III JORNADA DE ACTUALIZACIÓN EN
URO-ONCOLOGÍA:
UPDATE 2026

Madrid, 17 de febrero de 2026

¿Qué biomarcadores importan en el carcinoma urotelial? ¿Cómo debemos determinarlos?

Dra. Eugenia García Fernández. Servicio de Anatomía Patológica. Hospital Universitario La Paz

OVERVIEW

- Introducción
- Inmunoterapia sistémica
- Biomarcadores para terapia dirigida:
  - FGFR3
  - Nectina-4
  - Trop-2
  - HER2 (ERBB2)

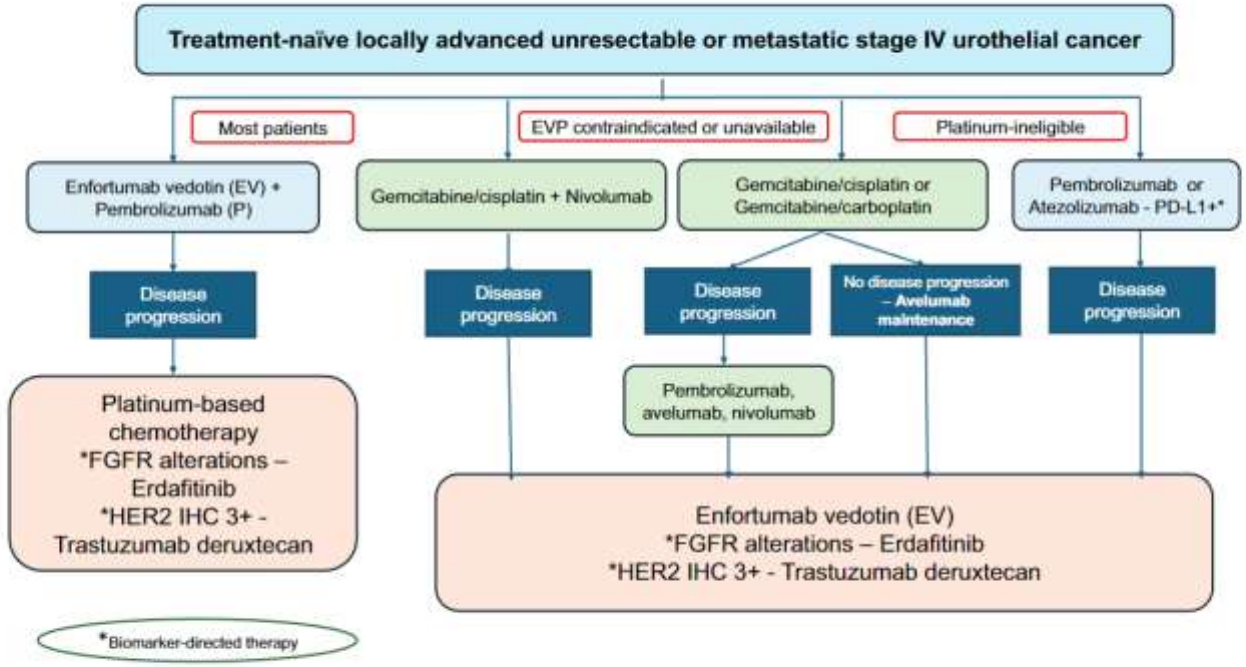
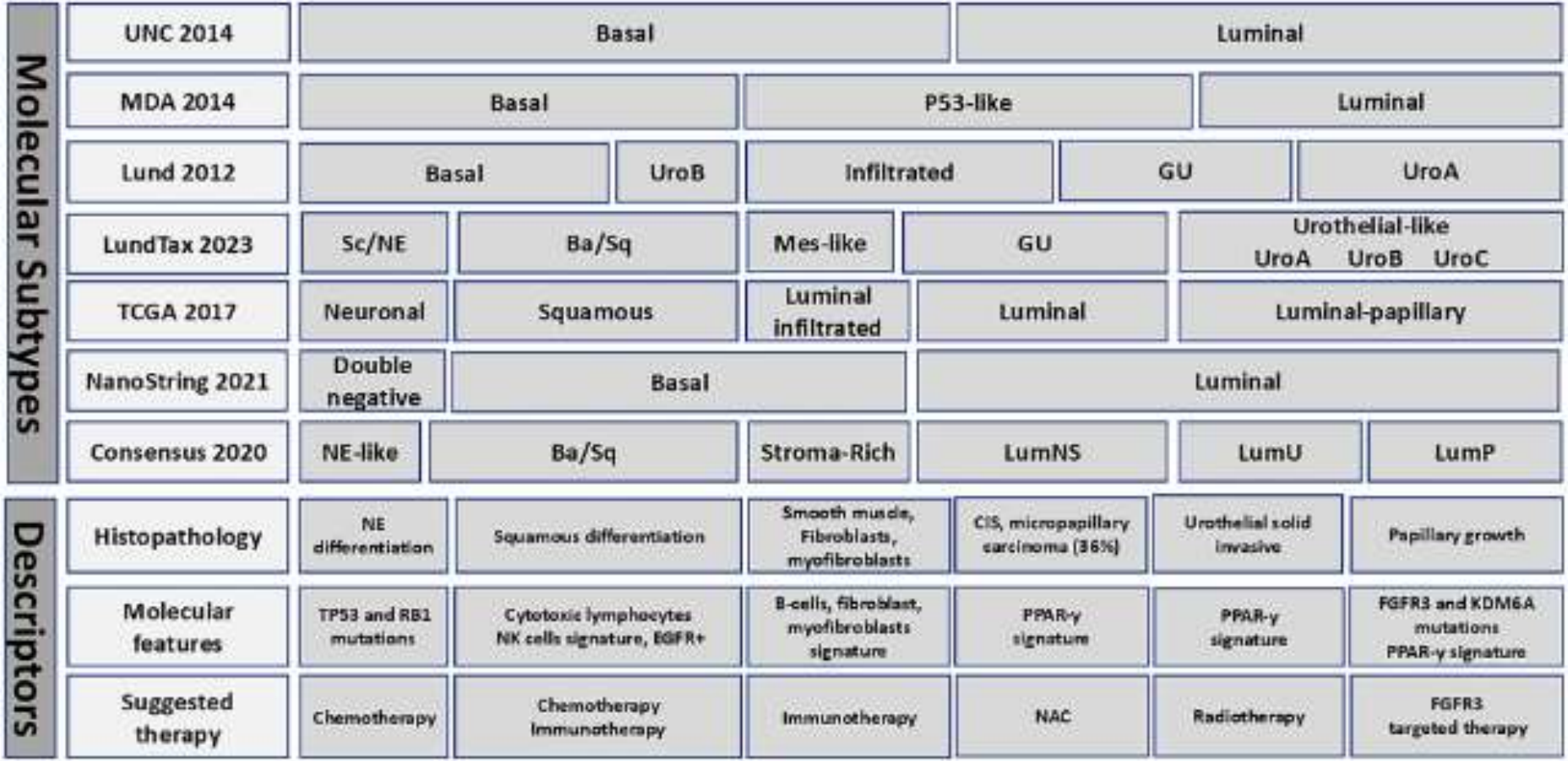


Figure 1. Treatment algorithm for stage IV metastatic urothelial carcinoma or locally advanced unresectable urothelial carcinoma.

Legends/Abbreviations: Enfortumab vedotin (EV); Pembrolizumab (P); Fibroblast growth factor receptor (FGFR); Human Epidermal Growth Factor Receptor-2 (HER2); Immunohistochemistry (IHC); Programmed death ligand-1 positive (PD-L1+).

Yu, E. M., Linville, L., Hwang, M. W., Kim, Y., Li, K., & Aragon-Ching, J. B. (2026). Harnessing genomic profiling for improved urothelial cancer outcomes. *Expert Review of Anticancer Therapy*, *26*(1), 93–104. https://doi.org/10.1080/14737140.2025.2575827


Molecular Subtypes
UNC 2014
Basal
Luminal
MDA 2014
Basal
P53-like
Luminal
Lund 2012
Basal
UroB
Infiltrated
GU
UroA
LundTax 2023
Sc/NE
Ba/Sq
Mes-like
GU
Urothelial-like
UroA UroB UroC
TCGA 2017
Neuronal
Squamous
Luminal infiltrated
Luminal
Luminal-papillary
NanoString 2021
Double negative
Basal
Luminal
Consensus 2020
NE-like
Ba/Sq
Stroma-Rich
LumNS
LumU
LumP
Descriptors
Histopathology
NE differentiation
Squamous differentiation
Smooth muscle, Fibroblasts, myofibroblasts
CIS, micropapillary carcinoma (36%)
Urothelial solid invasive
Papillary growth
Molecular features
TP53 and RB1 mutations
Cytotoxic lymphocytes NK cells signature, EGFR+
B-cells, fibroblast, myofibroblasts signature
PPAR-γ signature
PPAR-γ signature
FGFR3 and KDM6A mutations PPAR-γ signature
Suggested therapy
Chemotherapy
Chemotherapy Immunotherapy
Immunotherapy
NAC
Radiotherapy
FGFR3 targeted therapy

1. Normal Urothelium

Early pre-malignant changes

Key Biomarkers: KMT2A and KDM6A
CDKN2A alterations; 9p/9q deletions
(early chromosomal loss)

2. Hyperplasia / Dysplasia

Early pre-malignant changes

Key Biomarkers: TERT promoter mutations
CDKN2A alterations; 9p/9q deletions
(early chromosomal loss)

3. Papillary Low-Grade (Ta)

Exophytic, non-invasive tumor
Molecular Subtype: Luminal Papillary (LumP)
Clinical Note: High recurrence (~60%), low progression (~4%)

Key Biomarkers: FGFR3, HRAS, STAG2 mutations
KRT20 expression and CDKN2A deletion
TERT promoter mutation

4. Lamina Propria Invasion / CIS(T1)

CIS (Carcinoma in Situ-flat lesion)
Papillary High-Grade T1
Molecular Subtype: Lumina and/or Basal features

Key Biomarkers: TP53, CDKN2A
HIF-1α, VEGF (angiogenesis)
EMT markers: SNAIL, ZEB1, TWIST

Lopez-Beltran A, Blanca A, Downes MR, Cimadamore A, Montironi R, Cheng L. Molecular pathology of bladder cancer. Histopathology. 2026 Jan;88(1):65-85. doi: 10.1111/his.15555. PMID: 41384708

FGFR3

QTP, HER2

ICI

5. Muscle Invasion (≥T2)

High-grade MIBC
Molecular Subtype: Consensus classification from multiple systems (TCGA, Lund, MDA, UNC)

5A. Luminal Papillary (LumP)
Papillary growth
Prognosis: Generally favorable
Therapy: FGFR3 inhibitors (e.g., Erdafitinib)

