la tirosin kinasa.

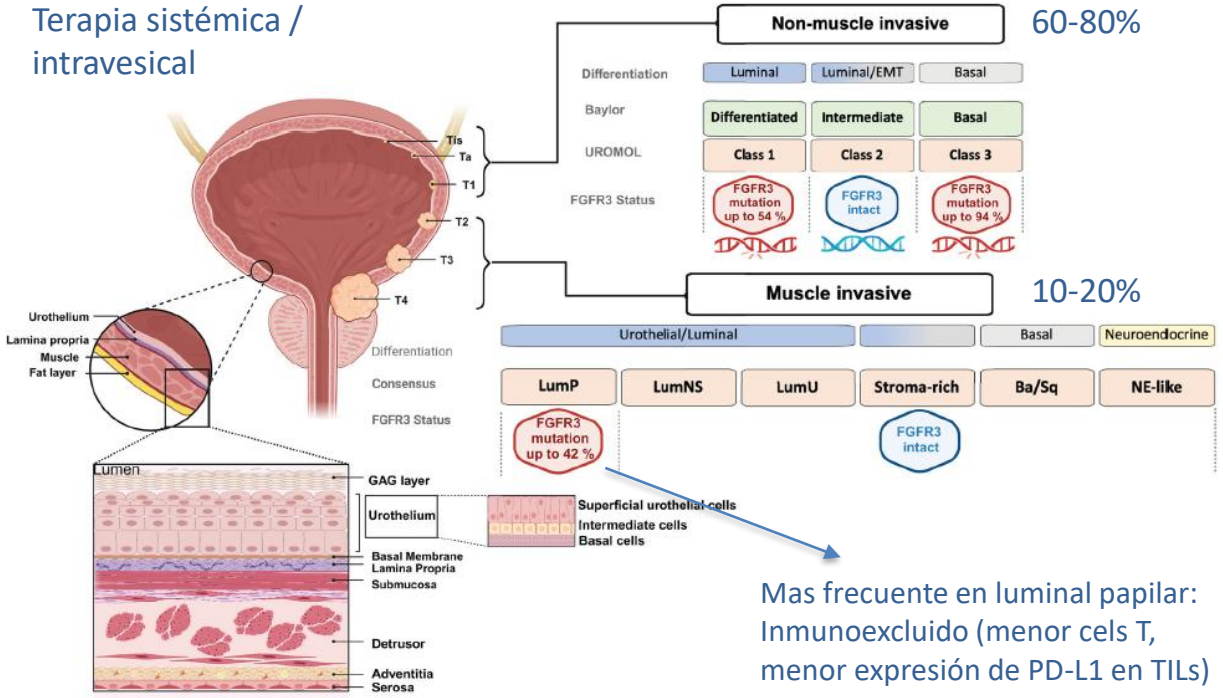
Erdafitinib: inhibidor pan-FGFR (1-4)

Eturi A et al. Molecules 2024; 29: 1896

FGFR3

NOERAPARAST ET AL. *Cancer Communications. 2024;44:1189–1208.* CANCER COMMUNICATIONS 1191

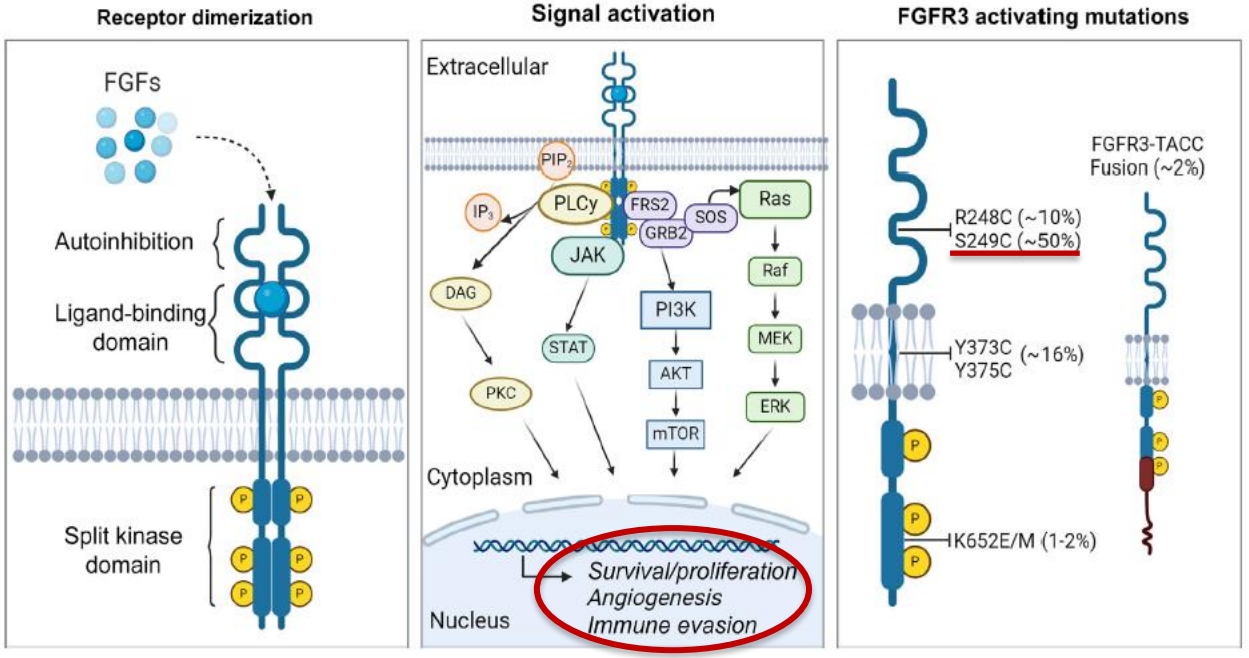
Terapia sistémica / intravesical



TUS: 37%

Mas frecuente en luminal papilar: Inmunoexcluido (menor cels T, menor expresión de PD-L1 en TILs)

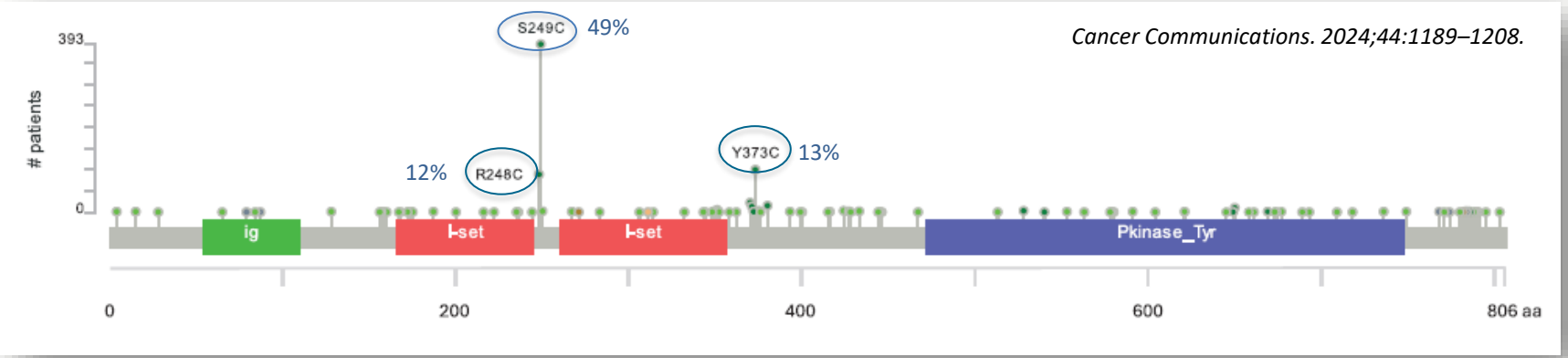
FGFR3



Alteraciones *FGFR3* en BCL2001 II
- 75%: Mutaciones / sobreexpresión
- 25%: Fusión genes constitutivamente activados (TACC3 y BAIAP2L1)

- No está constitutivamente activa en células no malignas

FGFR3



Cancer Communications. 2024;44:1189–1208.

- Mutaciones puntuales *FGFR3/2*
- Variantes estructurales

Fármacos inhibidores *FGFR3:* **Erdafitinib**

Relación con microambiente tumoral (no inflamado). Reduce expresión PD-L1
Paradójicamente no parecen influir en la respuesta a la inmunoterapia sistémica.

Potenciales mecanismos de resistencia (vía PI3K/mTOR)

No es BM de falta de respuesta a IT

Sweis RF et al. Cancer Immunol Res 2016;4:563–8.
Wang L et al. Eur Urol 2019; 76:599-603.
Lindskrog SV et al. Nat Commun 2021;12:2301.

FGFR3

BM de respuesta a erdafitinib

FDA approves erdafitinib for locally advanced or metastatic urothelial carcinoma

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On January 19, 2024, the Food and Drug Administration approved erdafitinib (Balversa, Janssen Biotech) for adult patients with locally advanced or metastatic urothelial carcinoma (mUC) with susceptible FGFR3 genetic alterations, as determined by an FDA-approved companion diagnostic test, whose disease has progressed on or after at least one line of prior systemic therapy. Erdafitinib is not recommended for the treatment of patients who are eligible for and have not received prior PD-1 or PD-L1 inhibitor therapy. This approval amends the indication previously granted under accelerated approval for patients with mUC with susceptible FGFR3 or FGFR2 alterations after prior platinum-containing chemotherapy.

N Engl J Med 2023;389:1961-71.

ORIGINAL ARTICLE

Cohort 1 BCL 3001

Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma

Yohann Loriot, M.D., Ph.D., Nobuaki Matsubara, M.D., Se Hoon Park, M.D., Ph.D., Robert A. Huddart, M.B., B.S., Ph.D., Earle F. Burgess, M.D., Nadine Houede, M.D., Severine Banek, M.D., Valentina Guadalupi, M.D., Ja Hyeon Ku, M.D., Ph.D., Begoña P. Valderrama, M.D., Ben Tran, M.B., B.S., Spyros Triantos, M.D., Yin Kean, M.S., Sydney Akapame, Ph.D., Kris Deprince, M.D., Sutapa Mukhopadhyay, Ph.D., Nicole L. Stone, Ph.D., and Arlene O. Siefker-Radtke, M.D., for the THOR Cohort 1 Investigators*

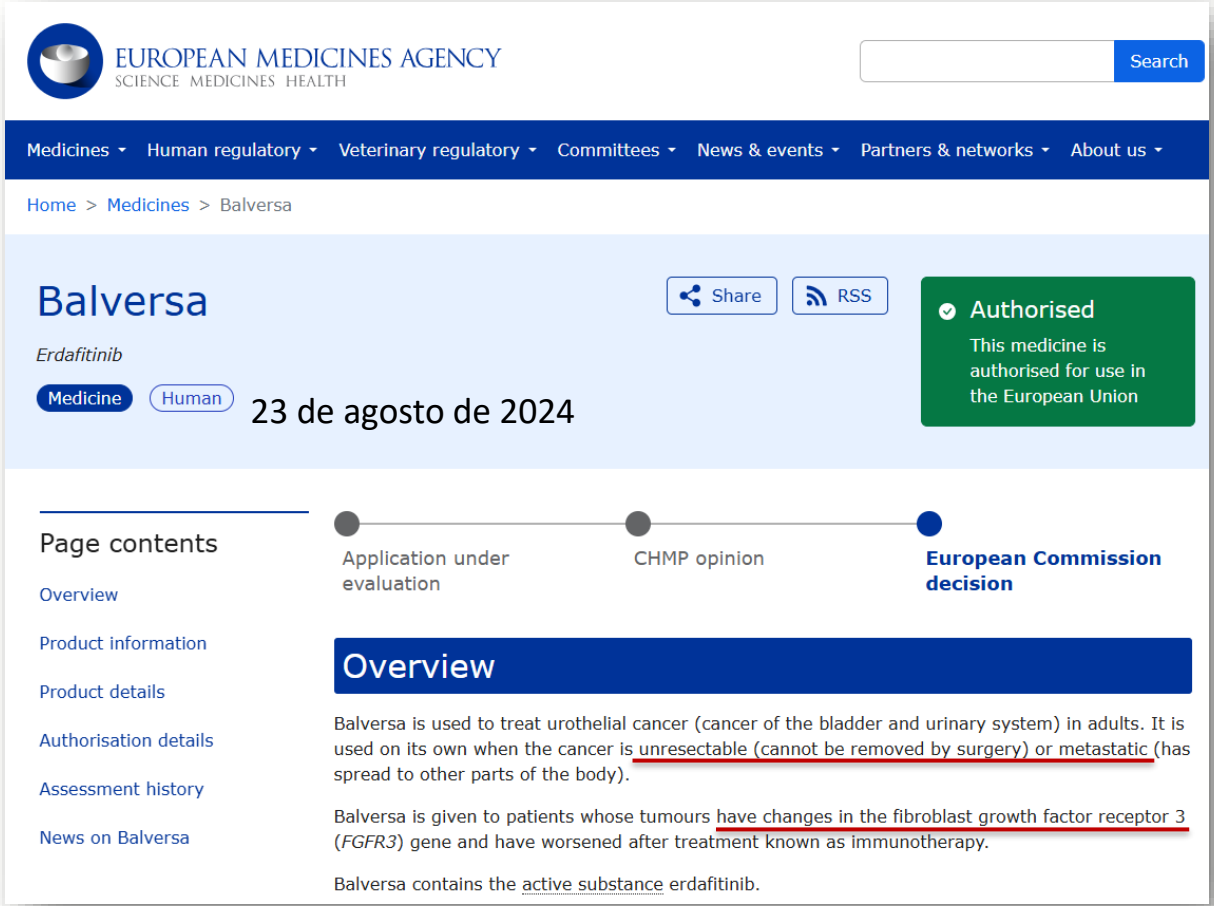
***FGFR3* mutations** (R248C, S249C, G370C, and Y373C) o **FGFR2/3 fusions** (FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR2-BICC1 y FGFR2-CASP7) en muestras archivadas. RT-PCR (Qiagen)

Ann Oncol 2024;35 107-117.

ORIGINAL ARTICLE

Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select *FGFR* alterations: cohort 2 of the randomized phase III THOR trial☆

A. O. Siefker-Radtke[1*], N. Matsubara[2], S. H. Park[3], R. A. Huddart[4], E. F. Burgess[5], M. Özgüroğlu[6], B. P. Valderrama[7], B. Laguerre[8], U. Basso[9], S. Triantos[10], S. Akapame[10], Y. Kean[10], K. Deprince[11], S. Mukhopadhyay[12] & Y. Loriot[13], for the THOR cohort 2 investigators[i]



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Balversa

Erdafitinib

Medicine | Human

23 de agosto de 2024

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Authorised
This medicine is authorised for use in the European Union

Page contents

- Overview
- Product information
- Product details
- Authorisation details
- Assessment history
- News on Balversa

Application under evaluation → CHMP opinion → **European Commission decision**

Overview

Balversa is used to treat urothelial cancer (cancer of the bladder and urinary system) in adults. It is used on its own when the cancer is unresectable (cannot be removed by surgery) or metastatic (has spread to other parts of the body).

Balversa is given to patients whose tumours have changes in the fibroblast growth factor receptor 3 (*FGFR3*) gene and have worsened after treatment known as immunotherapy.

Balversa contains the active substance erdafitinib.