Key Mutations: FGFR3, KDM6A
Genetic Alterations: PPARG, CDKN2A
Markers: KRT20, GATA3, UPK1A, UPK2

5B. Luminal Unstable (LumU)
Mixed pattern and unstable
Prognosis: Intermediate
Therapy: Chemo, anti-HER2, radiotherapy

Key Mutations: TP53, ERCC2, TMB and APOBEC
Genetic Alterations: Genomic instability profile, PPARγ signature, ERBB2, and cell cycle activity
Markers: KRT20, GATA3, FOXA1

5C. Luminal Non-Specified (LumNS)
Variable pattern; fibroblast infiltration
Prognosis: Intermediate
Therapy: Possible ICIs

Key Mutations: TP53, ELF3
Genetic Alterations: Immune infiltration, PPARG
Markers: GATA3, FOXA1; lower KRT20 expression

5D. Basal / Squamous (Ba/Sq)
Squamous-like Pattern
Prognosis: Poor; more aggressive phenotype
Therapy: Chemo and ICIs

Key Mutations: TP53, RB1, NFE2L2
Genetic Alterations: EGFR overexpression, frequent immune activation
Markers: High KRT5/6, KRT14; low GATA3; high PD-L1

5E. Neuroendocrine-like (NE-like)
Small-cell or large-cell neuroendocrine carcinoma
Prognosis: Very poor; highly aggressive
Therapy: Platinum chemo; ± ICI

Key Mutations: TP53, RB1 (both inactivated)
Genetic Alterations: high proliferation; NE transcriptional program, cell cycle activity
Markers: CHGA, SYP, NCAM1

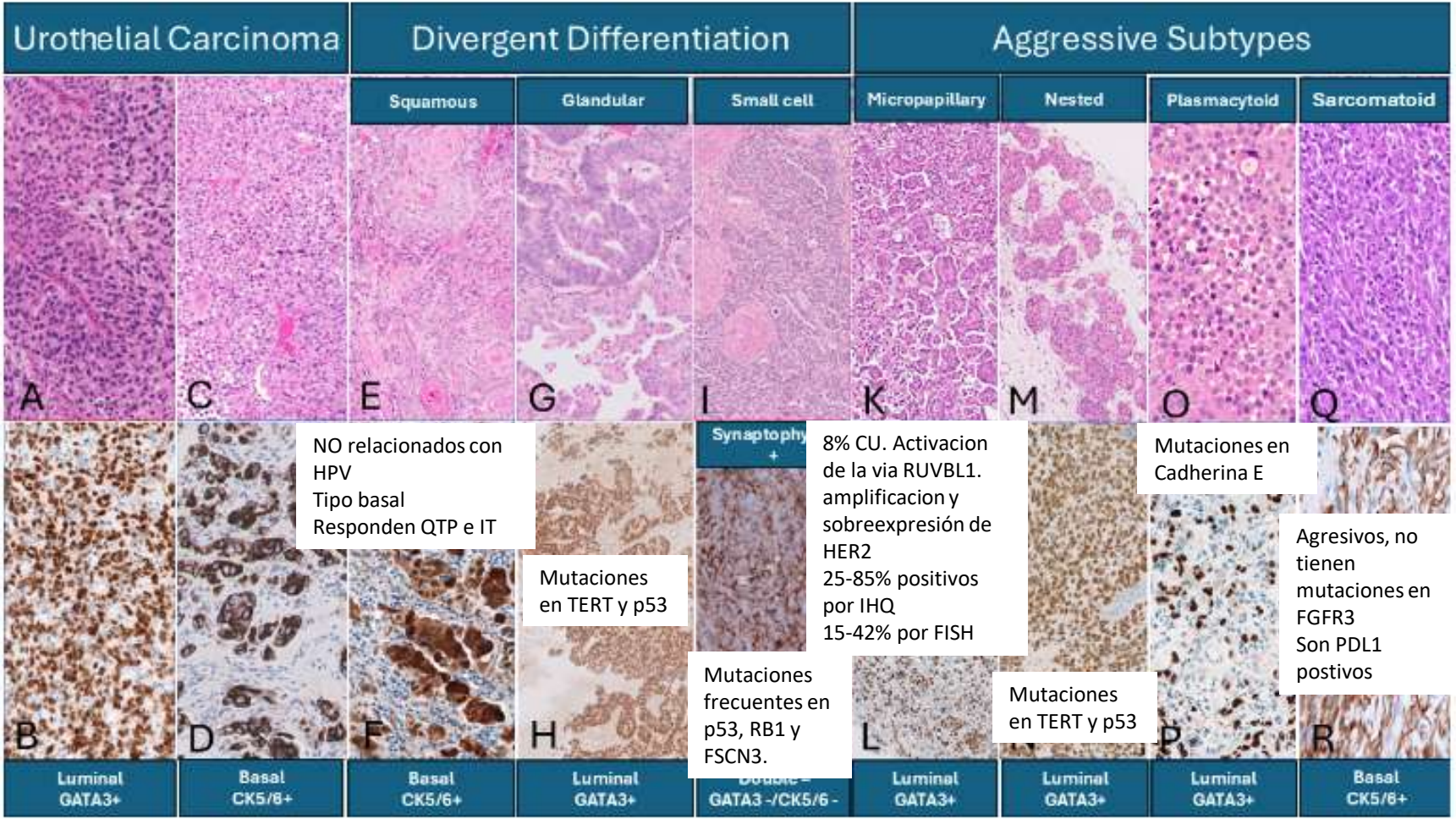
5F. Stroma-rich
Abundant stromal
Prognosis: Intermediate
Therapy: ICI (context-dependent)

Key Mutations: Not mutation-defined
Genetic Alterations: Stromal signaling pathways
Markers: Stromal, muscle, and immune genes

6. Metastasis

Stage: Distant spread (~50%)
(lymph nodes, liver, bone, lungs)
Therapy: Chemo, ICI, and clinical trial
Targeted Therapies

Key Mutations:TP53 and RB1 mutations
Genetic Alterations: VEGF (angiogenesis)
PD-L1, MMPs, EMT-related genes



- Lopez-Beltran A, Blanca A, Downes MR, Cimadamore A, Montironi R, Cheng L. Molecular pathology of bladder cancer. Histopathology. 2026 Jan;88(1):65-85. doi: 10.1111/his.15555. PMID: 41384708

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https://doi.org/10.1007/s00345-020-03498-0

TOPIC PAPER

PD-L1 testing in urothelial bladder cancer: essentials of clinical practice

Mathieu Rouanne[1,2] · Camélia Radulescu[3] · Julien Adam[4,5] · Yves Allory[3,6,7]

Received: 16 July 2020 / Accepted: 13 October 2020 / Published online: 3 November 2020

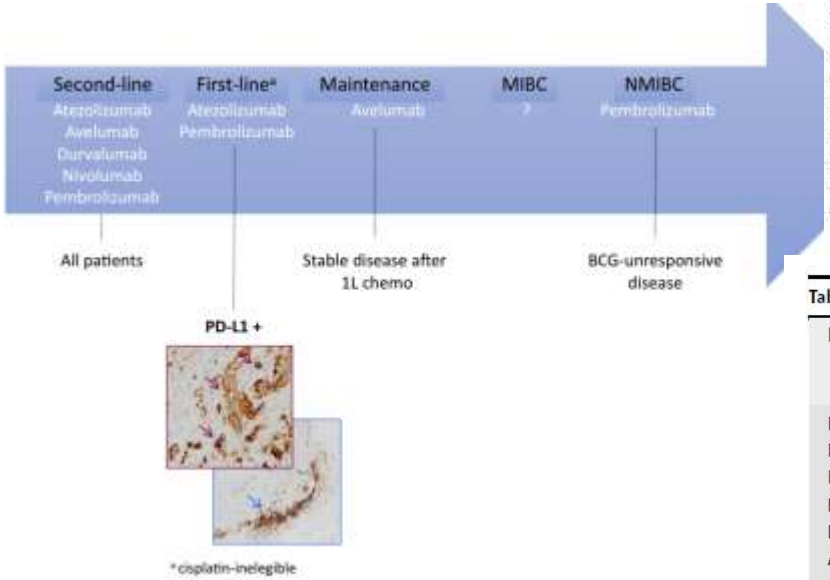


Fig. 3 Indications for anti-PD-L1 monoclonal antibody in UC

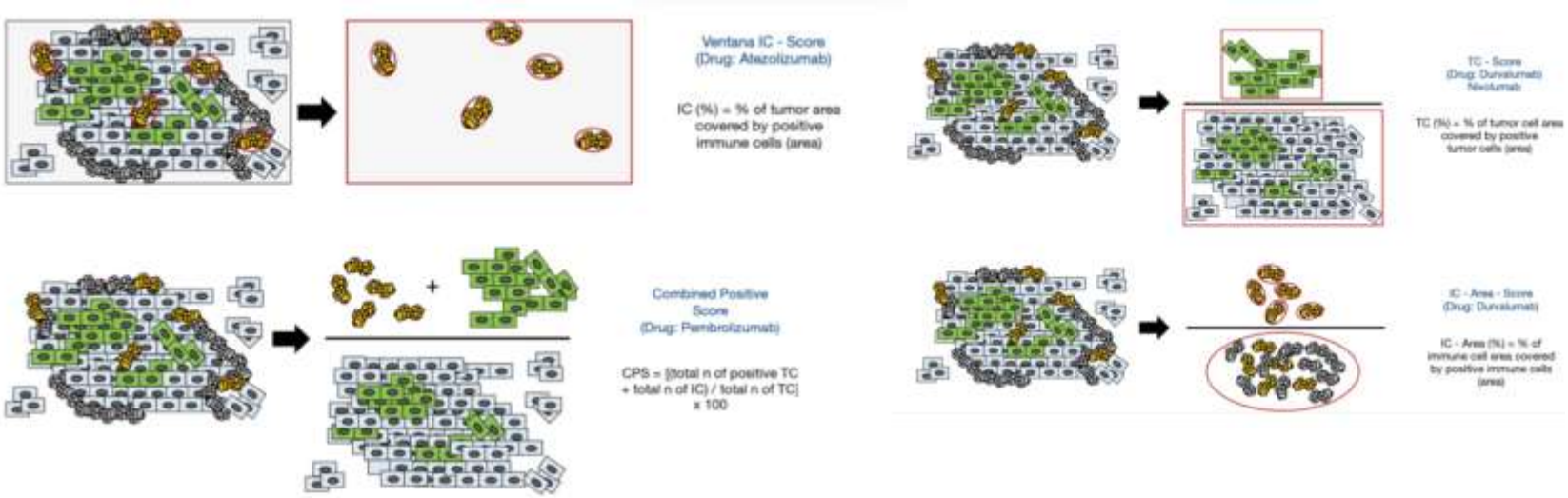
Table 2 PD-L1 expression as a predictive biomarker of response to anti-PD(L)1 mAb in UC

Clinical Trial ID	Anti-PD(L)1 mAb	Clinical setting	No. of patients	Study phase	Assay
IMvigor 210 cohort 2	Atezolizumab	2nd line	310	Phase II	SP142
IMvigor 211	Atezolizumab	2nd line	931	Phase III	SP142
IMvigor130	Atezolizumab	1st line	851	Phase III	SP142
IMvigor 210 cohort 1	Atezolizumab	1st line cisplatin-ineligible	119	Phase II	SP142
ABACUS	Atezolizumab	Neoadjuvant		Phase II	SP142
JAVELIN Solid Tumor	Avelumab	2nd line	249	Phase Ib	73-10
JAVELIN Bladder 100	Avelumab	Maintenance	700	Phase III	SP263
NCT01693562	Durvalumab	2nd line	191	Phase I/II	SP263
CheckMate 032	Nivolumab	2nd line	78	Phase I/II	28-8
CheckMate 275	Nivolumab	2nd line	265	Phase II	28-8
KEYNOTE 045	Pembrolizumab	2nd line	542	Phase III	22C3
KEYNOTE 052	Pembrolizumab	1st line cisplatin-ineligible	370	Phase II	22C3
PURE-01	Pembrolizuamb	Neoadjuvant	112	Phase II	22C3
KEYNOTE 057	Pembrolizumab	BCG-unresponsive	148	Phase II	22C3

mAb monoclonal antibody, *IC* immune cells, *TC* tumor cells

Table 1. Immunotherapy trials and association between PD-L1 score and response [39]

Drug	Trial name (setting)	Biomarker	Scoring	Association between PD-L1 score and response
Pembrolizumab	KEYNOTE-045 (Advanced, second line)	22C3	TC + IC	No
Pembrolizumab	KEYNOTE-052 (Advanced, first line)	22C3	TC + IC	Yes
Pembrolizumab	KEYNOTE-057 (NMIBC)	Not reported	TC + IC	No
Nivolumab	CheckMate 274 (Adjuvant)	28-8	TC	Yes
Nivolumab	CheckMate 275 (Advanced, second line)	28-8	TC	Yes
Avelumab	JAVELIN Solid Tumor (Advanced, second line)	73-10	TC + IC	No
Avelumab	Javelin Bladder 100 (Maintenance)	73-10	TC + IC	No



TPS(%)= CELULAS TUMORALES POSITIVAS X 100
TOTAL CELULAS TUMORALES

IC(%)= CELULAS INMUNES POSITIVAS ASOCIADAS AL TUMOR X 100
AREA TOTAL DEL TUMOR Y ESTROMA PERITUMORAL

CPS= CELULAS TUMORALES POSITIVAS + CELULAS INMUNES INTRATUMORALES X 100
TOTAL CELULAS TUMORALES

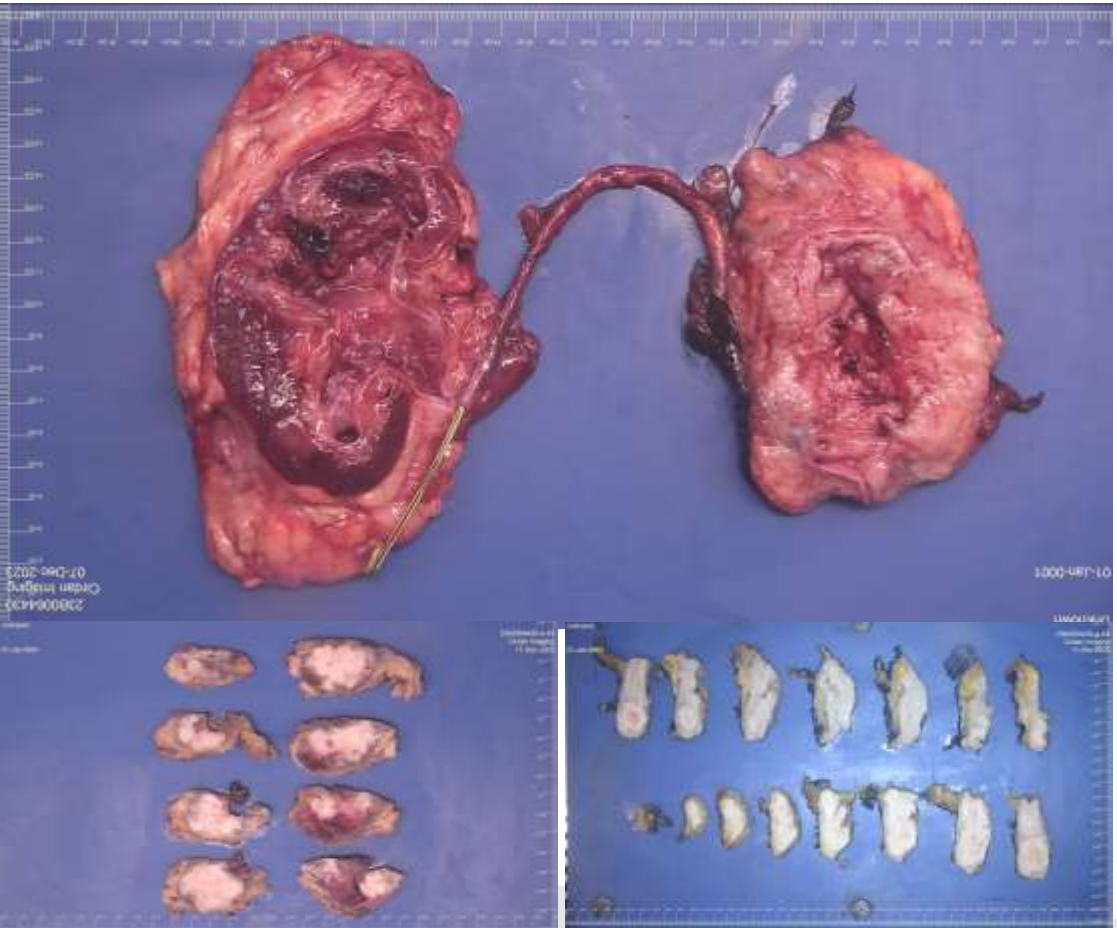
Table 4. Comparison of PD-L1 immunostainings in selected anti-PD-1/anti-PD-L1 agents

Characteristics	Durvalumab	Atezolizumab		Nivolumab		Pembrolizumab		Avelumab[a]
Manufacturer	AstraZeneca	Roche		Bristol-Meyers Squibb		Merck		Merck/Pfizer
Target	PD-L1	PD-L1		PD-1		PD-1		PD-L1
PD-L1 assay	Ventana SP263	Ventana SP142		Dako 28–8		Dako 22C3		Dako 73–10
Cell-types scored for UC	TIC and TC	TIC		TC		TC and TIC		TC
Line of therapy (L)	≥1 L	≥2 L	1 L (cispla-inel)	≥2 L	≥2 L	2 L	1 L (cisplat-inel)	≥2 L
PD-L1 cut offs								
High/positive	≥25% TC or TIC	≥5% TIC	≥5% TIC	≥1% TC	≥1%, ≥5% TC	≥10% CPS	≥10% CPS	≥5% TC
Low/negative	<25% TC and TIC	<1% TIC	<1% TIC	<1% TC	<1% TC	NA	<10% CPS	No visible staining

Abbreviations: cispla-inel, cisplatin ineligible; CPS, combined positive score (tumour and immune cell PD-L1 expression); NA, not available; TC, tumour cells; TIC, tumour infiltrating immune cells.

[a]Currently used as maintenance for metastatic urothelial cancer after systemic chemotherapy. In this case, Ventana SP263 is used as a biomarker of PD-L1 detection and reported (Javelin Bladder 100) as High/Positive (≥25% TC or TIC) vs. Low/Negative (<25% TC and TIC).

- Lopez-Beltran A, Blanca A, Downes MR, Cimadamore A, Montironi R, Cheng L. Molecular pathology of bladder cancer. Histopathology. 2026 Jan;88(1):65-85. doi: 10.1111/his.15555. PMID: 41384708



Se ha realizado determinación de PD-L1 en el bloque X-Bloque X (carcinoma urotelial en vejiga) con

los siguientes resultados:

Anticuerpo: 28-8.

- Plataforma de inmunohistoquímica: DAKO.
- Porcentaje de células tumorales positivas (TPS): 25%
- Porcentaje de células inmunes positivas: 65%
- CPS: 45

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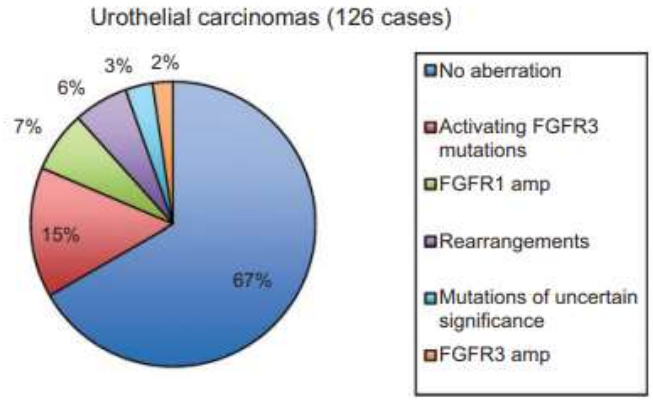
Clinical Cancer Research

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]



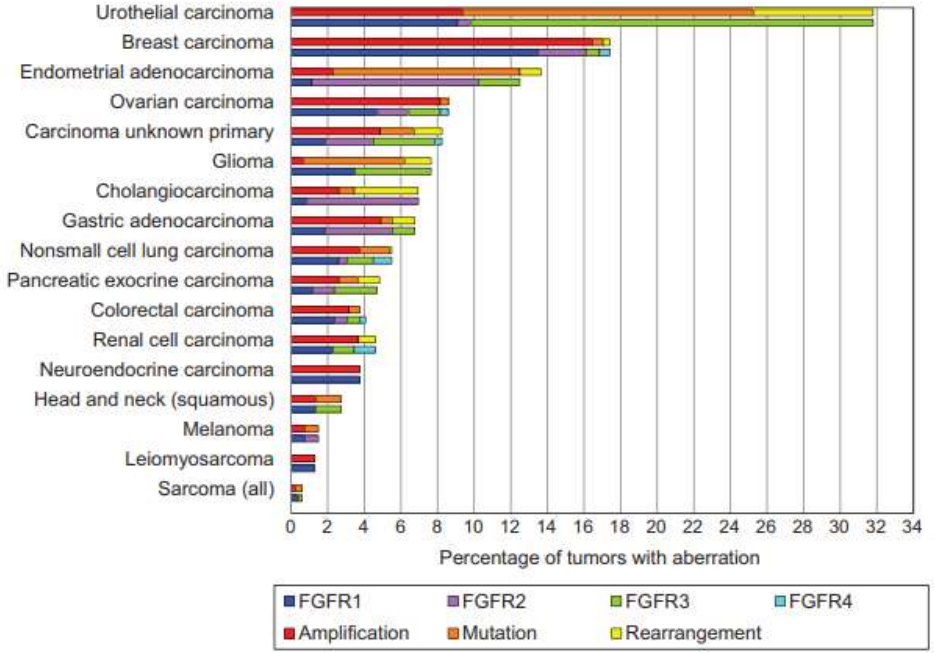


Figure 4.