FGFR3

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2024
Muscle Invasive Bladder Cancer

NCCN Guidelines Index
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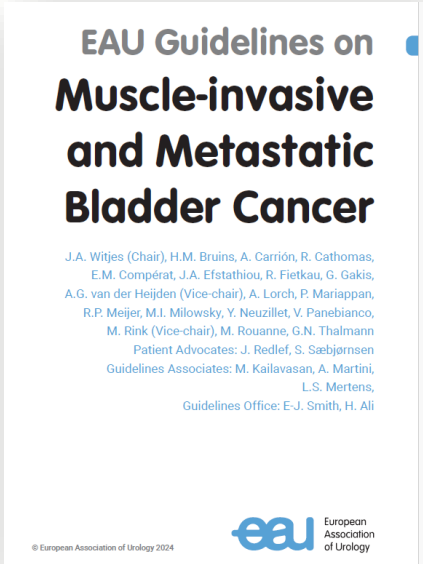
Discussion

Molecular/Genomic Testing

The panel recommends that molecular/genomic testing be performed for stages IVA and IVB bladder cancer and may be considered for stage IIIB. This testing should be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[240] The NCCN Bladder Cancer Panel recommends that molecular/genomic testing be conducted early, ideally at diagnosis of advanced bladder cancer, to facilitate treatment decision-making and to prevent delays in administering later lines of therapy. In addition to determining eligibility for FDA-approved therapies, molecular/genomic testing may be used to screen for clinical trial eligibility.

Principles of Systemic Therapy (BL-G 2 of 7).

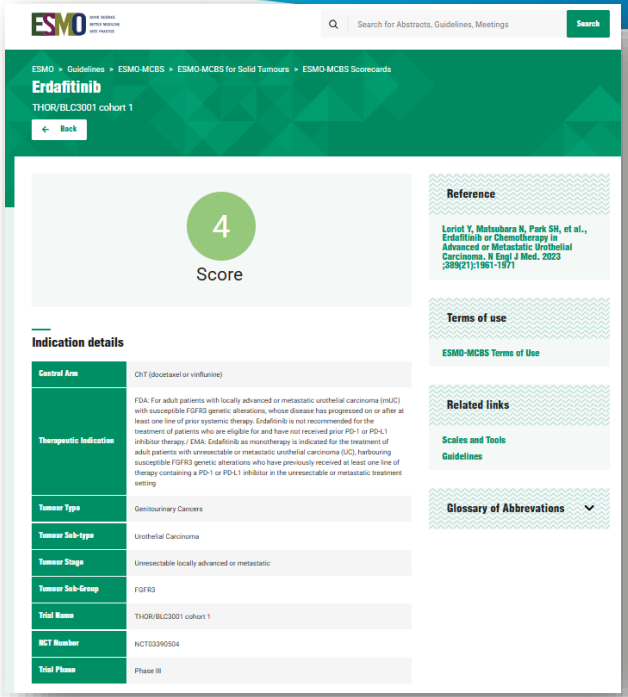
Molecular/genomic testing in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory, including FGFR RGQ RT-PCR for *FGFR3* genetic alterations and IHC for HER2 overexpression. See Discussion.


EAU Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

J.A. Witjes (Chair), H.M. Bruins, A. Carrión, R. Cathomas, E.M. Compérat, J.A. Efstathiou, R. Fietkau, G. Gakis, A.G. van der Heijden (Vice-chair), A. Lorch, P. Mariappan, R.P. Meijer, M.I. Milowsky, Y. Neuzillet, V. Panebianco, M. Rink (Vice-chair), M. Rouanne, G.N. Thalmann
Patient Advocates: J. Redlef, S. Sæbjørnsen
Guidelines Associates: M. Kailavasan, A. Martini, L.S. Mertens,
Guidelines Office: E-J. Smith, H. Ali

European Association of Urology


ESMO

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Erdafitinib

THOR/BLC3001 cohort 1

Back

4

Score

Indication details

Control Arm	ChT (docetaxel or vinflunine)
Therapeutic Indication	FDA: For adult patients with locally advanced or metastatic urothelial carcinoma (mUC) with susceptible FGFR3 genetic alterations, whose disease has progressed on or after at least one line of prior systemic therapy. Erdafitinib is not recommended for the treatment of patients who are eligible for and have not received prior PD-1 or PD-L1 inhibitor therapy./ EMA: Erdafitinib as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting
Tumour Type	Genitourinary Cancers
Tumour Sub-type	Urothelial Carcinoma
Tumour Stage	Unresectable locally advanced or metastatic
Tumour Sub-Group	FGFR3
Trial Name	THOR/BLC3001 cohort 1
NCT Number	NCT03390504
Trial Phase	Phase III

Reference

Loriot Y, Matsubara N, Park SH, et al., Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2023 ;389(21):1961-1971

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Glossary of Abbrevations

7.7.5 *Current status of predictive biomarkers*

The most important advance in recent years has been the recognition of alterations in FGFR3 including mutations and gene fusions as a predictive marker for response to FGFR inhibitors [234]. It is recommended to screen mUC patients ideally at diagnosis of metastatic disease for FGFR3 alterations to plan optimal treatment including trials.

In conclusion, apart from FGFR3 alterations, there are currently no further validated predictive molecular markers that are routinely used in clinical practice.

Table 1 – FGFR inhibitors tested in urothelial cancer

Inhibitor	Mechanism	Target	Binding site	Delivery	Primary cancer trials	Clinical trial	FDA approval	Most common grade ≥3 AEs	Clinically notable AEs (any grade)	References
Second generation (FGFR selective)										
Erdafitinib (JNJ-42756493)	TKI RTI	FGFR1–4	ATPc	Oral	UC	Phase 3	UC	Overall 45.9% PPE (9.6%), STM (8.1%), anemia (7.4%), HPP (5.2%)	HPP (80%), PPE (51.1%), nail disorders (66.7%), SRD (5.2%), RPED (1.5%)	[35,43]
Rogaratinib (BAY1163877)	TKI RTI	FGFR1–4	ATPc	Oral	UC	Phase 2/3	Under review	Overall 47.7% Asthenia (9.3%), lipase ↑ (8.2%), diarrhea (4.7%), anemia (3.5%)	HPP (45.3%), PPE (NR), nail disorders (NR), retinal disorder grade >2 (7.0%)	Collin 2018 [41]
Infigratinib (BGJ398)	TKI RTI	FGFR1–3	ATPc	Oral	UC/CGC	Phase 1/3 (discontinued)	CGC	Overall 68.7% Lipase ↑ (10.4%), PPE (7.5%), anemia (7.5%), HPO (7.5%), hyponatremia (6.0%)	HPP (46.3), PPE (11.9%), dry eye/blurred vision (26.8%), central serous retinopathy and RPED (17%)	[39] Javale 2021
Pemigatinib (INCB054828)	TKI RTI	FGFR1–3	ATPc	Oral	UC	Phase 2	CGC	Overall 36.5% STM (8.8%), anemia (8.1%), UTI (7.3%), asthenia (4.6%)	HPP (53.5%), NTX (40%), dry eye (26.9%), SRD (13.1%), HPO (8.5%), vitreous detachment (2.3%)	Lui 2020 [54]
Fexagratinib (AZD4547)	TKI RTI	FGFR1–3	ATPc	Oral	Lung, breast	Phase 2 (breast)	No	Overall 41.0% Mucositis (14.0%), AST ↑ (8.0%), PPE (6.0%), ALT ↑ (6.0%)	HPP (50.0%), NTX (26.0%), dry rye (22.0%), RPED (21.2%), HPO (8.0%)	Chae 2020 Coombes 2022
Tasurgratinib (E7090)	TKI type V	FGFR1–3	ATPc	Oral	CGC	Phase 2 (CGC)	No [a]	N/A	N/A	Miyano 2016 Koyama 2020
Derazantinib (ARQ 087)	TKI	FGFR1–3	ATPc	Oral	UC/CGC	Phase 2	No	N/A	Retinal events (16.0%), NTX (6.1%), STM (4.0%), PPE (0%)	Hall 2016 Necchi 2023
LY2874455	TKI RTI	FGFR1–4	ATPc	Oral	Gastric/ NSCLC	Phase 1	No	N/A	N/A	Michael 2017 Dehghanian 2021
Futibatinib (TAS-120)	TKI IRTI	FGFR1–4	KD P-loop	Oral	CGC	Phase 2	No	HPP, AST ↑, STM, fatigue	N/A	Goyal 2023
Third generation (FGFR subtype–specific)										
TYRA-300	TKI	FGFR3	KD GMR	Oral	UC	Phase 1	No	N/A	N/A	Starrett 2022
LOXO-435	TKI	FGFR3	KD GMR	Oral	UC	Phase 1	No	N/A	N/A	Iyer 2023
LY3076226	ADC	FGFR3	ECR	Systemic	UC	Phase 1	No	N/A	N/A	Kollmannsberger 2021
Vofatamab (B-701)	mAb	FGFR3	LBD	Systemic	UC	Phase 2	No	N/A	N/A	Necchi 2019 Siefker-Radtke 2023
MFGR1877S	mAb	FGFR3	LBD	Systemic	STs	Phase 1	No	N/A	N/A	O'Donnell 2012
First generation (nonselective TKIs)										
Dovitinib (TKI258)	TKI RTI	VEGFR1–3 FGFR1–3 PDGFRA/B	ATPc	Oral	RCC	Phase 3 (aRCC)	No [b]	Hypertriglyceridemia (14%), fatigue (10%), HTN (8%), diarrhea (7%)	N/A	[34] Motzer 2014

FGFR3

Cancer Treatment Reviews 115 (2023) 102530

Role of *FGFR3* in bladder cancer: Treatment landscape and future challenges

Claudia Maria Ascione [a,1], Fabiana Napolitano [a,1], Daniela Esposito [a], Alberto Servetto [a], Stefania Belli [a], Antonio Santaniello [a], Sarah Scagliarini [b], Felice Crocetto [c], Roberto Bianco [a,1], Luigi Formisano [a,1,*]

Future Oncol. (2022) 18(21), 2599–2614

Targeting *FGFR3* alterations with adjuvant infigratinib in invasive urothelial carcinoma: the phase III PROOF 302 trial

Sumanta K Pal*,[1], Diederik M Somford[2], Petros Grivas[3], Srikala S Sridhar[4], Shilpa Gupta[5], Joaquim Bellmunt[6,7], Guru Sonpavde[8], Mark T Fleming[9], Seth P Lerner[10], Yohann Loriot[11], Jean Hoffman-Censits[12], Begoña P Valderrama[13], Corina Andresen[14], Marco J Schnabel[15], Suzanne Cole[16] & Siamak Daneshmand[17]

Computers in Biology and Medicine 162 (2023) 106976

FGFR3 mutation characterization identifies prognostic and immune-related gene signatures in bladder cancer

Pei-Hang Xu [a,b,1], Siyuan Chen [b,c,1], Yanhao Wang [a,b,1], Shengming Jin [a,b], Jun Wang [d,e,f,**], Dingwei Ye [a,b,***], Xiaodong Zhu [b,c,****], Yijun Shen [a,b,*]

m*FGFR3* marcador predictivo respuesta a inhibidores *FGFR*

- Mutaciones *FGFR3:* mayor beneficio trat anti FGFR3
- Mutuamente excluyentes con m*TP53* y *RB1*
- Bajo TMB, bajo PD-L1 y más alteraciones *MDM2*

- **Reto: método de detección (NGS vs RT-PCT)**
- NCCN y ESMO: RT-PCR : Therascreen FGFR kit, Qiagen como companion diagnostic
- NGS

Cancer Treatment Reviews 115 (2023) 102530

Role of *FGFR3* in bladder cancer: Treatment landscape and future challenges

Claudia Maria Ascione [a,1], Fabiana Napolitano [a,1], Daniela Esposito [a], Alberto Servetto [a], Stefania Belli [a], Antonio Santaniello [a], Sarah Scagliarini [b], Felice Crocetto [c], Roberto Bianco [a,1], Luigi Formisano [a,1,*]

FGFR3

Clin Cancer Res. 2023 November 14; 29(22): 4586–4595. doi:10.1158/1078-0432.CCR-23-1283.

Clinical and genomic landscape of FGFR3-altered urothelial carcinoma and treatment outcomes with erdafitinib: a real-world experience

Brendan J. Guercio[1,2], Michal Sarfaty[3,4], Min Yuen Teo[1,5], Neha Ratna[1], Cihan Duzgol[6], Samuel A. Funt[1,5], Chung-Han Lee[1,5], David H. Aggen[1,5], Ashley M. Regazzi[1], Ziyu Chen[7], Michael Lattanzi[8], Hikmat A. Al-Ahmadie[9], A. Rose Brannon[7], Ronak Shah[7], Carissa Chu[10], Andrew T. Lenis[11], Eugene Pietzak[5,10], Bernard H. Bochner[5,10], Michael F. Berger[7], David B. Solit[1,5,7], Jonathan E. Rosenberg[1,5], Dean F. Bajorin[1,5], Gopa Iyer[1,5]

Discordancia del 26% (32 pacientes) en la alteración del *FGFR3* en pacientes con lesiones primarias y metastásicas emparejadas.

El grado de heterogeneidad tumoral intrapaciente subraya la **importancia de la biopsia y el perfil molecular actualizados inmediatamente antes del inicio de la terapia.**

J Urol. 2015 Jan;193(1):325-30. doi: 10.1016/j.juro.2014.06.026. Epub 2014 Jun 13.

FGFR3 expression in primary invasive bladder cancers and matched lymph node metastases

Rafal Turo [1], Patricia Harnden [2], Helene Thygesen [3], Achim Fleischmann [4], George N Thalmann [5], Roland Seiler [6], William R Cross [1], Margaret A Knowles [7]

Discordancia (27/106 pacientes, **26%**) en la alteración del *FGFR3* (**IHQ**) en pacientes con lesiones primarias y metastásicas

Annals of Oncology 27: 1311–1316, 2016
doi:10.1093/annonc/mdw170
Published online 18 April 2016

Tumor heterogeneity of *fibroblast growth factor receptor 3* (*FGFR3*) mutations in invasive bladder cancer: implications for perioperative anti-FGFR3 treatment

D. Pouessel[1,2,†], Y. Neuzillet[3,†], L. S. Mertens[3], M. S. van der Heijden[4], J. de Jong[5], J. Sanders[5,6], D. Peters[6], K. Leroy[7], A. Manceau[7], P. Maille[8], P. Soyeux[1], A. Moktefi[8], F. Semprez[1], D. Vordos[9], A. de la Taille[1,9], C. D. Hurst[10], D. C. Tomlinson[10], P. Harnden[10], P. J. Bostrom[11,21], T. Mirtti[12], S. Horenblas[3], Y. Loriot[13], N. Houédé[14], C. Chevreau[15], P. Beuzeboc[16], S. F. Shariat[17,19], A. I. Sagalowsky[17], R. Ashfaq[18], M. Burger[20], M. A. S. Jewett[21], A. R. Zlotta[21,22], A. Broeks[6], B. Bapat[23], M. A. Knowles[10], Y. Lotan[17], T. H. van der Kwast[24], S. Culine[2,25], Y. Allory[1,8,26,‡] & B. W. G. van Rhijn[3,20,21,22,23*,‡]

Concordancia (10 con mutaciones/ 201 pacientes) en la alteración del *FGFR3* (DNA) en pacientes con lesiones primarias y metastásicas

FGFR3

- Herramientas de pre-screening
- Patrones morfológicos ligados a mutaciones de ***FGFR3***