Distribution of FGFR aberrancies in urothelial cancers. Cancers included urothelial carcinomas (transitional cell carcinomas) of the bladder, renal pelvis, ureter, and not specified. The majority of aberrations were activating mutations in *FGFR3*, including S249C (8 instances), R248C (6 instances), Y373C (2 instances), G370C (2 instances), and K650M (1 instance). Three of these *FGFR3* mutations are also about to transform cells *in vitro* (S249C, S248C, Y737C; Supplementary Table S4). Frequencies are expressed as percentages of all 126 cases. There were 44 aberrations in 40 cases (4 cases had more than one aberration), so the total is greater than 100%.

III JORNADA DE ACTUALIZACIÓN EN **URO-ONCOLOGÍA:**
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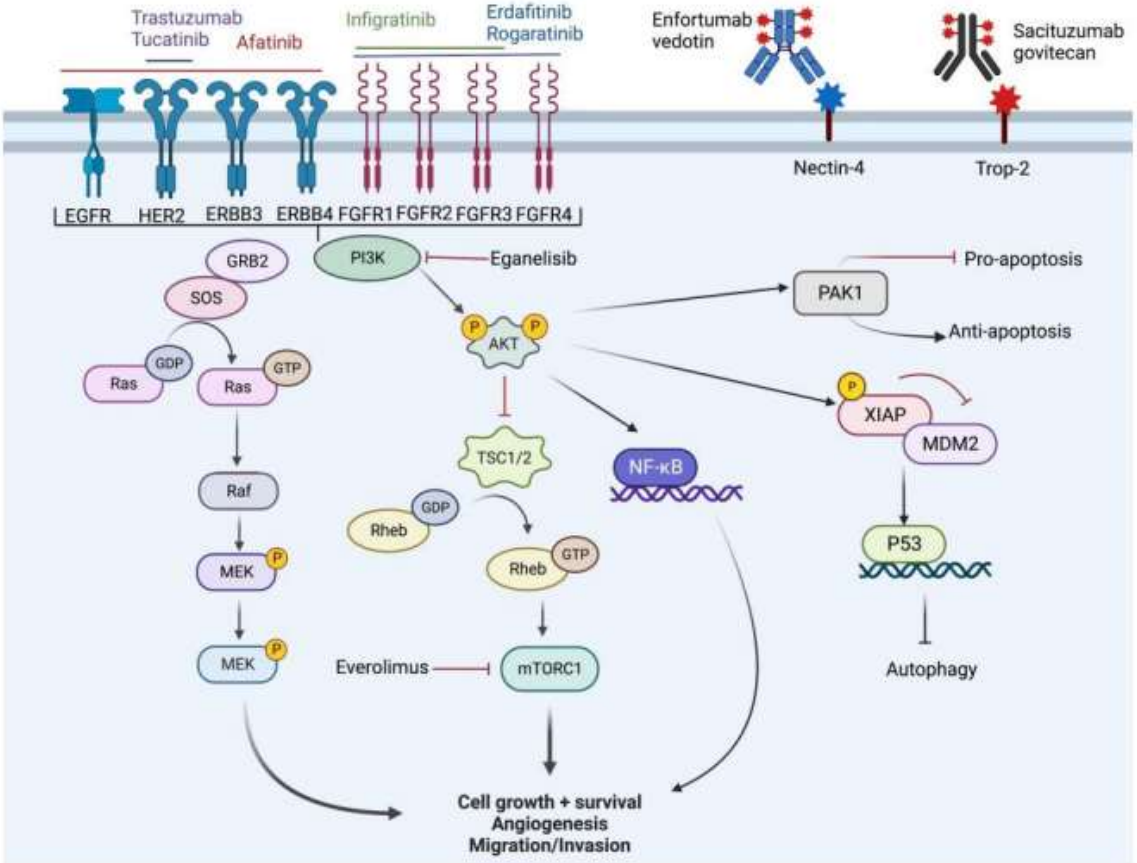

cancers
MDPI
Review

Targeted Therapies in Advanced and Metastatic Urothelial Carcinoma

Andrew B. Katims [1,*], Peter A. Reisz [1], Lucas Nogueira [1], Hong Truong [1], Andrew T. Lenis [1], Eugene J. Pietzak [1], Kwanghee Kim [2,*] and Jonathan A. Coleman [1]

[1] Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[2] Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
* Correspondence: katimsa@mskcc.org (A.B.K.); kimk3@mskcc.org (K.K.)

- *FGFR3* codifica un receptor de superficie que juego un rol pivotal en en proliferación celular, diferenciación y supervivencia
- Se describen mutaciones activadoras, amplificaciones y fusiones del gen.
- 80% de los Ta papilares bajo grado
- 50% de los T1
- 10-15% de los T2
- 0-15% de los Carinoma in situ.

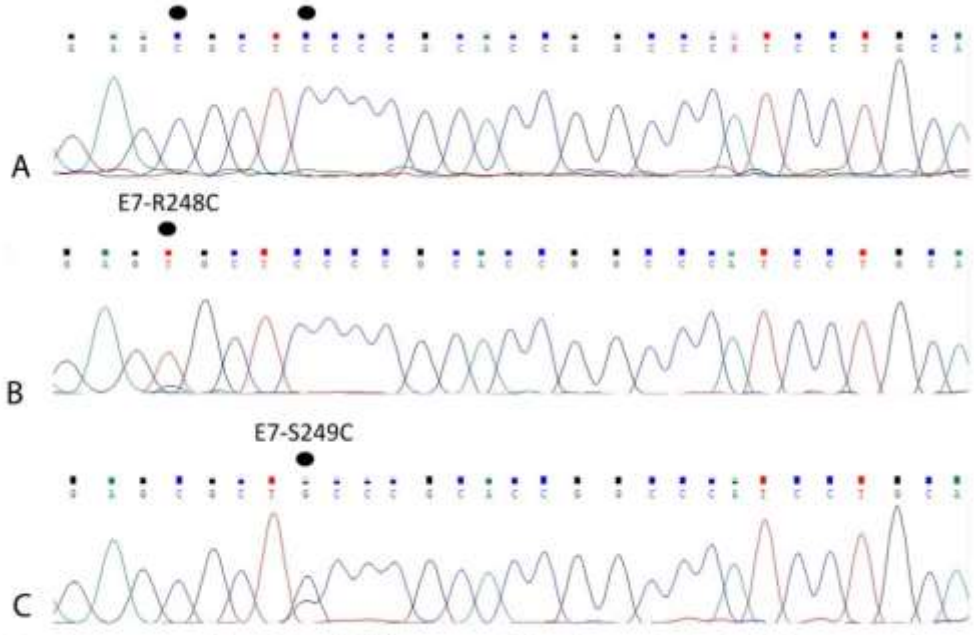

Figure 4. DNA sequencing of the FGFR3 gene. (A) Wild-type sequence. (B) Electropherogram showing the c.742C>T mutation resulting in the R248C substitution. (C) Electropherogram showing the c.746C>G mutation resulting in the S249C substitution.

Determinar las mutaciones y fusiones de FGFR3 es necesario para identificar pacientes suceptibles de tratamiento con Erdafitinib.

- Protocolos PCR para hot spots
- Next-generation sequencing (NGS) on ADN o ARN
- Tecnicas especificas RT-qPCR assays que cubran FGFR2/3 mutaciones y fusiones
- Mutaciones puntuales activantes: S249C; Y373C; R248C; G370C
- Fusiones: FGFR3–TACC3

nature communications

Article

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

Check for updates

Pierre-Antoine Bannier[1,2,3], Charlie Saillard[1], Philipp Marx[1], Maxime Fontaine[1], Charles Maussion[1], Christian Marek[1,2,3], Niklas Klümper[4,5,6], Johannes Breyer[4], Ralph Wirtz[7], Daniel Stöhr[3,4,5], Bernd Schmitz-Drolet[11], Bernd Wullich[3,4,5], Arndt Hartmann[3,5,6], Sebastian Foersch[3,5] & Markus Eckstein[3,4,5]

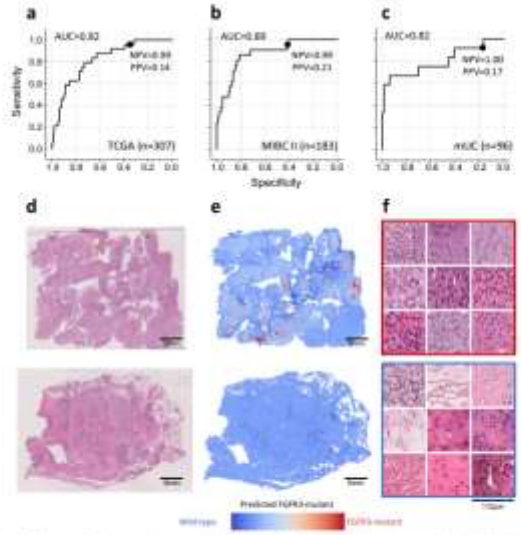

Fig. 2 | FGFR3 mutation prediction. **a**–**c** Receiver operating curves (ROC) of the FGFR3MUT model on TCGA MIBC (left), MIBC II (middle), and mUC (right). The area under the ROC curve (AUC) is displayed in the upper-left corner. **d** Thumbnail of a FGFR3-mutant case (top) and wild-type case (bottom). **e** The FGFR3 mutation prediction heatmaps showing a probability of each 112 × 112 µm tile harboring FGFR3-mutated features, for a FGFR3-mutant case (top), and wild-type case (bottom). **f** Corresponding most predictive regions of the FGFR3 mutation status (top) and wild-type status (bottom) across the mUC cohort. We inspected the 100 most predictive tiles of the slide and sampled 9 representative tiles. Regions predictive of FGFR3 mutations revealed monomorphous conventional urothelial tumor morphology and low desmoplastic tumor stroma content. Conversely, regions predictive of the wild-type status contained pleomorphic tumor morphology and desmoplastic tumor content. Source data are provided as a Source Data file.