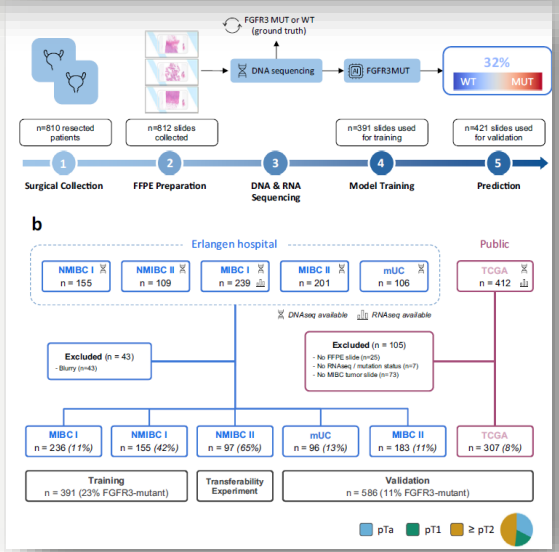
nature communications *2024 Dec 30;15(1):10914.*

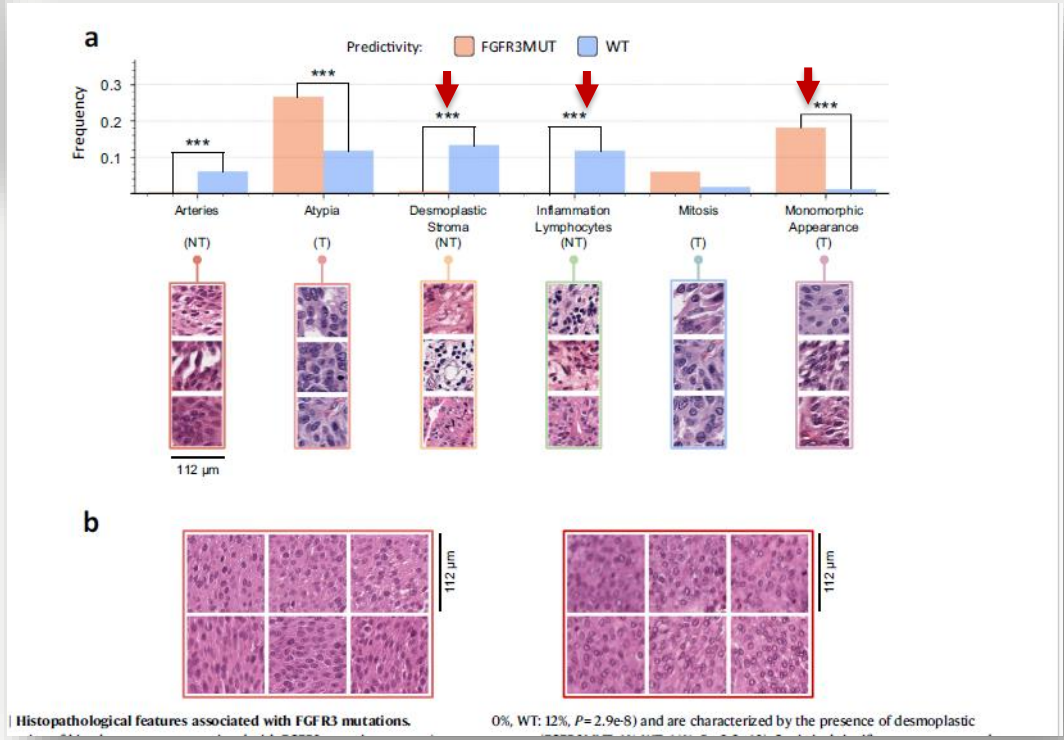
Article https://doi.org/10.1038/s41467-024-55331-6

AI allows pre-screening of FGFR3 mutational status using routine histology slides of muscle-invasive bladder cancer

Received: 17 April 2024
Accepted: 9 December 2024
Published online: 30 December 2024

Pierre-Antoine Bannier[1], Charlie Saillard[1], Philipp Mann[1], Maxime Touzot[1], Charles Maussion[1], Christian Matek[2,3,4], Niklas Klümper[5,6,7], Johannes Breyer[8], Ralph Wirtz[9], Danijel Sikic[3,4,10], Bernd Schmitz-Dräger[11], Bernd Wullich[3,4,10], Arndt Hartmann[2,3,4], Sebastian Försch[12] & Markus Eckstein[2,3,4]





Histopathological features associated with FGFR3 mutations. 0%, WT: 12%, *P*= 2.9e-8) and are characterized by the presence of desmoplastic

FGFR3

TABLE 1 Overview of recent key preclinical and clinical findings on FGFR3 mutations in BLCA.

Recent findings on FGFR3 mutations in BLCA	Preclinical	Clinical
Related to TME and CPIs		
Immune-inert phenotype in FGFR3 mutated tumors in mice	✓	
Downregulation of PD-L1 in FGFR3 active status	✓	
Impact on anti-tumor activity of CD8+ T-cells	✓	
Improved antitumor effect upon combining FGFR3 and PD-1 targeting	✓	
Reduced T-cell infiltration and inert microenvironment associated with FGFR3 mutations in BLCA patients		✓
FGFR3 mutation impacts response to CPIs by both T-cell infiltration and stroma-associated EMT markers		✓
Cold tumors not always in inverse relationship with responsiveness to CPIs in FGFR3-altered BLCA patients		✓
Related to FGFR3 inhibition and resistance		
EGFR and PI3K identified as co-targets	✓	
Sensitivity in FGFR3 resistant cell lines when co-targeting EGFR	✓	
bypassing mechanisms through effectors of AKT pathway	✓	
Heterogenous phenotypic switches in FGFR3-resistant subclones derived from the same cell	✓	
Upregulation of various genes including IGF1R, EGFR, ERBB2, ERBB3, and MET	✓	
Quisinostat synergizes with Erdafitinib by suppressing FGFR3 protein translation	✓	
Resistance to Erdafitinib in FGFR3 mutant cells induced by P4HA2 and HIF-1α	✓	
NRG1-HER3 axis mediates resistance to Erdafitinib and sensitizes to HER3-targeting in FGFR3 mut BLCA mouse xenografts	✓	
Secondary mutations at gatekeeper residue sites	✓	
HRAS mutation was found in some FGFR3-resistant sub-clones	✓	
Resistance hotspot mutations on residues V555 and N540		✓
Genetic alterations within AKT pathway effectors		✓
Poorer outcome upon baseline co-occurrence of FGFR3 and TP53 mutations		✓

Different phenomena discovered preclinically or clinically concerning the impact of FGFR3 alterations on TME, response to CPIs, and response and resistance to FGFR inhibition are summarized.
Abbreviations: BLCA, Bladder Cancer; CPIs, Checkpoint Inhibitors; FGFR3, Fibroblast Growth Factor Receptor 3; FGFR, Fibroblast Growth Factor Receptor; TME, Tumor Microenvironment.

Noeraparast M et al Cancer Communications. 2024;44:1189–1208.

La secuenciación prospectiva del ctDNA reveló la adquisición durante el tratamiento con erdafitinib de **mutaciones en *FGFR*3, AKT1 y *TP53***, lo que sugiere posibles mecanismos de **resistencia adquirida.**

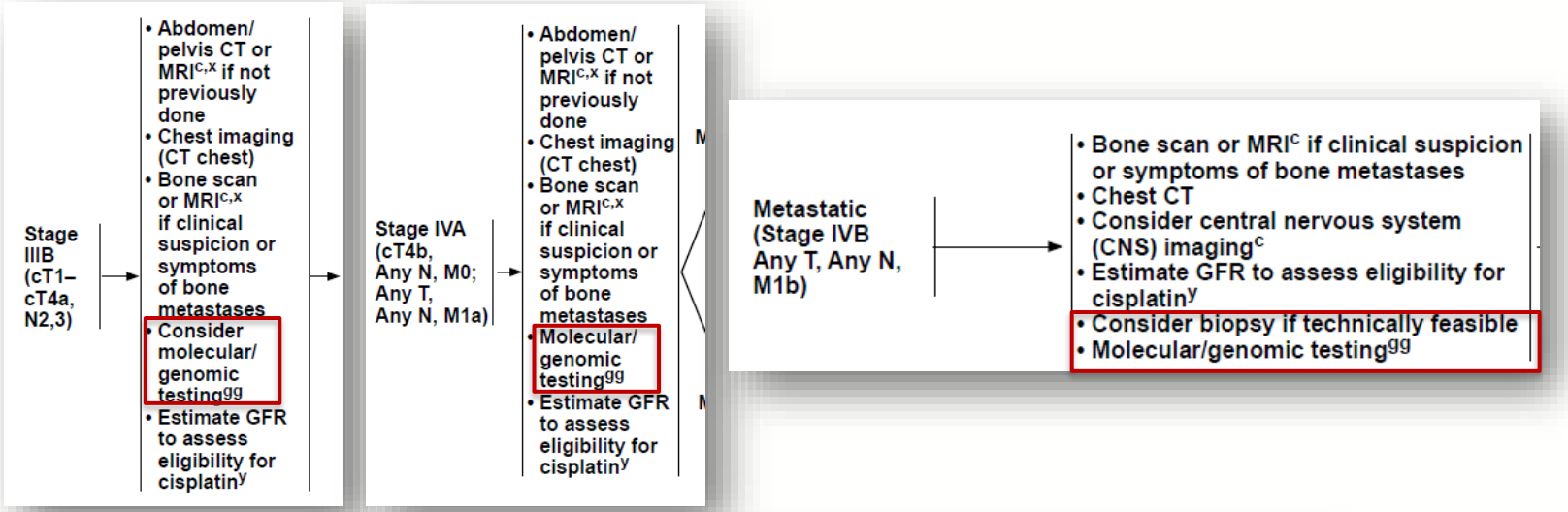
Guercio BJ et al. Clin Cancer Res 2023;29:4586–95.

HER2

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2024
Bladder Cancer

NCCN Guidelines Index
Table of Contents
Discussion



[dd] Principles of Systemic Therapy (BL-G 2 of 7).

[gg] Molecular/genomic testing in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory, including FGFR RGQ RT-PCR for *FGFR3* genetic alterations and IHC for HER2 overexpression. See Discussion.

HER2

- Receptor de la tirosin kinasa
- Grupo de receptores de factores de crecimiento epitelial
- Influye en crecimiento, supervivencia y movilidad celular

Vlachou et al 7

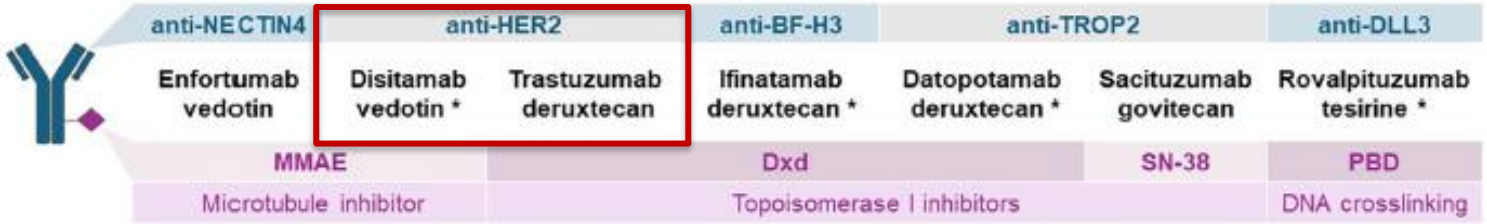


Figure 1. Mechanism of antibody drug conjugates (ADCs) used in urothelial cancer.
ADC targets are presented in blue, and payload is presented in purple. * represents ADCs in ongoing clinical trials that have not been approved.

Vlachou E etal. Clinical Medicine Insights. Oncology; 2024 18: 1–10

HER2

Tonni E et al. Int. J. Mol. Sci. 2024, 25, 9696.

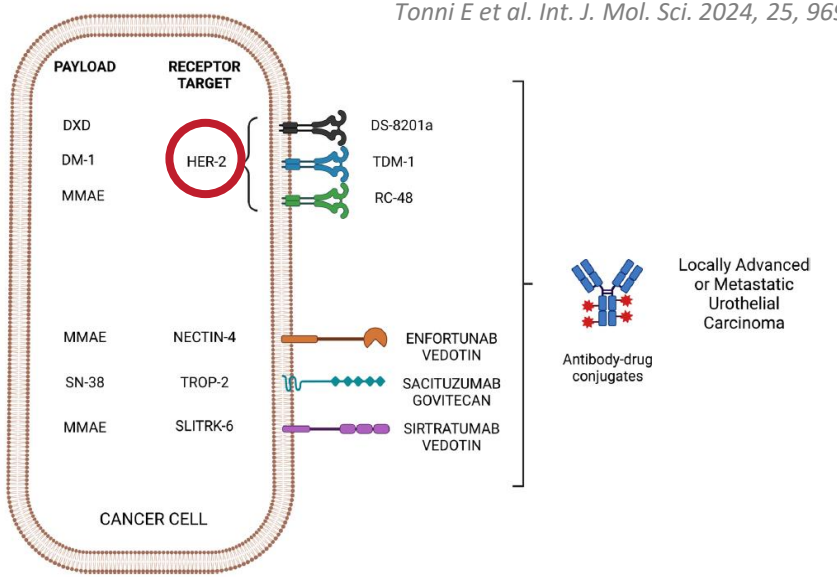


Fig. 1 Different types of ADCs tested in urothelial cancer. *DXD* deruxtecan, *DM-1* emtansine, *MMAE* monomethyl auristatin E, *HER2* human epidermal growth factor receptor 2, *T-DM1* trastuzumab emtansine, *TROP-2* Trophoblast cell surface antigen 2, *SLITRK* Slit- and Trk-like protein

Sobreexpresión de HER2 en CU

- 3er cáncer (dp mama y estómago) (7-80%)
- 10-20 % sobreexpresión IHQ en CU invasivo
- LA y m: 6.7% - 37.5% HER2+ and 13.4% to 56.3% HER2-low
- 5 % **amplificación**: + en metástasis GL (15%)
  + en **luminales** (GU)
- **56% en micropapilares,** 36% CU, 20% escamosos
- Correlación con progresión y mal pronostico
- En tumores más agresivos: >3cm, AG, T3, metast, CIS

- *Behzatoglu, Ket al. Human Epidermal Growth Factor Receptor 2 Overexpression in micropapillary and other variants of urothelial carcinoma. Eur. Urol. Focus 2018, 4, 399–404.*
- *Kai Gan,et al. The Clinical Significance and Prognostic Value of HER2 Expression in Bladder Cancer: A Meta-Analysis and a Bioinformatic Analysis. Front Oncol. 2021; 1:11:653491*
- *Dángelo A et al. An update on antibody–drug conjugates in urothelial carcinoma: state of the art strategies and what comes next Cancer Chemotherapy and Pharmacology 2022; 90:191–205.*
- *Scherrer E et al. HER2 expression in urothelial carcinoma, a systematic literature review. Front Oncol 2022;12:1011885.*
- *Helal DS et al. Immunohistochemical based molecular subtypes of muscle-invasive bladder cancer: association with HER2 and EGFR alterations, neoadjuvant chemotherapy response and survival. DiagnPathol 2023; 18:11.*
- *Sanguedolce F et al. HER2 expression in bladder cancer: a focused view on its diagnostic, prognostic, and predictive role. Int. J. Mol. Sci. 2023; 24: 3720.*
- *Qu M, et al. Advances in HER2-Targeted Treatment for Advanced/Metastatic Urothelial Carcinoma. Bladder (San Franc). 2023;10:e21200012.*