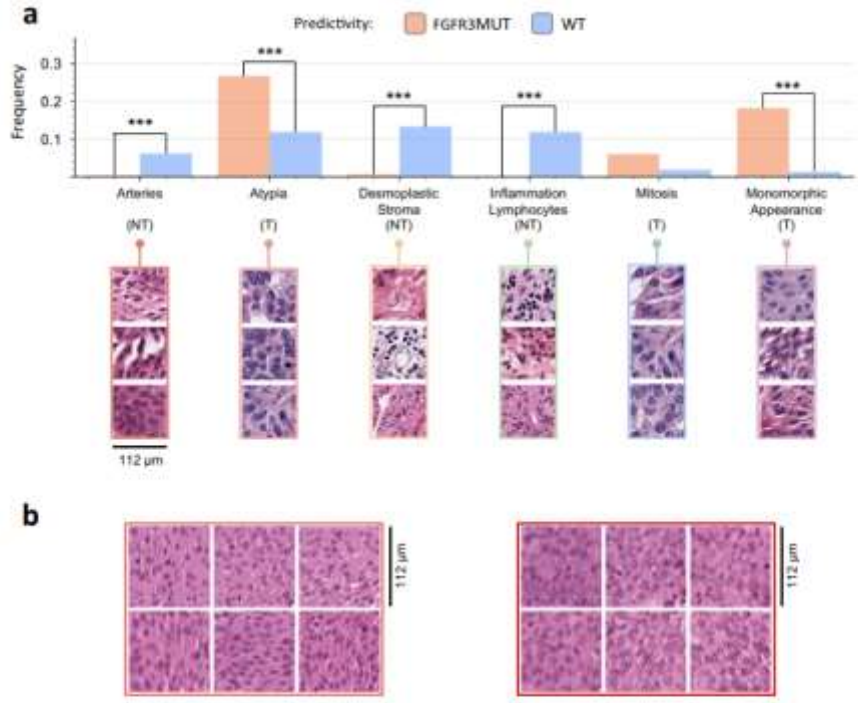

Fig. 5 | Histopathological features associated with FGFR3 mutations. **a** Proportion of histology patterns associated with FGFR3 mutation status. A pathologist (M.E.) independently examined 400 representative tiles from TCGA MIBC, equally divided between FGFR3-mutant ($n = 200$) and wild-type ($n = 200$), to identify patterns indicative of each status. Tumor-associated patterns are denoted by (T), whereas patterns identified in non-tumorous regions are represented by (NT). The detailed findings are presented in Supplementary Tables 8 and 9. Key observations include a monomorphic appearance (FGFR3MUT: 18%, WT: 1%, $P = 4.3e\text{-}13$) and atypia (FGFR3MUT: 27%, WT: 12%, $P = 5.0e\text{-}3$) in FGFR3-mutant tumors, while wild-type tumors typically elicit an immune response (FGFR3MUT: 0%, WT: 12%, $P = 2.9e\text{-}8$) and are characterized by the presence of desmoplastic stroma (FGFR3MUT: 1%, WT: 14%, $P = 9.8e\text{-}13$). Statistical significance was assessed using a two-sided z-test for proportions, with Bonferroni adjustment for multiple comparisons. Statistically significant differences were marked with the "*" symbol. **b** Comparison of top predictive tiles for the same metastatic FGFR3-mutant patient from the mUC cohort. The left slide shows the top predictive tiles on the primary site, while the right slide shows the top predictive tiles on the metastasis. For each group, we inspected the 50 most predictive tiles of the slide and sampled 6 representative tiles. Source data are provided as a Source Data file.

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Tumor Cell

T-Cell

Sacituzumab govitecan

Nucleus

DNA repair

Transcription of tumor survival, proliferation and angiogenesis genes

CTLA-4

PD-L1

PD-1

Downregulation of immune response

Nivolumab
Avelumab
Pembrolizumab

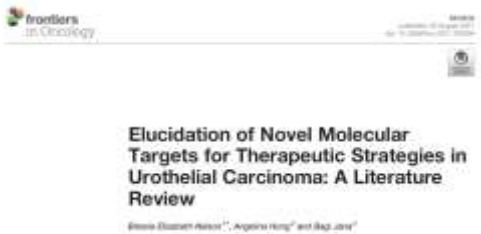
PI3K/AKT

MEK/ERK

STAT

FGFR

Erdafitinib


frontiers in Oncology

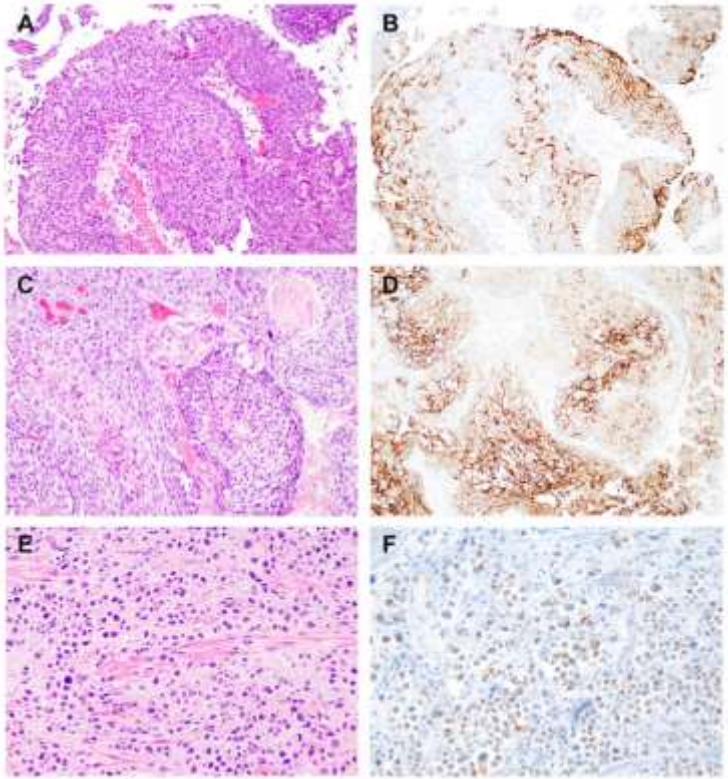
Elucidation of Novel Molecular Targets for Therapeutic Strategies in Urothelial Carcinoma: A Literature Review

EV internalized by cell, monomethyl auristatin E (MMAE) released

Nectin-4

Enfortumab vedotin (EV)

Enfortumab vedotin: anticuerpo monoclonal frente a nectina-4 (molécula de adhesión) conjugado con un agente citotóxico (MMAE) que impide la formación de microtúbulos



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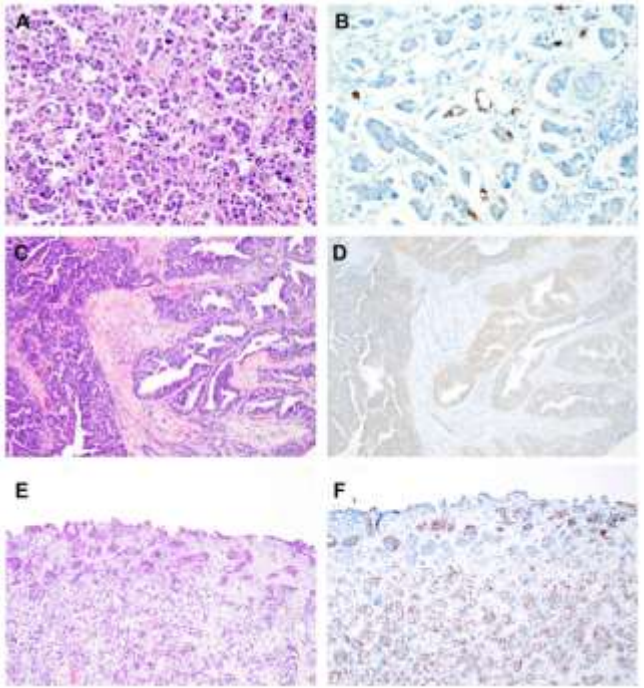
Expression of Nectin-4 in Bladder Urothelial Carcinoma and in Morphologic Variants and Non-Urothelial Histotypes

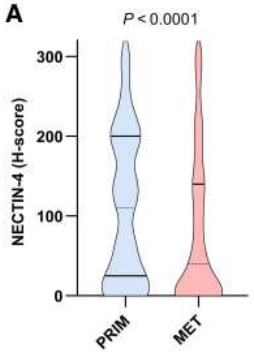
Jean H. Hoffman-Censits, MD[2,3,4,*], Kara A. Lombardo, BS[2,4,*], Vamsi Parimi, MD, MPH[1], Sonia Kamanda, MD[1], Woonyoung Choi, PhD[2,4], Noah M. Hahn, MD[2,3,4], David J. McConkey, PhD[2,3,4], Bridget M. McGuire, BS[2], Trinity J. Bivalacqua, MD, PhD[2,3], Max Kates, MD[2,3], Andres Matoso, MD[1,2,3,4]

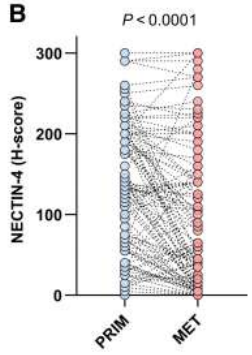
- 169 pacientes
- 70% convencionales y escamosos
- 60% adenocarcinomas y plasmocitoides
- 50% subtipo en nidos
- 30% micropapilar
- 10% sarcomatoides
- 0% neuroendocrinos

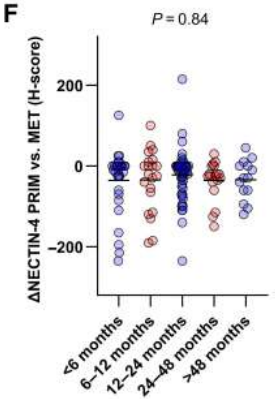


Membranous NECTIN-4 Expression Frequently Decreases during Metastatic Spread of Urothelial Carcinoma and Is Associated with Enfortumab Vedotin Resistance

Niklas Klümper[1,2,3,4], Damien J. Ralser[2,3,5], Jörg Ellinger[2,3], 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[6,11], 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[5,16], Glen Kristiansen[3,4,16], Thomas Büttner[13], Oliver Hahn[17], Viktor Grünwald[18], Christopher Darr[16], Eva Ernst[19], Steffen Rausch[19], Jens Bedke[16], Katrin Schlack[20], Mahmoud Abbas[21], Stefanie Zschäbitz[22], Constantin Schwab[23], Alexander Mustea[2,5], Patrick Adam[24], Andreas Mameck[25], Bernd Wullich[4,7,8,9], Manuel Ritter[1,3,4], Arndt Hartmann[4,7,9,26], Jürgen Gschwend[6,11], Wilko Weichert[9,13], Franziska Erlmeier[4,7,9,13,16], Michael Hölzel[2,3], and Markus Eckstein[4,7,9,16]