HER2

- Eficacia agentes diana HER2: un reto
- Beneficio clínico de terapias anti-HER2 en HER2 +: varios ensayos han fallado en demostrar eficacia clínica con varios fármacos (trastuzumab, pertuzumab, lapatinib, afatinib, neratinib)
- Valor como biomarcador en CU es controvertido debido a:
    - Baja concordancia entre expresión proteica IHQ (HER2 +) y amplificación génica FISH (HER2 2+) (polisomías, mutaciones puntuales, translocación?)
    - Heterogeneidad en valoración de HER-2 en ensayos
    - Heterogeneidad en expresión entre subtipos histológicos
- Valoración IHQ vs FISH: Falta metodología estandarizada valoración HER2 en CU
- No igual valor como biomarcador que en mama

Valoración HER2 + por IHQ y FISH

No hay metodología standard para ca urotelial

COLLEGE of AMERICAN PATHOLOGISTS

Template for Reporting Results of Biomarker Testing of Specimens from Patients with Carcinoma of the Breast

Version: 1.5.0.1
Protocol Posting Date: March 2023
This biomarker template is not required for accreditation purposes but may be used to facilitate compliance with CAP Accreditation Program Requirements

COLLEGE of AMERICAN PATHOLOGISTS

Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of Gynecologic Origin

Version: 1.1.0.0
Protocol Posting Date: March 2023
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

Dual Probe ISH Group Definitions:
Group 1 = HER2/CEP17 ratio ≥2.0; ≥4.0 HER2 signals/cell
Group 2 = HER2/CEP17 ratio ≥2.0; <4.0 HER2 signals/cell
Group 3 = HER2/CEP17 ratio <2.0; ≥6.0 HER2 signals/cell
Group 4 = HER2/CEP17 ratio <2.0; ≥4.0 and <6.0 HER2 signals/cell
Group 5 = HER2/CEP17 ratio <2.0; <4.0 HER2 signals/cell

CAP Approved Breast.Bmk_1.5.0.1.REL_CAPCP

Table 4. Reporting Results of HER2 Testing by Immunohistochemistry (IHC)

Result	Criteria
Negative (Score 0)	No staining observed *or* Membrane stating that is incomplete and is faint/barely perceptible and within ≤10% of tumor cells
Negative (Score 1+)	Incomplete membrane staining that is faint/barely perceptible and within >10% of tumor cells*
Equivocal (Score 2+)†	Weak to moderate complete membrane staining in >10% of tumor cells *or* Complete membrane staining that is intense but within ≤10% of tumor cells*
Positive (Score 3+)	Complete membrane staining that is intense and >10% of tumor cells*

* Readily appreciated using a low-power objective and observed within a homogeneous and contiguous population of invasive tumor cells.
† Must order reflex test (same specimen using ISH) or order a new test (new specimen if available, using IHC or ISH).

CAP Approved Breast.Bmk_1.5.0.1.REL_CAPCP

Table 5. Reporting Results of *HER2* Testing by In Situ Hybridization (single-probe assay)

Result	Criteria (single-probe assay)
Negative	· Average HER2 copy number <4.0 signals/cell · Average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 0, 1+ or 2+ · Average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent dual probe ISH Group 5
Positive	· Average HER2 copy number ≥6.0 signals/cell · Average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 3+ · Average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent dual probe ISH Group 1

Table 6. Reporting Results of *HER2* Testing by In Situ Hybridization (dual-probe assay)

Result	Criteria (dual-probe assay)
Negative	· Group 5
Negative* (see comment)	· Group 2 and concurrent IHC 0-1+ or 2+ · Group 3 and concurrent IHC 0-1+ · Group 4 and concurrent IHC 0-1+ or 2+
Positive*	· Group 2 and concurrent IHC 3+ · Group 3 and concurrent IHC 2+ or 3+ · Group 4 and concurrent IHC 3+
Positive	· Group 1

*For Groups 2-4 final ISH results are based on concurrent review of IHC, with recounting of the ISH test by a second reviewer if IHC is 2+ (per 2018 CAP/ASCO Update recommendations).

VOLUME 36 · NUMBER 20 · JULY 10, 2018
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/ College of American Pathologists Clinical Practice Guideline Focused Update

Antonio C. Wolff, M. Elizabeth Hale Hammond, Kimberly H. Allison, Brittany E. Harvey, Pamela B. Mangu, John M.S. Bartlett, Michael Bilous, Ian O. Ellis, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, Lisa M. McShane, and Mitchell Dowsett

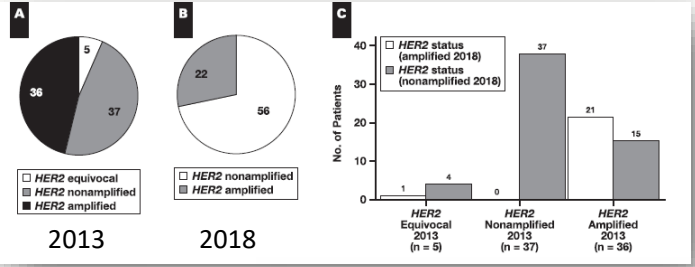
Valoración HER2 + por IHQ y FISH

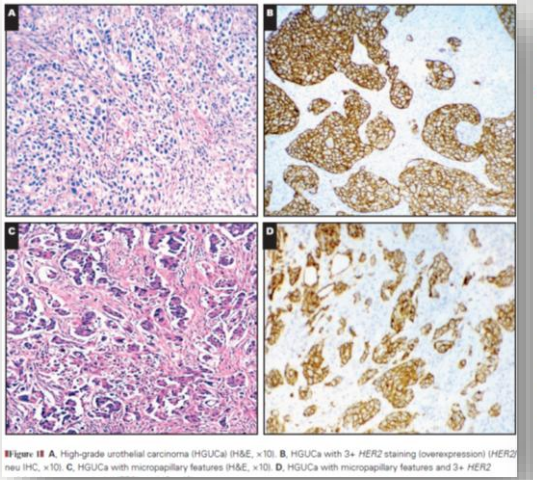
No hay metodología standard para ca urotelial

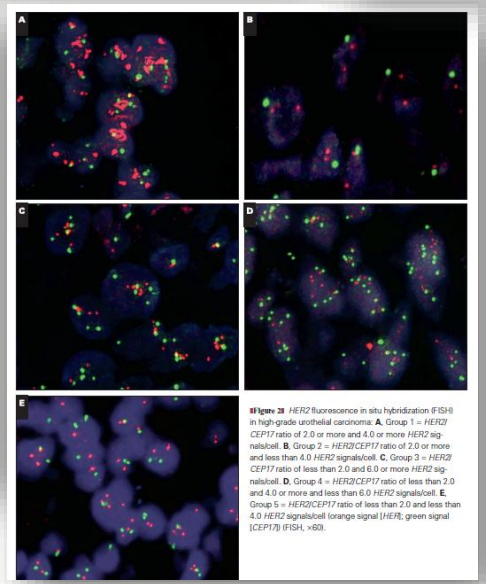
Reappraisal of *HER2* Amplification in High-Grade Urothelial Carcinoma Based on 2018 ASCO/CAP Clinical Practice Guidelines

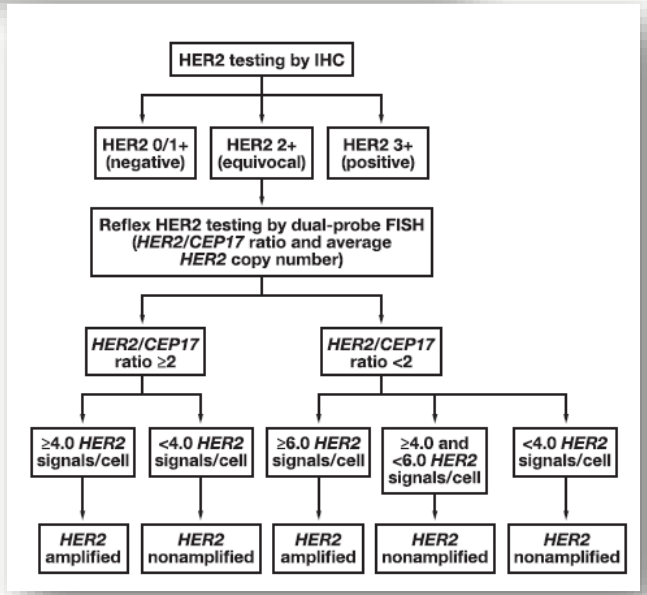
Sambit K. Mohanty, MD,[1,2,] Sourav K. Mishra, MD,[3,*] Ankit Tiwari, PhD,[1] Shivani Sharma, DNB, DCP,[2] Mohit Bhardwaj, PhD,[2] Niharika Pattnaik, MD,[1] Sunil Jaiswal, MS, DNB,[4] Manas R. Baisakh, MD,[5] Subodh Das, MS, MCh,[6] Manas R. Pradhan, MS, MCh,[6] Tapas R. Swain, DMLT,[1] Kaliprasad Satpathy, MS, MCh,[7] Sean R. Williamson, MD,[8] and Anil V. Parwani, MD, PhD[9]*

Am J Clin Pathol 2021;156:1130-1141









Valoración HER2 + por IHQ y FISH

Contribución de patología digital e inteligencia artificial

A Validation Study of Human Epidermal Growth Factor Receptor 2 Immunohistochemistry Digital Imaging Analysis and its Correlation with Human Epidermal Growth Factor Receptor 2 Fluorescence *In situ* Hybridization Results in Breast Carcinoma

Ramon Hartage[1,#], Aidan C. Li[2,#], Scott Hammond[1], Anil V. Parwani[1]

[1]Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA, [2]Department of NA, Jerome High School, Dublin, OH 43017, USA

[#]First two authors contributed equally

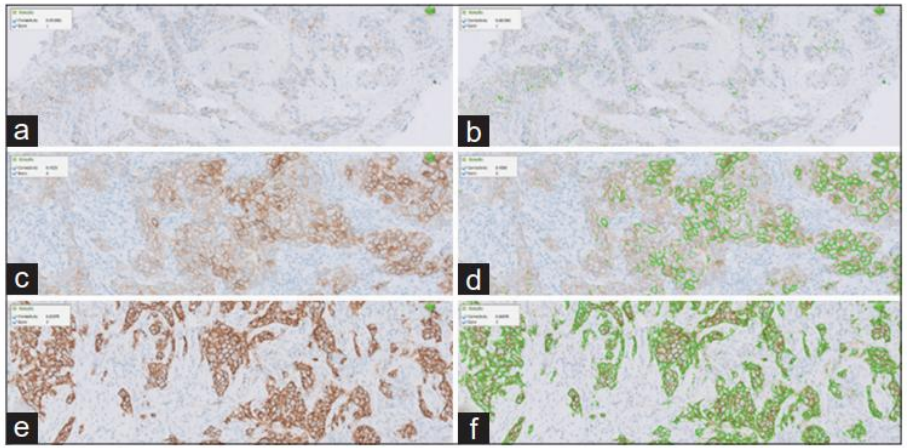


Table 3: The correlation between human epidermal growth factor receptor 2 digital image analysis scores and fluorescence *in situ* hybridization results in 442 cases with fluorescence *in situ* hybridization

	Visiopharm (%)			
	Negative (0/1+)	Equivocal (2+)	Positive (3+)	Total
FISH positive				
Group 1	3 (0.9)	6 (9)	53 (91.4)	62
Group 3	0 (0)	1 (1.5)	3 (4.5)	4
FISH negative				
Group 2	1 (0.3)	0 (0)	0 (0)	1
Group 4	36 (11.4)	24 (35.8)	2 (3.0)	62
Group 5	277 (87.4)	36 (53.7)	0	313
Total	317	67	58	442

HER2 FISH results were categorized into the following 5 groups according to ASCO/CAP HER2 guidelines: Group 1: HER2/CEP17 ratio ≥2.0 and average HER2 copy number ≥4.0 signals/cell; Group 2 HER2/CEP17 ratio ≥2.0 and average HER2 copy number <4.0 signals/cell; Group 3: HER2/CEP17 ratio <2.0 and average HER2 copy number ≥6.0 signals/cell; Group 4: HER2/CEP17 ratio <2.0 and average HER2 copy number ≥4.0 and <6.0 signals/cell; Group 5: HER2/CEP17 ratio <2 and average HER2 copy number <4.0 signals/cell. HER2: Human epidermal growth factor receptor 2, FISH: Fluorescence *in situ* hybridization, ASCO: American Society of Clinical Oncology, CAP: College of American Pathologist

Valoración HER2 + por IHQ y FISH

ADC (RC48): La heterogeneidad no influyó en el efecto de la droga
Eficaz en HER2 2+ y 3+ (criterios ASCO/CAP 2018) con o sin amplificación

Full Length Article
Journal of the National Cancer Center 3 (2023) 121–128

Assessment of the expression pattern of HER2 and its correlation with HER2-targeting antibody-drug conjugate therapy in urothelial cancer

Huizi Lei[1,†], Yun Ling[1,†], Pei Yuan[1], Xieqiao Yan[2], Lin Wang[3], Yanxia Shi[4], Xin Yao[5], Hong Luo[6], Benkang Shi[7], Jiyan Liu[8], Zhisong He[9], Guohua Yu[10], Weiqing Han[11], Changlu Hu[12], Zhihong Chi[2], Chuanliang Cui[2], Lu Si[2], Jianmin Fang[13,14], Jun Guo[15], Xinan Sheng[15,*], Aiping Zhou[3,*], Jianming Ying[1,*]

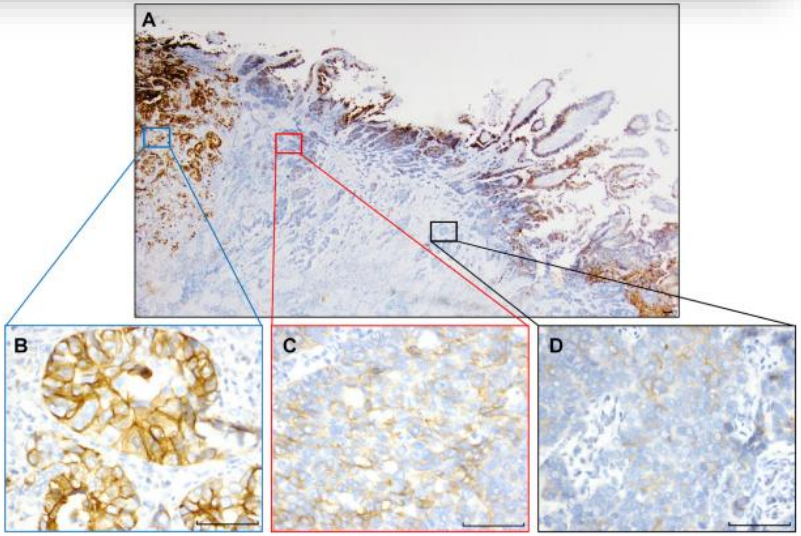
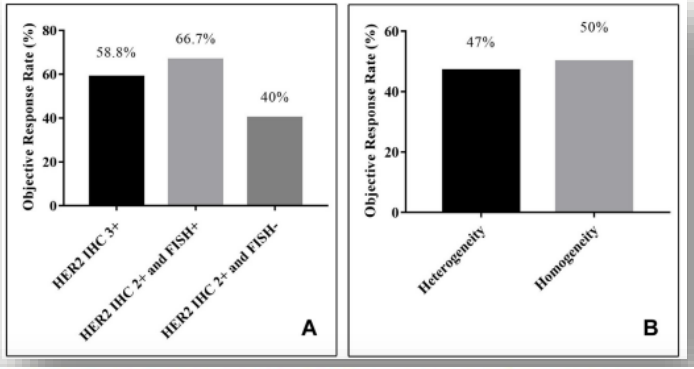
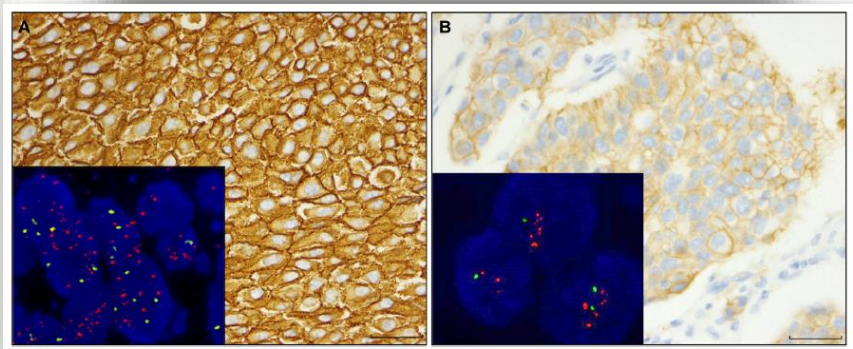


Fig. 2. HER2 protein heterogeneity. (A) One case of urothelial carcinoma (HER2 staining, original magnification 20 ×). (B) HER2 3+ (original magnification 400 ×). (C) HER2 2+ (original magnification 400 ×). (D) HER2 1+ (original magnification 400 ×). HER2, human epidermal growth factor receptor 2. Scale bar, 50 μm.





Tinción membrana (completa) y citoplasmática

HER2

- ADC: Actúan independientemente de la amplificación de HER2

- Determinación en metástasis en casos negativos en primario

Drugs	Trial	Phase	Line	Definition of HER2 status	Status
Afatinib Dimaleate	NCT02122172	2	Refractory	NA	Recruiting
Afatinib Dimaleate Afatinib Pertuzumab Trastuzumab Trastuzumab Emtansine	NCT02465060	2	Refractory	NA	Active, not recruiting
Trastuzumab Pyrotinib	NCT05318339	2	Refractory	NA	Recruiting
BDTX-189	NCT04209465	1/2	Refractory	NA	Terminated
TAS0728	NCT03410927	1/2	Refractory	NA	Terminated
Trastuzumab Tucatunib	NCT04579380	1	Refractory	NA	Active, not recruiting
Trastuzumab emtansine	NCT02675829	2	Refractory	HER2 amplification: NGS or ISH (HER2/CEP17 ratio ≥2.0)	Recruiting
Trastuzumab deruxtecan Nivolumab	NCT03523572	1b	Refractory	HER2 expressing: IHC 2+ or 3+ HER2 amplification: ISH*	Unknown status
Trastuzumab deruxtecan	NCT04639219	2	Refractory	HER2 mutations only	Active, not recruiting
Trastuzumab deruxtecan	NCT04482309	2	Refractory	NA	Active, not recruiting
RC48-ADC	NCT04879329	2	Second line	HER2 expressing: IHC 1+, 2+ or 3+	Not yet recruiting
RC48-ADC	NCT04073602	2	Refractory	HER2 negative: IHC - or 1+	Unknow status
RC48-ADC Triplizumab Gemcitabine Cisplatin Carboplatin	NCT05302284	3	First line	HER2 expressing: IHC 1+, 2+ or 3+	Recruiting
BDC-1001 Nivolumab	NCT04278144	1/2	Refractory	NA	Recruiting
MRG002	NCT04839510	2	Refractory	HER2 expressing: IHC 2 + or 3+	Recruiting
PRS-343 atezolizumab	NCT03650348	1b	Refractory	NA	Unkown status
PRS-343	NCT03330561	1	Refractory	NA	Completed (Last Update posted: January 20, 2022)
CAdVEC/CART	NCT03740256	1	Refractory	HER2 expressing: IHC 2+ or 3+	Recruiting
CT-0508	NCT04660929	1	Refractory	NA	Recruiting
ACE1702	NCT04319757	1	Refractory	HER2 expressing: HER2 2+ or 3+	Recruiting
DF1001	NCT04143711	1/2	Refractory	NA	Recruiting

IHC: immunohistochemistry; ISH: in situ hybridization; NGS: next-generation sequencing; CEP: centromeric probe for chromosome; *: scored by American

- *Qu M, et al. Advances in HER2-Targeted Treatment for Advanced/Metastatic Urothelial Carcinoma. Bladder (San Franc). 2023;10:e21200012.*

HER2-Low

Translational Andrology and Urology, Vol 13, No 11 November 2024

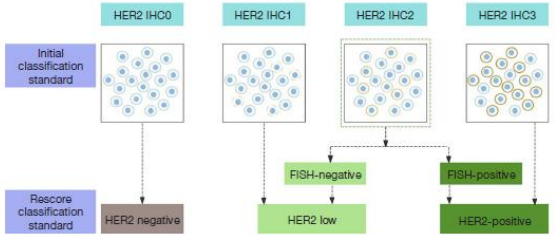


Figure 1 Algorithm for defining the HER2 expression spectrum according to ASCO/CAP guidelines. HER2-low expression is defined as IHC score 2+ with negative FISH results, or IHC score 1+. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists.

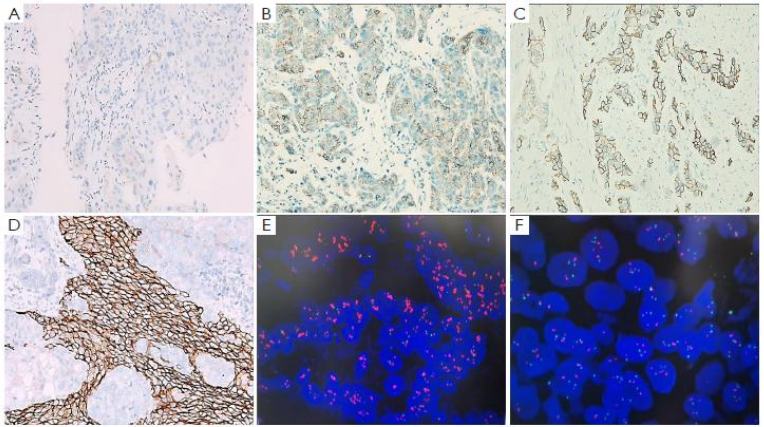


Figure 2 The HER2 immunohistochemical protein expression score was defined as: score 0 (no staining) (A); score 1+ (incomplete membrane staining) (B); score 2+ (complete but weak membrane staining in >10% of tumor cells) (C); score 3+ (strong membrane staining in >30% of tumor cells) (D); existence of *HER2* gene amplification (E); absence of *HER2* gene amplification (F). Magnification, 200×. HER2, human epidermal growth factor receptor 2.

- HER2-low: los mismos criterios que para la mama 2021
- Las mayores tasas de recidiva

No requieren biomarcadores para selección de pacientes

HER2 IHQ 3+

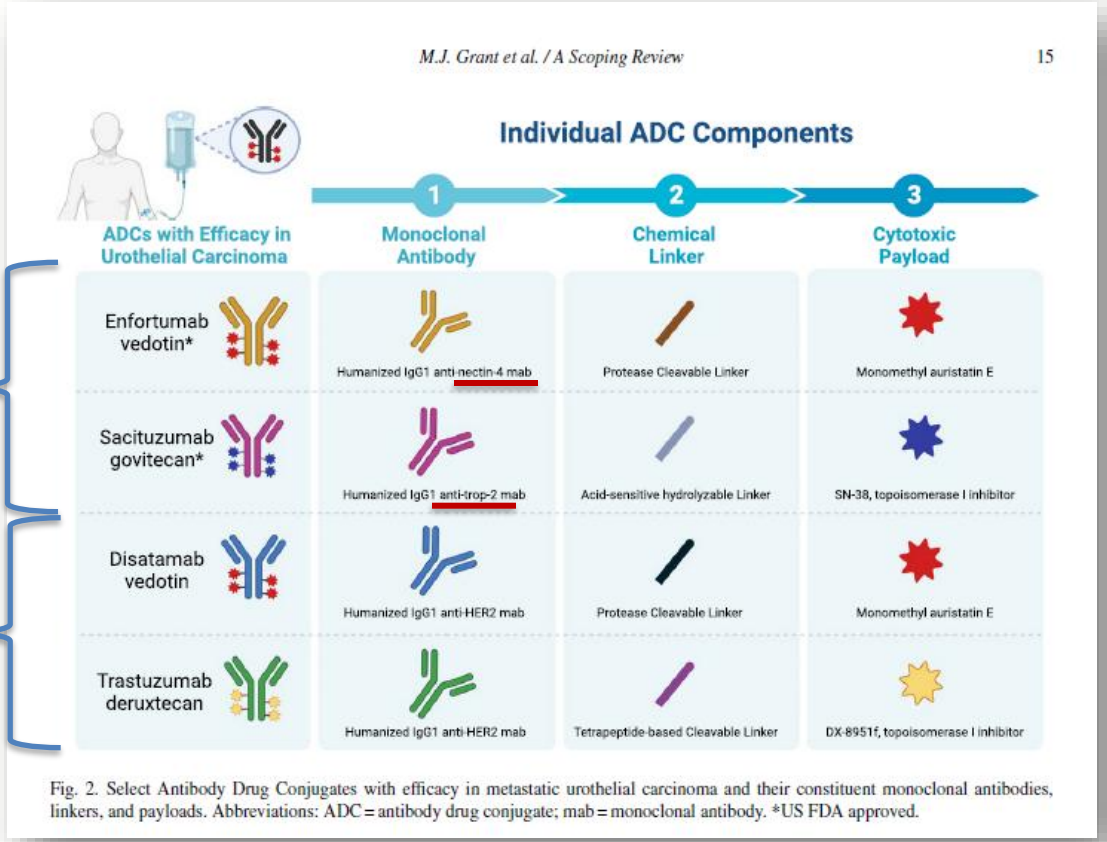


Fig. 2. Select Antibody Drug Conjugates with efficacy in metastatic urothelial carcinoma and their constituent monoclonal antibodies, linkers, and payloads. Abbreviations: ADC = antibody drug conjugate; mab = monoclonal antibody. *US FDA approved.

Grant JM et al. Bladder Cancer 10 (2024) 9–23

Nectina-4

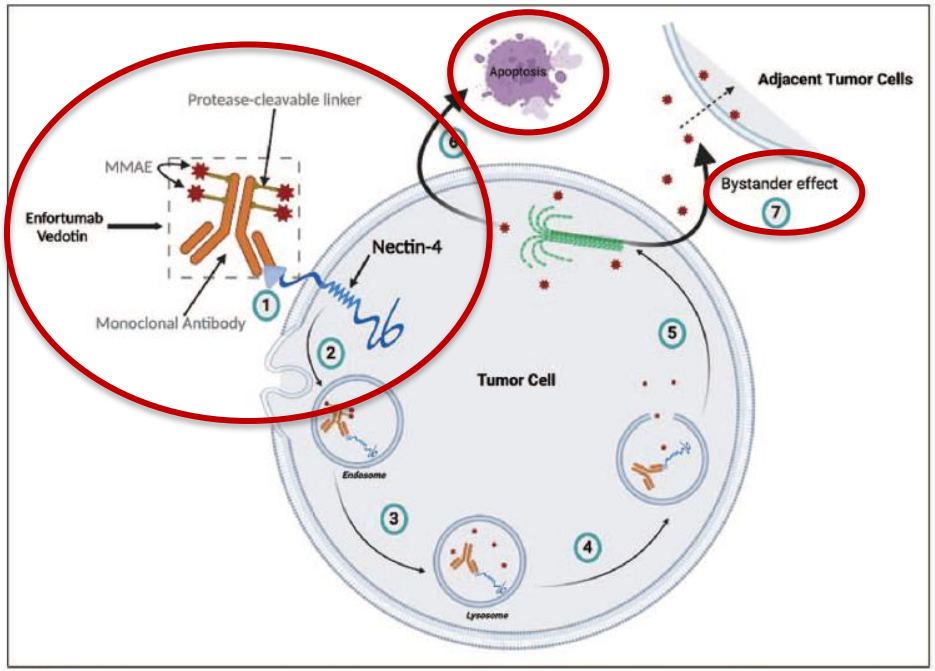
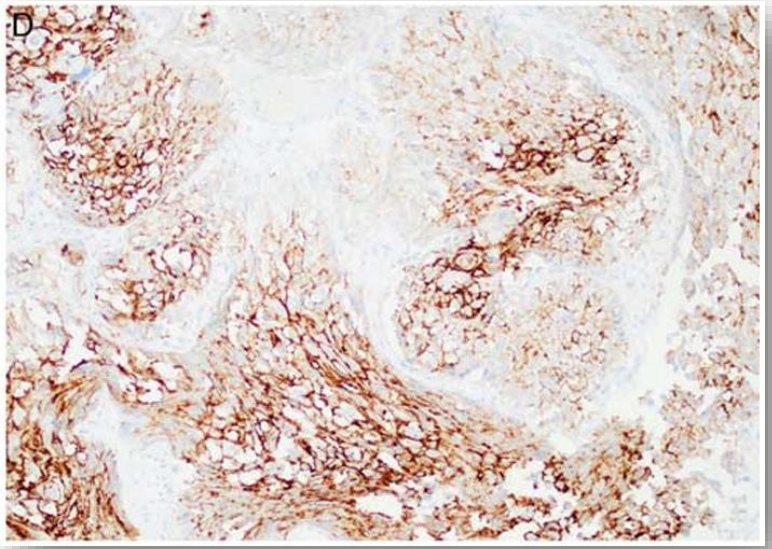


FIGURE 1. Enfortumab vedotin mechanism of action. (1) Target binding: EV selectively binds to cells that express nectin-4. (2 Internalization: EV-nectin-4 complex is internalized via receptor-mediated endocytosis. (3) Proteolytic cleavage: the complex travels to the lysosomes where the linker between the mAB and the is cleaved. (4) MMAE is released into the cytosol. (5) Microtubule disruption: MMAE binds to tubulin causing microtubule disruption. (6) Cell cycle arrest and apoptosis. (7) Bystander effect: passive toxin diffusion into adjacent tumor cells. *Created with BioRender.com.

Ruder S et al. Curr Opin Urol 2025, 35:000–000

- **Enfortumab vedotin**
- Molécula de adhesión
- En placenta y tejidos embrionarios
- Contribuye al crecimiento y proliferación de células tumorales
- Sobreexpresión asociada con metástasis vías WNT beta-catenina, *PI3K-AKT-mTOR* e interacciona con ERBB2 TK R
- EV → Parada ciclo celular y apoptosis

Nectina-4



Hoffman-Censits JH et al. Appl Immunohistochem Mol Morphol 2021;29:619–625

- La expresión IHQ de Nectina-4 se asume asociada a eficacia tratamiento con Enfortumab Vedotin (EV)
- EV-101 y EV-201: inclusión nectina-4 positivos
- La mayoría de los CU avanzados tienen alta expresión de Nectina-4
- 95% de CU H-score >150
- EV-301 no fue criterio de inclusión
- **No se exige su determinación IHQ**
- EV-302/KEYNOTE-A39: EV + Pembro superior a QT en mCU (1L): expresión de Nectina-4 no predecía respuesta a EV+P

Ruder S et al. Curr Opin Urol 2025, 35:000–000

Rosenberg JE et al. J Clin Oncol 2019; 37: 2592–600.
Rosenberg J et all. EV-101. J Clin Oncol 2020; 38: 1041–9.
Powles T et al. N Engl J Med 2021;384: 1125–35..
Powles t et al: N Engl J Med 2024;390: 875-88.
Powles T et al. Ann Oncol. 2024;35:S1137–38.