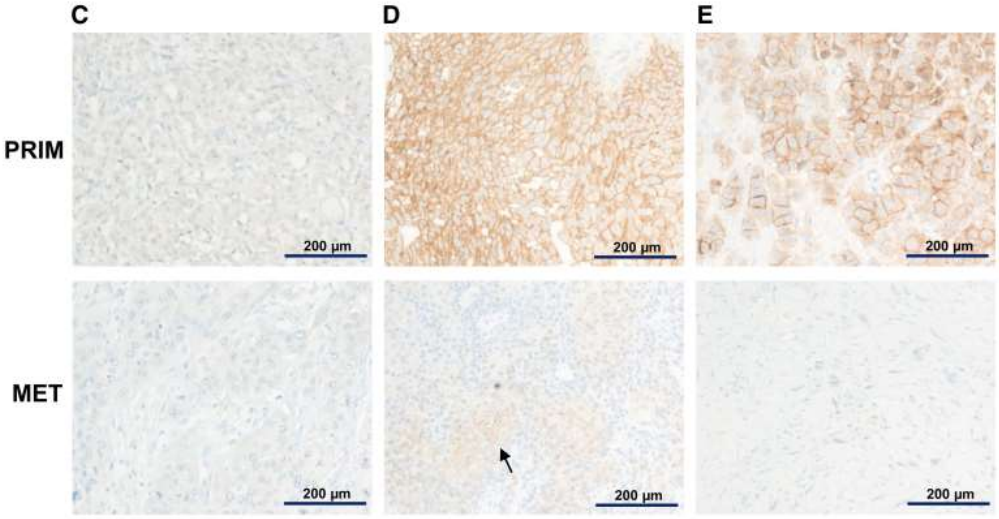


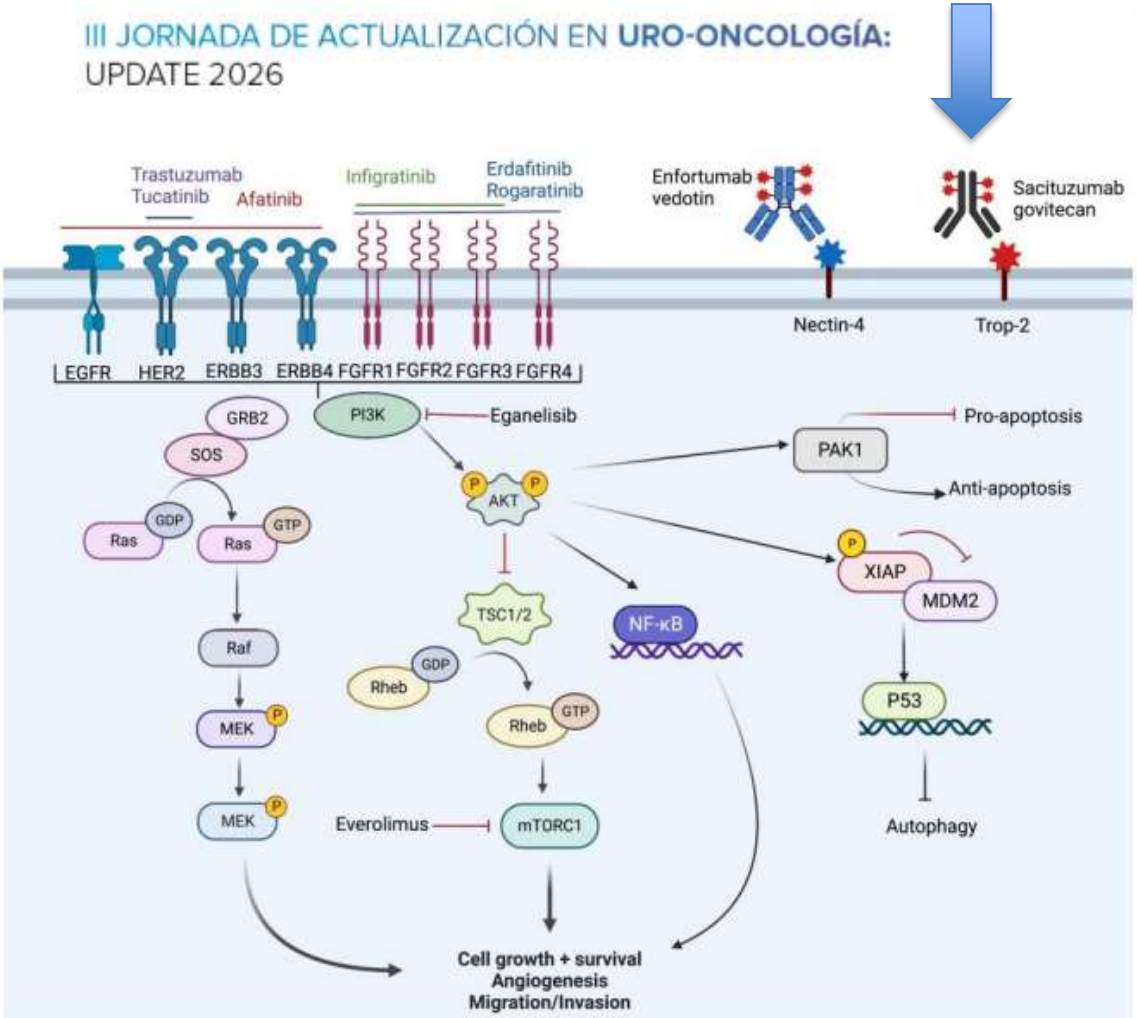




Translational Relevance

Enfortumab vedotin (EV) releases a cytotoxic agent into the urothelial carcinoma (UC) tumor cell via binding to the tumor surface protein NECTIN-4. Although EV is approved in the metastatic disease stage, the expression of its target in metastatic tissue is insufficiently studied. Here, we demonstrate that NECTIN-4 expression decreases substantially during metastatic evolution and is absent in more than one third of patients with metastatic UC. Further, in our multicenter EV-treated cohort, membranous NECTIN-4 expression predicts EV response and outcomes. Our data argue against the common practice of EV treatment without prior assessment of target protein expression and suggest that NECTIN-4 receptor status should be determined in a metastatic lesion before initiation of EV.





- Trop-2 (antígeno de superficie del trofoblasto). Aumentada en el CU y se correlaciona con empeoramiento de la enfermedad.
- SG es un anticuerpo anti Trop2 que se encuentra en la superficie de la célula tumoral e incorpora el inhibidor de la topoisomerasa I que rompe el DNA en la fase S de la mitosis.
- No es necesario demostrar expresión de Trop-2.
- Están aumentados en los CU, pero no en neuroendocrinos

Histopathology

Associations of *TACSTD2*/TROP2 and *NECTIN-4*/NECTIN-4 with molecular subtypes, PD-L1 expression, and *FGFR3* mutational status in two advanced urothelial bladder cancer cohorts

Veronika Bahlinger,[1,2,3] Annalena Brantz,[1,2,3] Pamela L Strissel,[1,2,3,4] Reiner Strick,[2,3,4] Fabienne Lange,[1,2,3] Carol I Geppert,[1,2,3] Niklas Klümper,[5,6] Michael Hölzel,[8] Sven Wach,[2,3,7] Helge Taubert,[2,3,7] Danijel Sikic,[2,3,7] Bernd Wullich,[2,3,7] Miriam Angeloni,[1,2,3] Fulvia Ferrazzi,[1,2,3,8] Lauri Diehl,[9] Maria Kovalenko,[9] Emon Elboudwarej,[9] Juliane M Jürgensmeier,[9] Arndt Hartmann[1,2,3] & Markus Eckstein[1,2,3]

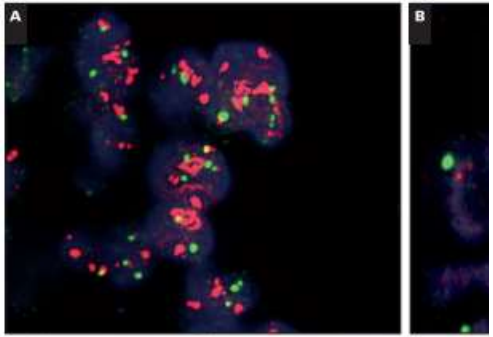
Conclusions: TACSTD2/TROP2 and NECTIN-4-/NECTIN-4 are widely expressed in aUC, independentof FGFR3 alterations or PD-L1 expression, thus repre-senting a suitable target for ADC treatment in themajority of aUC. The expression loss was associatedwith aggressive morphomolecular aUC subtypes, i.e.neuroendocrine(-like) and sarcomatoid aUC

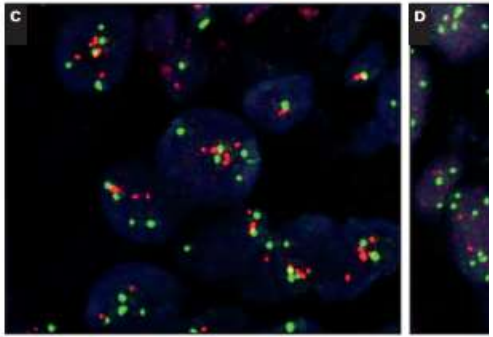
-ONCOLOGÍA:

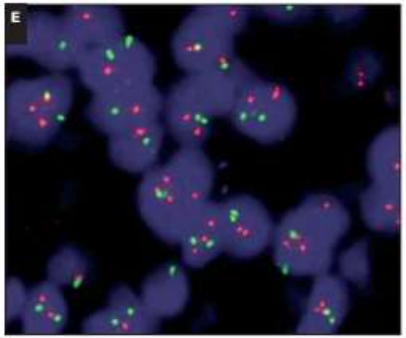
	Both markers expressed	No marker expression	Only TROP2 not expressed	Only Nectin 4 not expressed	Not available	
Total number	177	5	8	15	42	
Histology						
Neuroendocrine	2 (1.1)	4 (80.0)	4 (50.0)	0		
Sarcomatoid	11 (6.2)	1 (20.0)	2 (25.0)	3 (20.0)		
Large nested	6 (3.4)	0	0	1 (6.7)		
Squamous	46 (25.8)	0	0	7 (46.7)		
Other variants		0	0	0		
Not other specified	81 (45.5)	0	2 (25.0)	4 (26.7)		**P=0.0006**
Molecular subtypes						
Consensus subtypes						
Basal/squamous	80 (46.2)	2 (40.0)	3 (37.5)	13 (92.9)		
Luminal nonspecified	7 (4.0)	0	0	0		
Luminal Papillary	15 (8.7)	0	0	0		
Luminal Unstable	18 (10.4)	0	0	0		
Neuroendocrine-like	2 (1.2)	2 (40.0)	4 (50.0)	0		
Stroma-rich	51 (29.5)	1 (20.0)	1 (12.5)	1 (7.1)		**P<0.0001**
Protein-based subtypes						
Luminal	118 (66.7)	1 (20.0)	5 (62.5)	6 (40.0)		
Basal	59 (33.3)	3 (60.0)	1 (12.5)	9 (60.0)		
Double negative	0	1 (20.0)	2 (25.0)	0		**P<0.0001**
***FGFR3* alteration status**						
Altered	19 (10.7)	0	0	3 (20.0)		
Wild type	159 (89.3)	5 (100.00)	8 (100.0)	12 (80.0)		P=0.26
PD-L1 assessment						
Immune cell score (IC)						
IC < 5%	118 (66.3)	4 (80.0)	6 (75.0)	9 (60.0)		
IC ≥ 5%	60 (33.7)	2 (20.0)	2 (25.0)	6 (40.0)		P=0.80
Combined Positive Score (CPS)						
CPS < 10	99 (55.6)	3 (60.0)	6 (75.0)	9 (60.0)		
CPS ≥ 10	79 (44.4)	2 (40.0)	2 (25.0)	6 (40.0)		P=0.72

OVERVIEW

- Introducción
- Inmunoterapia sistémica
- Biomarcadores para terapia dirigida:
  - FGFR3
  - Nectina-4
  - Trop-2
  - HER2 (ERBB2)







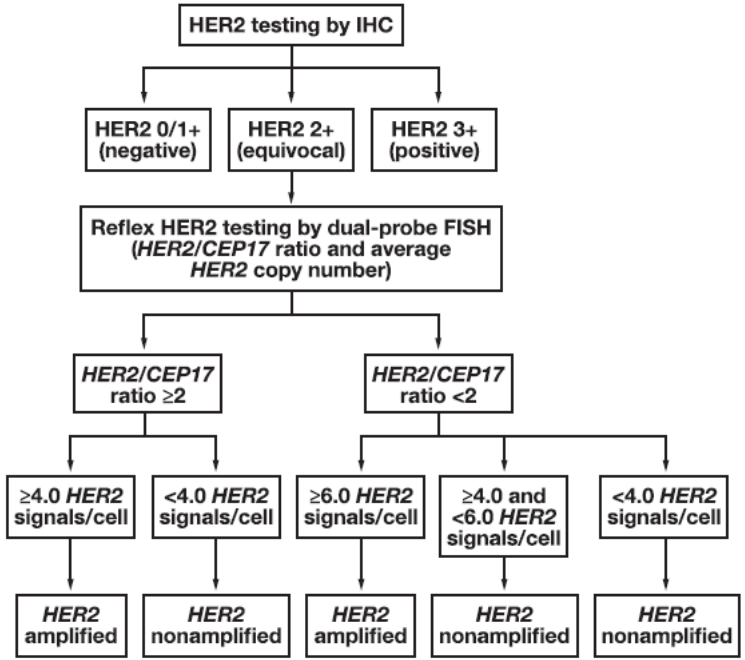
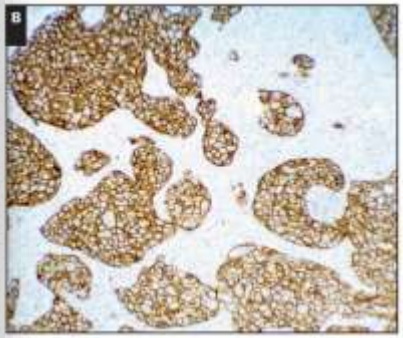
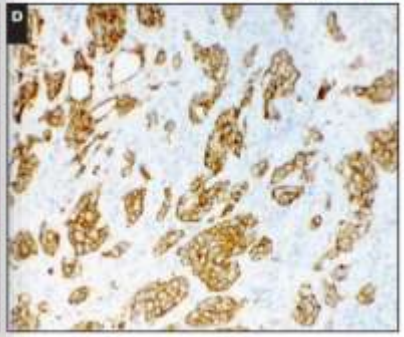


Figure 4 Algorithm for human epidermal growth factor receptor 2 (HER2) testing in high-grade urothelial carcinoma. First, immunohistochemistry (IHC) testing for HER2 should be performed. A fluorescence in situ hybridization (FISH) test is not required if the HER2 IHC test results are either negative (0 or 1+ score) or positive (3+ score), while a reflex FISH testing is recommended for HER2 IHC-equivocal (2+ score) tumors. The tumors with a 3+ score are considered

cation in High-Grade
on 2018 ASCO/CAP Clinical





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Determinants of sensitivity to HER2-targeted antibody drug conjugates in urothelial cancer

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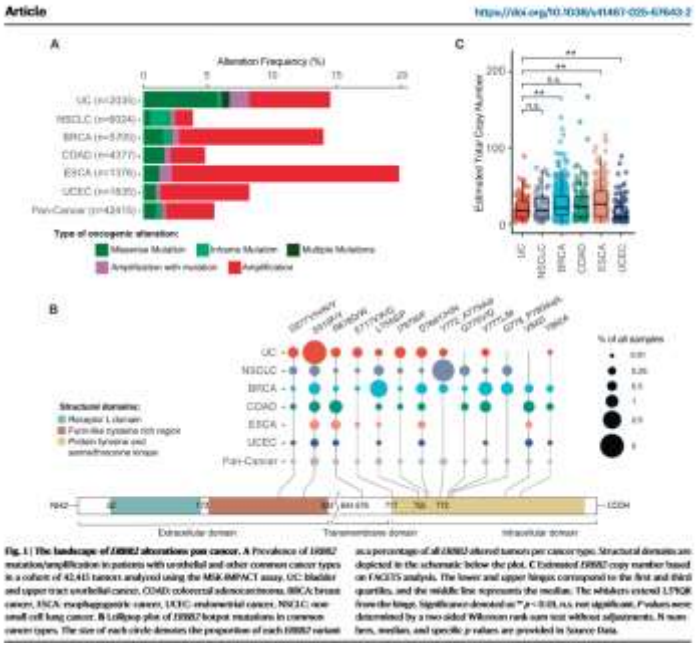

Fig. 1 | The landscape of *ERBB2* alterations pan cancer. **A** Prevalence of *ERBB2* mutation/amplification in patients with urothelial and other common cancer types in a cohort of 42,415 tumors analyzed using the MSK-IMPACT assay. UC: bladder and upper tract urothelial cancer, COAD: colorectal adenocarcinoma, BRCA: breast cancer, ESCA: esophagogastric cancer, UCEC: endometrial cancer, NSCLC: non-small cell lung cancer. **B** Lollipop plot of *ERBB2* hotspot mutations in common cancer types. The size of each circle denotes the proportion of each *ERBB2* variant as a percentage of all *ERBB2*-altered tumors per cancer type. Structural domains are depicted in the schematic below the plot. **C** Estimated *ERBB2* copy number based on FACETS analysis. The lower and upper hinges correspond to the first and third quartiles, and the middle line represents the median. The whiskers extend 1.5*IQR from the hinge. Significance denoted as **$p < 0.01$, n.s. not significant. *P* values were determined by a two-sided Wilcoxon rank sum test without adjustments. N numbers, medians, and specific *p* values are provided in Source Data.

- Las alteraciones en HER/ERBB2 están presentes en un 14.5% de los carcinomas uroteliales (amplificaciones y mutaciones), con heterogenicidad significativa entre los distintos subtipos y estadios.
- Existe discordancia entre el primario y las metastasis. En 30 con primario y MTS (12 fueron discordantes; 5 solo en el primario y 7 solo en la MTS)
- En ensayos con trastuzumab deruxtecan, co-mutación y amplificación de *ERBB2* se asoció con repuesta clínica excepcional
- Las alteraciones de HER2 se correlacionan con mayor estadio, mayor grado histológico, metástasis ganglionares y un fenotipo más agresivo.
- En cáncer vesical músculo-invasivo, la positividad para HER2 se asocia con menor respuesta a quimiorradiación y a terapias trimodales de preservación vesical.
- Los ADCs anti-HER2, como trastuzumab deruxtecán y disitamab vedotina, han demostrado actividad clínica significativa en enfermedad metastásica, incluso en tumores con baja expresión de HER2.
- Los subtipos luminales presentan mayor frecuencia de alteraciones en ERBB2, lo que puede orientar la selección de terapias dirigidas.
- La evaluación precisa del estado de HER2 mediante inmunohistoquímica y, cuando es necesario, pruebas de amplificación génica, es esencial para identificar candidatos a terapias anti-HER2.

- HER 2 +: 6,7-37,5% pacientes
- HER 2 LOW: 13,4-56,3% de los pacientes

Tumores de vía urinaria alta mayor expresión de HER2

Subtipo Luminal también tiene mayor expresión

Wester 2002	Observational	21	81.0%	>67% of tumor cells should be stained; staining should be moderate to intense (++ or +++); staining pattern should be membranous, with or without concomitant cytoplasmic staining; Dako anti-HER2 rabbit polyclonal antibody A0485 (IHC)
Carlsson 2015	Observational	72	83.3%	IHC 2+ or 3+; Dako anti-HER2 rabbit polyclonal antibody A0485 (IHC)
Weighted average: 25.4%				
Earlier stage UC				
Lae 2010	Observational	1,005	11.4%	IHC 2+ or 3+; Dako anti-HER2 rabbit polyclonal antibody A0485 (IHC)
Kiss 2017*	Observational	127	18.9%	IHC 3+; Dako HercepTest (IHC)
Mejri 2014	Observational	21	19.0%	IHC 2+ or 3+; Leica antibody NCL-N-CB11 (IHC)
Eriksson 2017	Observational	292	21.1%	HER2 amplified tumors with IHC 2+ or 3+ in >10% of cells; Ventana PATHWAY anti-HER-2/neu (4B5) (IHC)
Narase 2010	Observational	46	21.7%	IHC 3+; Dako HercepTest (IHC)
Kosaai 2021*	Observational	32	25.0%	IHC 2+ or 3+; N/A
Coogan 2004	Observational	54	26.0%	IHC 2+ or 3+; Ventana monoclonal anti-human HER-2 protein CB11 (IHC)
Jimenez 2001	Observational	80	27.5%	IHC 2+ or 3+; Dako c-erbB-2 primary antibody (IHC)
Bolenz 2010	Observational	134	28.1%	IHC 1+, 2+, or 3+ (in ≥10% of tumor cells); Dako anti-HER2 rabbit polyclonal antibody A0485 (IHC)
Chiang 2019	Observational	41	29.3%	IHC 2+ or 3+; Ventana Benchmark (IHC)
Soria 2016	Observational	354	35.6%	IHC 2+ or 3+; Dako HercepTest (IHC)
Hansel 2008*	Observational	53	35.8%	IHC 2+ or 3+; Ventana PATHWAY anti-HER-2/neu (4B5) (IHC)
Matsubara 2008	Observational	40	42.5%	IHC 2+ or 3+; Dako HercepTest (IHC)
Leite 2021	Observational	25	44.0%	N/A; Biocare EP3 clone (IHC)
Rotterud 2005	Observational	19	47.4%	++ or +++; BioGenex StrAviGen MultiLink Kit (IHC)
Tabriz 2021*	Observational	84	52.4%	IHC 2+ or 3+; Dako anti-HER2 rabbit polyclonal antibody A0485 (IHC)
Kolla 2008	Observational	90	55.6%	IHC 2+ or 3+; BioGenex CB11 antibodies (IHC)
Chakravarti 2005	Pooled analysis of clinical trials	55	60.0%	IHC 1+, 2+, or 3+; Zymed (IHC)
Latif 2003	Observational	25	76.0%	IHC 2+ or 3+; Ventana monoclonal anti-human HER-2 protein CB11 (IHC), Vysis (FISH)

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HER2 expression in urothelial carcinoma, a systematic literature review

Emilie Scherrer, Ashley Kang, Lisa M. Bloudek and Vadim S. Koshkin

TABLE 4 Overview of HER2+ across all studies.