Nectina-4

Review Articles

JCO Precis Oncol. 2024 Dec;8 e2400470

Nectin-4 Positivity in Genitourinary Malignancies: A Systematic Review

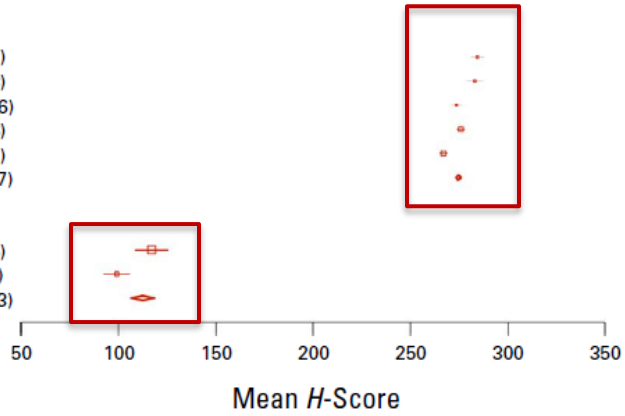
Emanuele Crupi, MD[1,2]; Tiago Costa de Padua, MD[1]; Laura Marandino, MD[1]; Giuseppe Fallara, MD[3]; Filippo Pederzoli, MD[4]; Alessia Cimadamore, MD[5]; Emanuele C. Goetz, MD[6]; Antonio Cigliola, MD[1]; Damiano A. Patané, MD[1]; Chiara Mercinelli, MD[1]; Valentina Tateo, MD[1]; Andrea Salonia, MD[2,7]; Alberto Briganti, MD[2,7]; Francesco Montorsi, MD[2,7]; Joshua J. Meeks, MD[8]; Philippe E. Spiess, MD[9]; Omar Alhalabi, MD[10]; Jianjun Gao, MD[10]; Ashish M. Kamat, MD[11]; Petros Grivas, MD[12,13]; Andrea Necchi, MD[1,2]; and Daniele Raggi, MD[1]

H-Score= Intensidad x % células positivas

- Negativo: 0-14
- Débil: 15-99
- Moderado: 100-199
- Intenso: 200-300

N4 *H*-Score Among Prospective EV 101, EV 201, EV 302, and Retrospective Studies

EV Studies	Number of Patients	Mean *H*-Score
EV-101	152	284.3 (281-287.7)
EV-201 cohort 1*	120	283 (278.8-287.3)
EV-201 cohort 2*	80	273.7 (270.8-276.6)
EV-302 EV arm	394	275.9 (273.8-278)
EV-302 Cht arm	406	267 (264.8-269.1)
Weighted mean (95% CI)		274.5 (273.2-275.7)
Retrospective		
Klümper et al[26]	137	117 (108.5-125.5)
Miyake et al[23]	64	99.1 (92.4-105.8)
Weighted mean (95% CI)		111.3 (105.3-117.3)



Expresión de membrana vs citoplasmática

Nectina-4

Mini Review

EUROPEAN UROLOGY FOCUS 10 (2024) 224–226

Biomarkers of Response to Anti-NECTIN4 Antibody-Drug Conjugate Enfortumab Vedotin in Urothelial Cancer

Niklas Klümper[a,b,c,*], *Markus Eckstein*[d,e,f]

- Sobreestimación de la expresión de membrana de Nectina-4 en CU
- Ac utilizados en EV-101 y EV-103 no comerciales
- La expresión de **membrana** de Nectina-4 sí se correlaciona con la respuesta a EV

Nectina-4

673 Poster Session

J Clin Oncol 2024;42(4 Suppl) 673.

Occurrence of *NECTIN4* amplification in solid tumors and enfortumab vedotin response in metastatic urothelial cancer.

Niklas Klümper, Ngoc Khanh Tran, Stefanie Zschaebitz, Oliver Hahn, Friedemann Zengerling, Dora Nagy, Glen Kristiansen, Philipp Ivanyi, Camilla Marisa Grunewald, Christopher Darr, Katrin Schlack, Steffen Rausch, Manuel Ritter, Kerstin Junker, Arndt Hartmann, Viktor Grünwald, Michael Hölzel, Markus Eckstein; Department of Urology,

- FISH Nectina-4 en 77 pacientes mUC tratados con EV

- Alteración número de copias de Nectina-4 (25% CU) se asocia a fuerte expresión de membrana
- Pacientes con amplificación de Nectina-4 (18%) : ORR >90% con EV en monoterapia con larga supervivencia / 32% sin amplificación

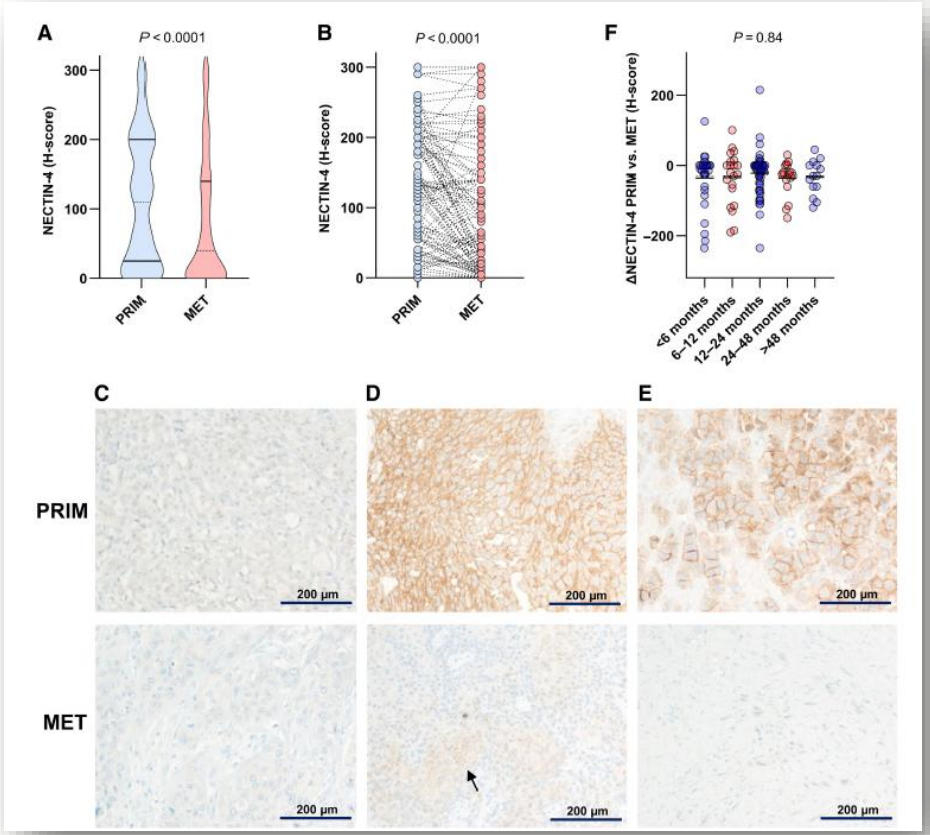
Nectina-4

CLINICAL CANCER RESEARCH | PF

Clin Cancer Res 2023;29:1496–505.

Membranous NECTIN-4 Expression Frequently Decreases during Metastatic Spread of Urothelial Carcinoma and Is Associated with Enfortumab Vedotin Resistance

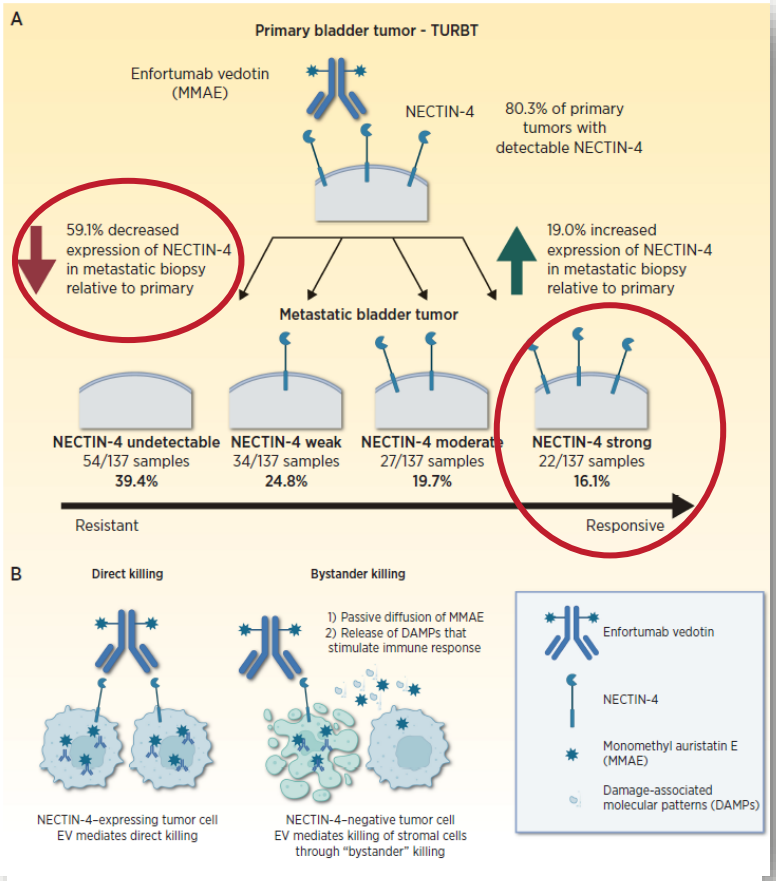
Niklas Klümper[1,2,3,4], Damian J. Ralser[2,3,5], Jörg Ellinger[1,3], Florian Roghmann[4,6], Julia Albrecht[1,2,3], Eduard Below[2,3], Abdullah Alajati[1,3], Danijel Sikic[4,7,8,9], Johannes Breyer[4,9,10], Christian Bolenz[4,11], Friedemann Zengerling[4,11], Philipp Erben[4,12], Kristina Schwamborn[9,13], Ralph M. Wirtz[4,14], Thomas Horn[9,15], Dora Nagy[3,16], Marieta Toma[3,16], Glen Kristiansen[3,4,16], Thomas Büttner[1,3], Oliver Hahn[17], Viktor Grünwald[18], Christopher Darr[18], Eva Erne[19], Steffen Rausch[19], Jens Bedke[19], Katrin Schlack[20], Mahmoud Abbas[21], Stefanie Zschäbitz[22], Constantin Schwab[23], Alexander Mustea[3,5], Patrick Adam[24], Andreas Manseck[25], Bernd Wullich[4,7,8,9], Manuel Ritter[1,3,4], Arndt Hartmann[4,7,9,26], Jürgen Gschwend[9,15], Wilko Weichert[9,13], Franziska Erlmeier[4,7,9,13,19], Michael Hölzel[2,3], and Markus Eckstein[4,7,9,26]



137 pacientes y 47 tratados EV

- 20% negativos
- Alta expresión de membrana → mejor ORR y PFS
- Menor expresión IHQ en metástasis que en primario
- Detección antes de iniciar tratamiento con EV en metástasis

Nectina-4



Basado en Klümper et al .Clin Cancer Res 2023;29:6149–505.

CLINICAL CANCER RESEARCH | *Clin Cancer Res 2023;29:1377–80*

Scratching the Surface: NECTIN-4 as a Surrogate for Enfortumab Vedotin Resistance

David H. Aggen[1], Carissa E. Chu[2], and Jonathan E. Rosenberg[1]

- Expresión IHQ dinámica con progresión
- Downregulación de Nectina-4 → pérdida de polaridad → metástasis
- Menor expresión IHQ de membrana en **metástasis** que en primario→ resistencia a EV
- Punto de corte en relación con respuesta a EV ¿?

Nectina-4

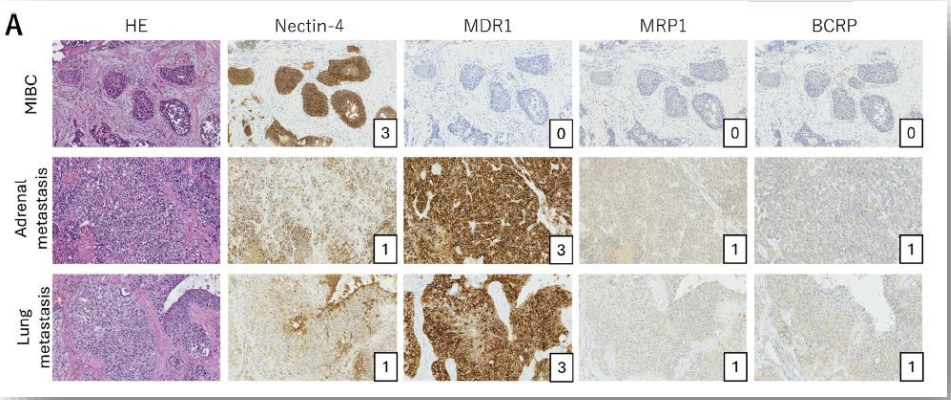
BJUI Compass. 2025;6:e488.

Predictive role of ABC transporters in the efficacy of enfortumab vedotin for urothelial carcinoma

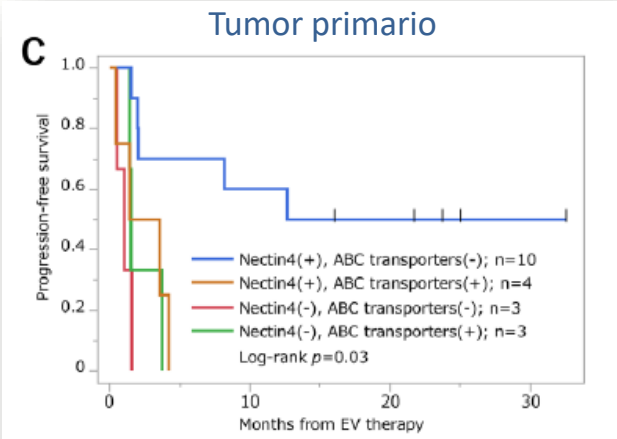
Toshiki Kijima[1] | Atsuko Takada-Owada[2] | Hiroki Shimoda[3] | Hidetoshi Kokubun[1] | Toshitaka Uematsu[1] | Kohei Takei[1] | Hironori Betsunoh[1] | Masahiro Yashi[1] | Kazuyuki Ishida[2] | Takao Kamai[1]

20 pacientes

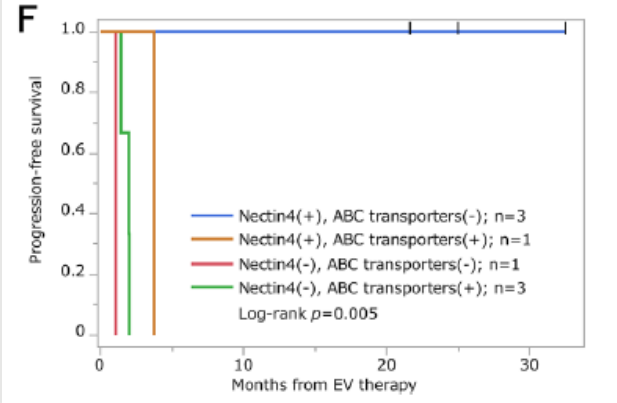
Disminución de expresión de Nectina-4 con progresión no MI-MI-Metástasis
MMAE, la carga útil citotóxica de EV, es un sustrato para los transportadores ABC
Alta expresión de Nectina-4 y ABC transportadores negativos→ PFS más larga
Aumento de expresión transportadores ABC con progresión→ ¿resistencia?