Study	Study design	N	HER2+	HER2+ criteria and assay
LA/mUC				
Bellmunt 2015	Observational	93 (Greece)/88 (Spain)	4.3% (Greece)/21.6% (Spain)	IHC 3+; N/A
Fleischmann 2011	Observational	150	8.7%	IHC 2+ or 3+; Dako HercepTest (IHC), Abbott/Vysis PathVysion HER2 DNA Probe Kit (FISH)
Grigg 2021	Observational	85	10.6%	2018 ASCO/CAP guidelines for breast cancer; Ventana PATHWAY anti-HER-2/neu (4B5) (IHC)
Oudard 2015	Clinical trial, phase II	563	10.8%	IHC 2+ or 3+ and FISH+; Dako HercepTest (IHC), Dako HER2 FISH pharmDx Kit (FISH)
Powles 2017	Clinical trial, phase III	446	13.5%	IHC 2+ or 3+; Novocastra antibodies HER2 (NCL-CBE-356) (IHC)
Rink 2012	Observational	22	18.2%	IHC 3+; CTC Veridex CellSearch tumor phenotyping reagent HER2/neu (IHC)
de Pinieux 2004	Observational	36	25.0%	+++; Novocastra HER-2/neu antibody CB11 (IHC)
Zhou 2021	Clinical trial, phase Ib/II	14	28.6%	IHC 3+; IHC 2+ and ISH+; N/A
Sheng 2021	Clinical trial, phase II	133	32.3%	IHC 2+ or 3+; Ventana PATHWAY anti-HER-2/neu (4B5) (IHC)
Banerji 2019	Clinical trial, phase I	16	37.5%	ASCO/CAP guidelines for breast and gastric cancer; IHC 3+ or ISH+; N/A
Wülfing 2009	Clinical trial, phase II	57	43.9%	IHC 2+ or 3+; Dako HercepTest (IHC)
Nocchi 2013	Observational	52	46.2%	IHC 2+ or 3+; N/A
Soria 2017	Observational	152	47.0%	IHC 2+ or 3+; Dako HercepTest (IHC)
Hussain 2007	Clinical trial, phase II	109	52.3%	IHC 2+ or 3+; Dako HercepTest (IHC)
Goodman 2016	Observational	11	54.5%	IHC 2+ or 3+; Dako HER2 monoclonal mouse anti-human (IHC)
Kumar 2015	Observational	9	66.7%	IHC 2+ or 3+; Novocastra HER-2/neu monoclonal antibody clone CB11 (IHC)
Gandour-Edwards 2002	Observational	39	71.8%	IHC 2+ or 3+; BioGenex c-erbB2 primary antibody (IHC)

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).

C. HER2 (ERBB2) Testing

Scientific rationale: A subset of breast carcinomas (approximately 15% to 20%) overexpress human epidermal growth factor receptor 2 (HER2; HUGO nomenclature *ERBB2*). Protein overexpression is usually due to gene amplification. Assays for gene copy number, mRNA quantity, and protein generally give similar results; gene amplification correlates with protein overexpression in about 95% of cases. In a small subset of carcinomas (probably <5%), protein overexpression may occur by different mechanisms. Overexpression is both a prognostic and predictive factor.

Clinical rationale: HER2 status is primarily evaluated to determine patient eligibility for anti-HER2 therapy. It may identify patients who have a greater benefit from anthracycline-based adjuvant therapy.

Methods: HER2 status can be determined in formalin-fixed paraffin-embedded tissue by assessing protein expression on the membrane of tumor cells using IHC or by assessing the number of HER2 gene copies using in situ hybridization (ISH). When both IHC and ISH are performed on the same tumor, the

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

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

Breast cancers with HER2 IHC score 1+ or HER2 IHC score 2+ and a negative ISH result are eligible for clinically appropriate HER2-targeted therapy and may be reported as “HER2 Low”.

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REVIEW

Cell-free Tumor DNA: a Promising Technology for Diagnosis, Surveillance and Therapeutic Decision in Urothelial Carcinoma of the Bladder

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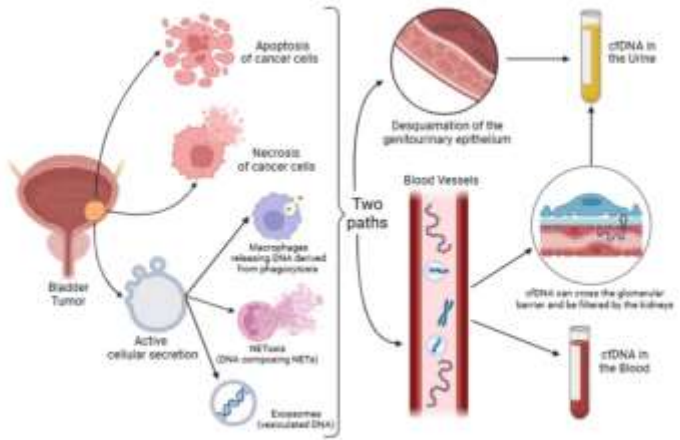

Fig. 1 Cell-free tumor DNA synthesis and elimination

Table 1 Recent studies using ctDNA / utDNA in urothelial carcinoma of the bladder

Possible use	*Biomarker*	*Study*	*Resumed findings*
Diagnosis	**utDNA**	*Cheng* et al. (2019) [21]	utDNA methylation and copy number aberration detected BC with a 93,5% sensitivity and a 95.8% specificity
	utDNA	*Xu* et al. (2019) [47]	Urine PCR showed 71% sensitivity, 88,6% specificity and AUC of 0.862 for BC diagnosis
	utDNA	*Zeng* et al. (2020) [46]	utDNA analysis with a sensitivity of 82.5%, specificity of 96,9% and accuracy of 89%
	utDNA	*Xu* et al. (2020) [48]	utDNA methylation identified upper tract carcinoma with 94% sensitivity and 93,1% specificity [AUC 0.961]
	ctDNA	*Klein* et al. (2021) [49]	BC identified via methylation ctDNA in stages I (33.3%), stage II (9.1%), stage III (75%) and stage IV (100%)
Prognosis	**ctDNA**	*Puntoni* et al. (2016) [53]	Serum VEGF in ctDNA found to be an independent prognostic factor for OS and BC specific survival
	ctDNA	*Christensen & Birkenkamp-Demtröder* et al. (2019) [22]	ctDNA post NAC associated with disease recurrence and pathological downstaging
	ctDNA	*Shohdy* et al. (2020) [54]	ctDNA measurements can predict durable treatment response in 90% of patients
	ctDNA	*Grivas* et al. (2020) [55]	ctDNA alterations (BRCA1 and RAF1) predicted shorter OS and failure-free survival
Therapy response	**ctDNA**	*Rosenberg* et al. (2016) [56]	The mutational load found in ctDNA was higher in metastatic BC patients with response to immunotherapy compared to non-responders
	ctDNA	*Powles* et al. (2021) [51]	ctDNA detected post-resection in 37% of the patients and associated with worse outcomes / ctDNA detection associated with improved response to adjuvant immunotherapy
	ctDNA	*Vandekerkhove* et al. (2021) [57]	Mutations of ERCC2 in ctDNA were associated with increased cisplatin-based chemotherapy sensitivity and improved PFS
	ctDNA	*Christensen* et al. (2023) [58]	ctDNA in blood prior to NAC and ctDNA in blood or urine after NAC were associated with lower response rates
	ctDNA	*Zang* et al. (2023) [59]	ctDNA copy number abnormalities could predict immunotherapy response with 90% accuracy
Disease recurrence	**utDNA**	*Birkenkamp-Demtroder* et al. (2016) [60]	Higher utDNA was found in patients with disease progression to MIBC compared to NMIBC recurrence
	utDNA	*Dudley* et al. (2019) [61]	utDNA detected in 91% of patients with recurrence, 2.7 months before clinical detection
	ctDNA	*Christensen & Birkenkamp-Demtröder* et al. (2019) [22]	ctDNA prior to NAC identified metastatic relapse with 100% sensitivity and 98% specificity / ctDNA detection was observable 96 days before imaging signs
	ctDNA	*Szabados* et al. (2022) [39]	ABBACUS trial—ctDNA was undetectable in patients with stable disease and detectable in 83% of patients with recurrence
	ctDNA	*Carrasco* et al. (2023) [62]	ctDNA predictive of tumor progression before cystectomy, 4 and 12 months after surgery
	utDNA	*Vedeld* et al. *(2023)* [46]	utDNA presented a sensitivity of 91% with < 1% false positive results and detected recurrence earlier than cystoscopy in 48% of the cases

Key: *ctDNA* Circulating Tumor DNA, *utDNA* Urinary Tumor DNA, *BC* Bladder Cancer, *AUC* Area Under the Curve, *OS* Overall Survival, *NAC* Neoadjuvant Chemotherapy, *PFS* Progression Free Survival, *MIBC* Muscle Invasive Bladder Cancer, *NMIBC* Non-Muscle Invasive Bladder Cancer

CONCLUSIONES

- La determinación de PD-L1 en biopsias de CU se ha ido adaptando, manteniéndose actualmente la determinación en Nivolumab.
- No se necesita determinar la expresión de Nectina-4 ni de Trop-2.
- Pacientes en los que se plantea tratamiento con inhibidores de FGFR (erdafitinib) es necesario el estudio molecular.
- HER2 se está consolidado como una diana terapéutica en el carcinoma urotelial, reforzando la importancia de su evaluación sistemática en la práctica clínica. Habrá una mayor demanda de determinación de HER2 en vejiga.

MUCHAS GRACIAS