Tumor primario

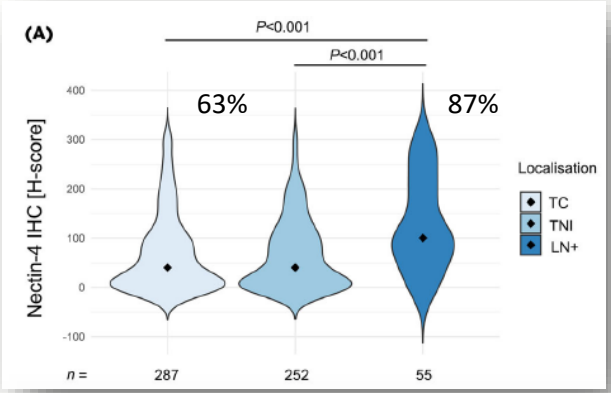


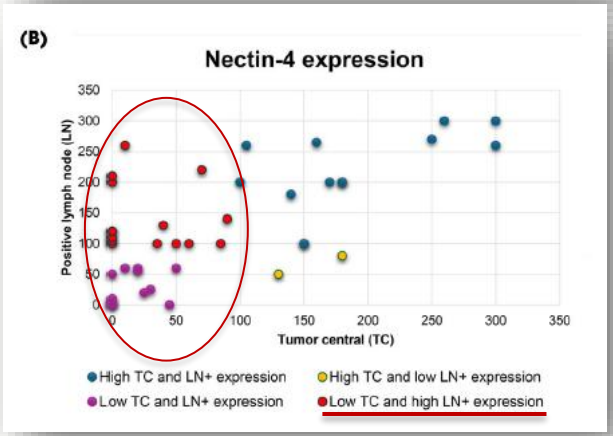
Metástasis



Nectina-4

314 pacientes no tratados con EV





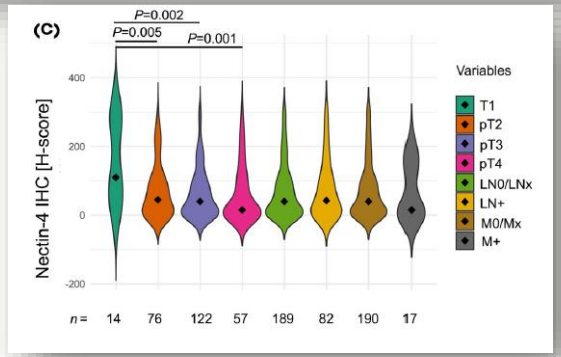
BJU Int 2025 doi:10.1111/bju.16643

BJUI
BJU International

Original Article

Spatial distribution and subtype-specific expression patterns of Nectin-4 in muscle-invasive bladder cancer

Csilla Olah[1], Lara Sichward[2], Boris Hadaschik[1], Christopher Darr[1], Viktor Grünwald[1,3], Ulrich Krafft[1], Barbara T. Grünwald[1,7], Osama Mahmoud[1,5], Mulham Al-Nader[1], Peter Nyirady[6], Henning Reis[4] and Tibor Szarvas[1,6]



- Mayor expresión IHQ en estadios más bajos
- No asociación con supervivencia global
- Baja expresión en Tm primario también puede tener beneficio trat EV
- **Menos expresión asociada a mayor beneficio con QT platinos Ad y neoad**

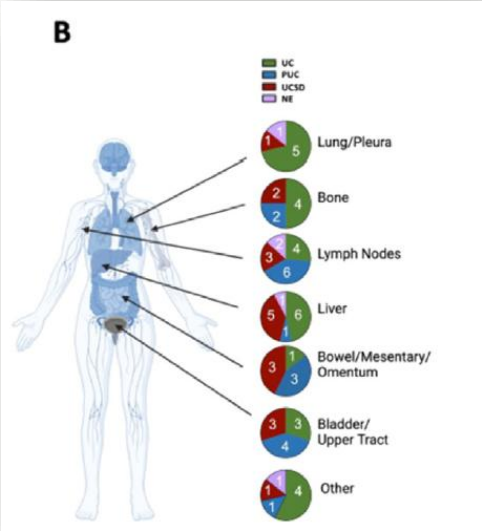
Nectina-4

Check for updates

Clinical Genitourinary Cancer, Vol. 21, No. 6, 669–678

Metastatic Bladder Cancer Expression and Subcellular Localization of Nectin-4 and Trop-2 in Variant Histology: A Rapid Autopsy Study

Fady Ghali,[1] Funda Vakar-Lopez,[2] Martine P. Roudier,[1] Jose Garcia,[1] Sonali Arora,[3] Heather H. Cheng,[4,5] Michael T. Schweizer,[4,5] Michael C. Haffner,[3,5] John K. Lee,[3,4,5] Evan Y. Yu,[4,5] Petros Grivas,[4,5] Bruce Montgomery,[4,5] Andrew C. Hsieh,[3,4] Jonathan L. Wright,[1,6] Hung-Ming Lam[1]



20 pacientes
67 muestras

- Tratados QT y ICI
- Expresión Nectina-4
- Primario = Metastásicos

Pathology - Research and Practice 237 (2022) 154072

Tumor expression of Nectin-1–4 and its clinical implication in muscle invasive bladder cancer: An intra-patient variability of Nectin-4 expression

Makito Miyake[a,*,1], Tatsuki Miyamoto[a], Takuto Shimizu[a], Sayuri Ohnishi[a], Tomomi Fujii[b], Nobutaka Nishimura[a], Yuki Oda[a], Yosuke Morizawa[a], Shunta Hori[a], Daisuke Gotoh[a], Yasushi Nakai[a], Kazumasa Torimoto[a], Nobumichi Tanaka[a,c], Kiyohide Fujimoto[a]

13 pacientes

- Primario = Metastásicos

Nectina-4

- Expresión IHQ variable en los subtipos de CU

BJU Int 2025 doi:10.1111/bju.16643

Original Article

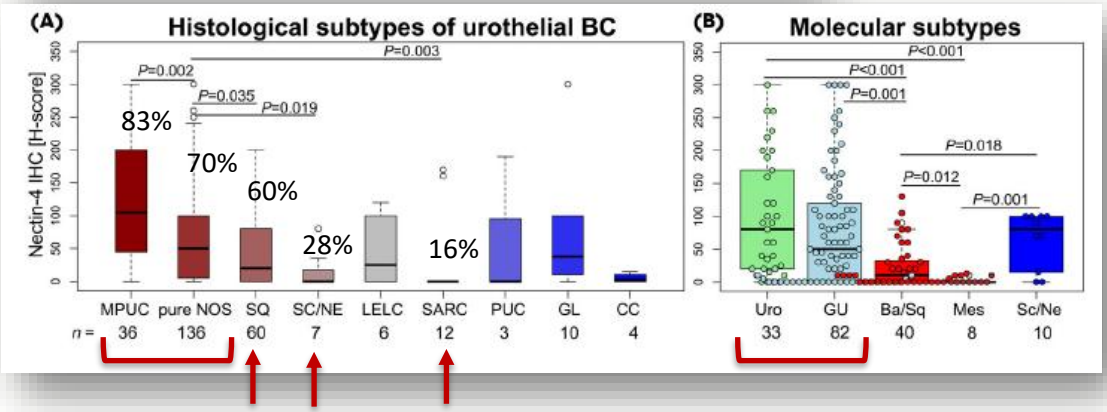
314 pacientes

BJUI BJU International

Spatial distribution and subtype-specific expression patterns of Nectin-4 in muscle-invasive bladder cancer

Csilla Olah[1], Lara Sichward[2], Boris Hadaschik[1], Christopher Darr[1], Viktor Grünwald[1,3], Ulrich Krafft[1], Barbara T. Grünwald[1,7], Osama Mahmoud[1,5], Mulham Al-Nader[1], Peter Nyirady[6], Henning Reis[4] and Tibor Szarvas[1,6]

- Mayor en luminales
- Pérdida de expresión→ más agresivos (NE y S)



cancers *Cancers* **2022**, *14*, 4411. https://doi.org/10.3390/cancers14184411

Article

Expression of Nectin-4 in Variant Histologies of Bladder Cancer and Its Prognostic Value—Need for Biomarker Testing in High-Risk Patients?

Severin Rodler [1,2,*], Lennert Eismann [1], Boris Schlenker [1], Jozefina Casuscelli [1,2], Isabel Brinkmann [1], Andrea Sendelhofert [3], Raphaela Waidelich [1], Alexander Buchner [1], Christian Stief [1], Gerald Bastian Schulz [1] and Stephan Ledderose [3]

(*Appl Immunohistochem Mol Morphol* 2021;29:619–625)

Expression of Nectin-4 in Bladder Urothelial Carcinoma, in Morphologic Variants, and Nonurothelial Histotypes

Jean H. Hoffman-Censits, MD,†‡ Kara A. Lombardo, BS,*‡ Vamsi Parimi, MD, MPH,§ Sonia Kamanda, MD,§ Woonyoung Choi, PhD,*‡ Noah M. Hahn, MD,*†‡ David J. McConkey, PhD,*†‡ Bridget M. McGuire, BS,* Trinity J. Bivalacqua, MD, PhD,*† Max Kates, MD,*† and Andres Matoso, MD*†‡§*

Hoffman-Censits JH, et al. Appl Immunohistochem Mol Morphol 2021; 29: 619–25. ***UC NOS:68%; SQ:70%; MPUC: 28%; SC/NE: 21%; SARC: 10%***
Fan Y et al. Front Oncol 2022; 12: 858865. ***US NOS: 68%; MPUC: 79%; Sc/NE: 0%;***
Rodler S et al. Cancers 2022; 14: 4411. ***SQ: 91,5%; Adeno: 100%; SARC: 23% No relación con OS ni PFS***
Chu CE et al. Clin Cancer Res. 2021; 27: 5123–5130. ***Mayor en subtipo luminal***

Nectina-4

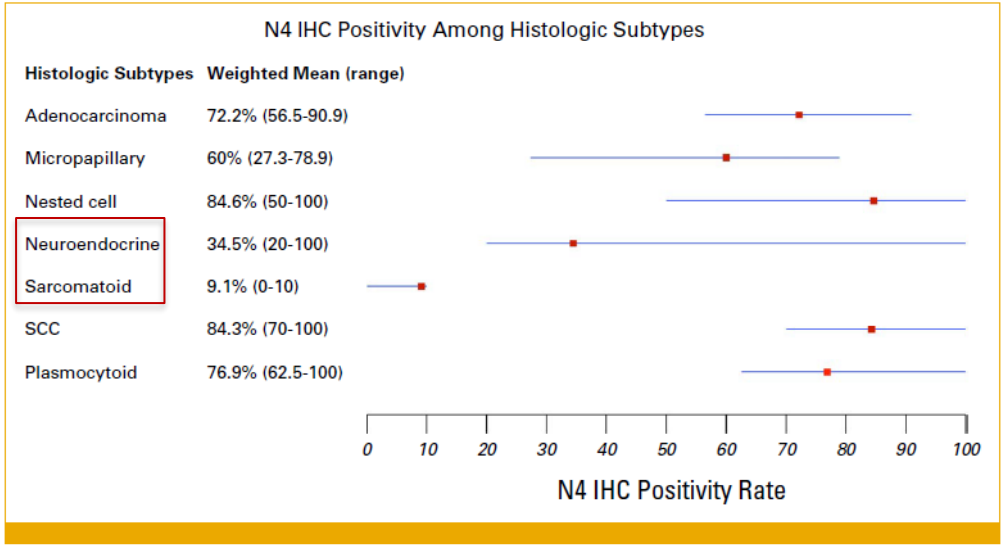
Review Articles

JCO Precis Oncol. 2024 Dec;8 e2400470

Nectin-4 Positivity in Genitourinary Malignancies: A Systematic Review

Emanuele Crupi, MD[1,2]; Tiago Costa de Padua, MD[1]; Laura Marandino, MD[1]; Giuseppe Fallara, MD[3]; Filippo Pederzoli, MD[4]; Alessia Cimadamore, MD[5]; Emanuele C. Goetz, MD[6]; Antonio Cigliola, MD[1]; Damiano A. Patané, MD[1]; Chiara Mercinelli, MD[1]; Valentina Tateo, MD[1]; Andrea Salonia, MD[2,7]; Alberto Briganti, MD[2,7]; Francesco Montorsi, MD[2,7]; Joshua J. Meeks, MD[8]; Philippe E. Spiess, MD[9]; Omar Alhalabi, MD[10]; Jianjun Gao, MD[10]; Ashish M. Kamat, MD[11]; Petros Grivas, MD[12,13]; Andrea Necchi, MD[1,2]; and Daniele Raggi, MD[1]

Nectin-4 Positivity in Genitourinary Malignancies



TROP-2

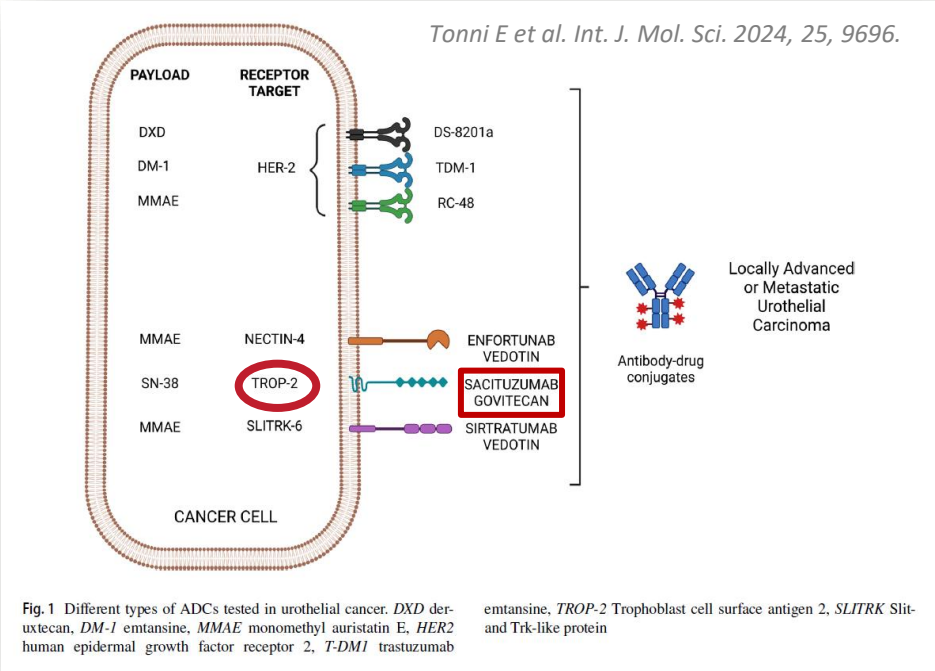
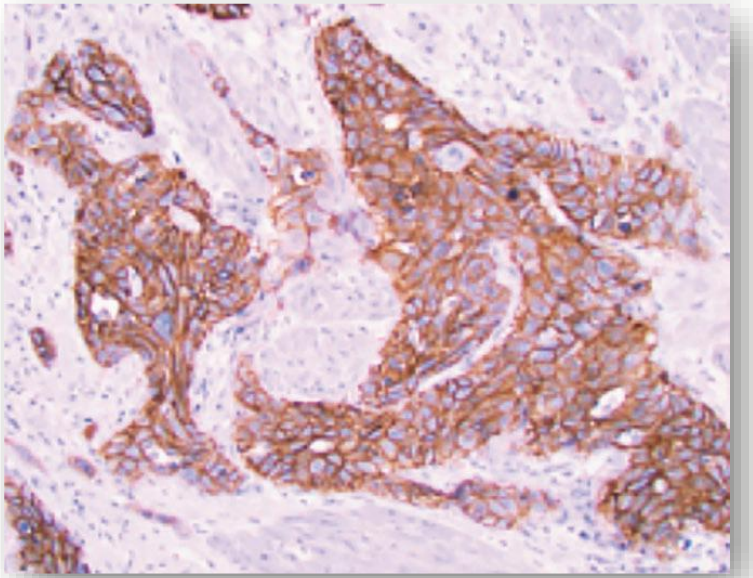


Fig. 1 Different types of ADCs tested in urothelial cancer. *DXD* deruxtecan, *DM-1* emtansine, *MMAE* monomethyl auristatin E, *HER2* human epidermal growth factor receptor 2, *T-DM1* trastuzumab emtansine, *TROP-2* Trophoblast cell surface antigen 2, *SLITRK* Slit- and Trk-like protein

- **Sacituzumab govetican**
- Trophoblast cell-surface antigen 2
- Glicoproteína transmembrana involucrada en la señal del calcio, adhesión celular y autorenovación de las stem cells
- Sobreexpresada en CU y otros carcinomas (próstata, pulmón, mama TN)
- Sobrexpresión se asocia a activación de la vía ERK-MAPK→ progresión del ciclo celular, proliferación y supervivencia

TROP-2

2+ -3+ en urotelio normal y CU



- FDA: para CU localmente avanzado / metastásico resistente/refractario a platinos y anti PD1/PDL1
- No hay relación entre expresión de TROP-2 y respuesta a SG
- TROPHY-U-01 (no necesario valorar expresión TROP-2)
- Estudios preclínicos: se mantiene la expresión deTROP2 en células resistentes a EV y permanecen sensibles a SG
- Asociado con mayor agresividad y peor pronóstico

Chou J et al. Eur Urol Oncol. 2022; 5: 714–718
Vlachou E etal. Clinical Medicine Insights: Oncology2024 18: 1–10

Avellini C et al. Oncotarget 2017; 8: 8642-58653.
Tawaga ST et al. J Clin Oncol. 2021;392474–85. (TROPHY-U-01)

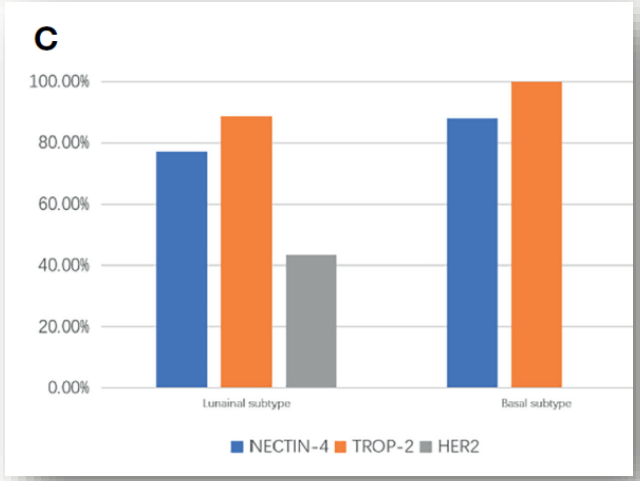
TROP-2

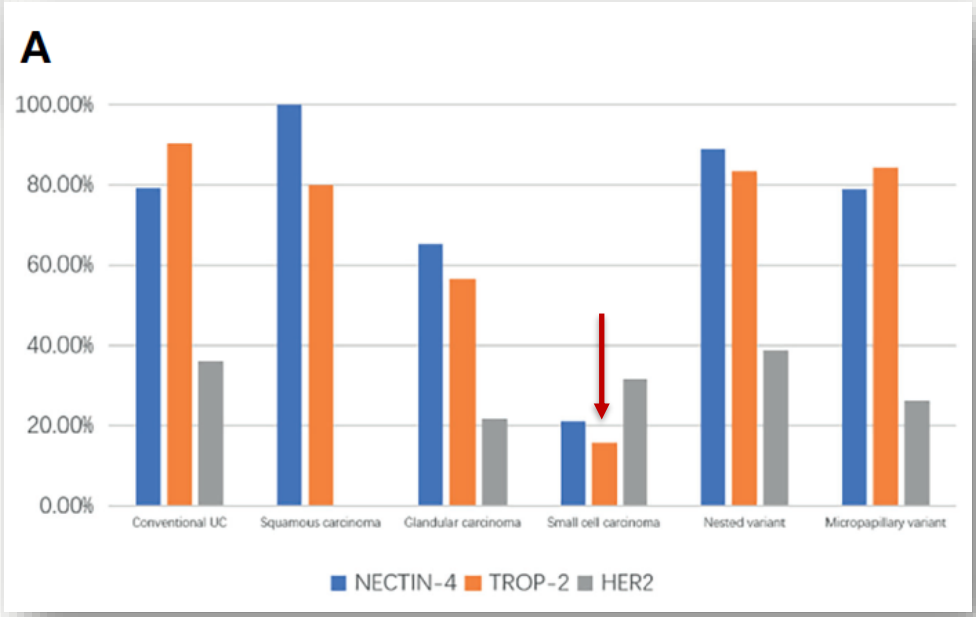
Head-to-Head Comparison of the Expression Differences of NECTIN-4, TROP-2, and HER2 in Urothelial Carcinoma and Its Histologic Variants

*Yu Fan†, Qinhan Li†, Qi Shen†, Zhifu Liu, Zhenan Zhang, Shuai Hu, Wei Yu, Zhisong He, Qun He and Qian Zhang**

Front Oncol. 2022;12 858865

- Sin diferencia luminal-basal
- Sobrexpresión en CU todos subtipos menos Ca NE





TROP-2

Trop-2 and Ephrin B2 expression in urothelial carcinoma with divergent differentiation and aggressive urothelial carcinoma subtypes

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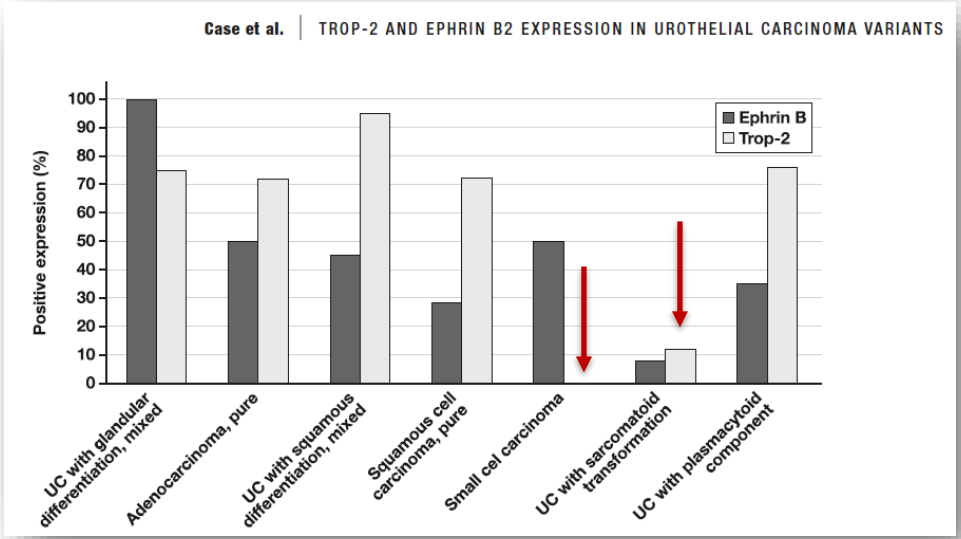

Results: Our results show Trop-2 expression was the highest in squamous cell carcinoma and UC with squamous differentiation, adenocarcinoma and UC with glandular differentiation, and plasmacytoid subtype, while ephrin B2 expression was highest in adenocarcinoma, UC with glandular differentiation, and small cell carcinoma.

TROP-2

Original Article

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TROP-2, NECTIN-4 and predictive biomarkers in sarcomatoid and rhabdoid bladder urothelial carcinoma

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Figure 1. Heat map for TROP-2, NECTIN-4 and other biomarkers in 35 undifferentiated urothelial bladder carcinoma (Red: positive; Green; negative).

Conclusion. Sarcomatoid and rhabdoid BUC do harbor positive expression of the ADC targets TROP-2 or NECTIN-4 in a relatively modest subset of cases, whereas the majority do not. Different combinations of other positive biomarkers may help the choice of medical therapies. Overall, these findings have important clinical implications for targeted therapy for BUC.

Otras alteraciones moleculares *MDM2*

Original research

MDM2 gene amplification as selection tool for innovative targeted approaches in PD-L1 positive or negative muscle-invasive urothelial bladder carcinoma

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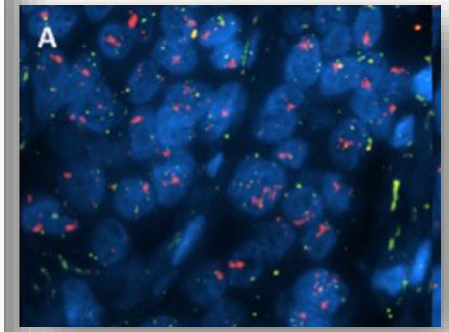
J Clin Pathol 2022;**75**:39–44.

pT2-3 y pN0/pN+



Amplificación de *MDM2* en CUMI o avanzado

- 9%[1] -12% de CU
- Independiente del fenotipo molecular (TCGA) y PD-L1
- Predictor independiente de recaída tumoral
- Predicción de mejor respuesta a terapias dianas simples (***MDM2* quimioinhibidores**) o combinadas (ICI)
- Alteración *TP53*/*MDM2*: **mejor respuesta a EV**

Somatic alterations of *TP53* and *MDM2* associated with response to enfortumab vedotin in patients with advanced urothelial cancer

Tanya Jindal, Xiaolin Zhu, Rohit Bose, Vipul Kumar, Edward Maldonado, Prianka Deshmukh, Chase Shipp, Stephanie Feng, Michelle S. Johnson, Austin Angelidakis, Daniel Kwon, Hala T. Borno, Ivan de Kouchkovsky, Arpita Desai, Rahul Aggarwal, Lawrence Fong, Eric J. Small, Anthony Wong, Sima Porten, Jonathan Chou, Terence Friedlar

Helen Diller Family Cancer

Front Oncol. 2023;13:1161089.

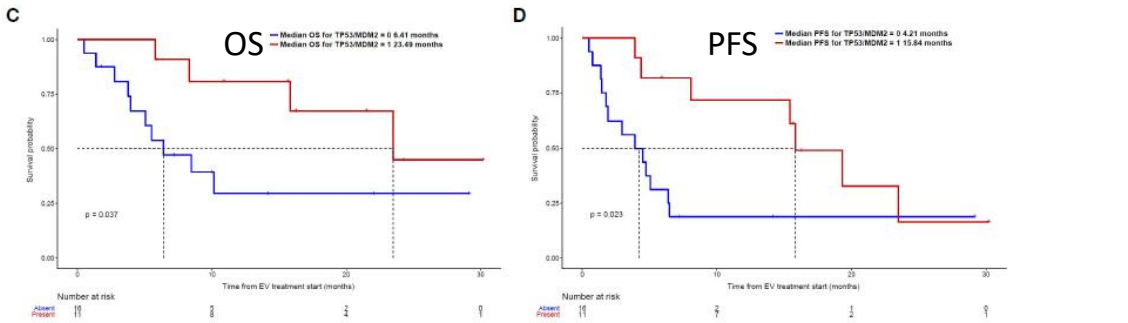


FIGURE 1
Kaplan-Meier curves: **(A)** OS and **(B)** PFS in patients with and without *TP53* alterations; **(C)** OS **(D)** PFS in patients with and without the composite *TP53/MDM2* alterations.

[1] *Robertson AG , et al. Cell 2017;171:540–56.*

Otras alteraciones moleculares

Table 1. Biomarkers for response to chemotherapy.

Molecular Target	Study [Ref.]	Results	Comments
DDR Genes			
NER pathway *ERCC1* **expression levels**	**Bellmunt et al.** [119]	Reduced levels of *ERCC 1* mRNA expression were associated with improved survival to cisplatin-based chemotherapy in mUC.	DDR genes are not validated biomarkers for response to chemotherapy (not routinely used in clinical practice). Clinical trials are evaluating the role of PARP inhibitors in DDR gene mutated UC [126].
	Urun et al. [120]	*ERCC1* positivity was associated with poor survival in mUC treated with cisplatin-based chemotherapy.	
ERCC2 **mutations**	**Van Allen et al.** [50], **Liu et al.** [121]	ERCC2 mutations were associated with pCR and improved OS to neoadjuvant cisplatin-based chemotherapy in MIBC.	
	Kim et al. [122]	*ERCC2*-associated mutation signature single-base substitution 5 (SBS5) was associated with improved responses in mUC.	
HRR pathway *BRCA* **mutations**	**Taber et al.** [123]	*BRCA2* mutations were associated with SBS5 signature and responses to platinum-based chemotherapy in MIBC	
RAD51 **mutations**	**Mullane et al.** [124]	High nuclear staining for *RAD51*was associated with poor outcome (worse OS) for mUC patients treated with cisplatin-based chemotherapy.	
Other DDR genes *ATM/RB1/FANCC* **mutations**	**Plimack et al.** [125]	*ATM/RB1/FANCC* mutations were associated with improved pathologic responses and survival in MIBC treated with neoadjuvant platinum-based chemotherapy.	
HER2/ERBB2 **alterations**	**Groenendijk et al.** [127]	*HER2* missense mutations (not amplifications) were associated with response to neoadjuvant chemotherapy with platinum in MIBC.	

DDR: Alteraciones en genes reparadores DNA y *ERCC2*

- Mutaciones: asociados **a mejor respuesta a terapias basadas en cisplatino e ICI**
- CU MI: m 2–14% en ***ATM***, *RB1, ERCC2, FANCC* y *RAD51B*
  m 3.7–12.3% en *BRCA 1/ 2*, *PALB2*, FANCD2, *ERCC2*
- Sobreexpresión de ***ATM***, *ERCC1*, *RAD51* y *PAR*: peor OS
- Inhibidores de PARP en investigación en CU

Alteraciones en vía *PI3K/AKT/MTOR*

- 36% de CU
- Inhibidores en investigación en CU

Inestabilidad de microsatélites

- 6-9% de CU (TU)
- Predictor de respuesta a ICI

- *Plimack ER et al. Eur Urol 2015; 68:959–67.*
- *Mohanty Sk et al.. J. Pers. Med. 2023; 13: 756.*
- *Van Allen EM et al.. Cancer Discov 2014;4:1140-1153.*
- *Mollica V et al.. Expert review of anticancer therapy 2020;20:755–763*

¿Qué biomarcadores debemos determinar en nuestros pacientes?

- **PD-L1** en según que inmunoterapia (nivolumab en España). Valor predictivo débil.
- **FGR3 en LA y metastásicos**: Predictivo de respuesta a terapia, mutaciones y fusiones, en la muestra más reciente, método ¿NGS vs RT-PCR?
- **HER 2**: controvertido, datos limitados de valor pronostico y predictivo, IHQ (ASCO/CAP 2018 mama y GI) y amplificación FISH en HER2 2+. Mayor expresión en CU micropapilar.
- **Nectina-4**: No necesaria su determinación, no predictiva repuesta EV, menor con progresión, en NE y sarcomatoide, mayor en luminales.
- **TROP-2:** No necesaria su determinación, no predictiva respuesta SG, menor en NE, sarcomatoide y rabdoide, peor pronostico.
- **Otros**: DDR→ mejor respuesta a platinos e ICI; MDM2 mejor respuesta a EV, MSI,….en estudio.

¡¡¡ Muchas gracias por la atención !!!

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