ACTUALIZACIÓN EN
URO-ONCOLOGÍA:
UPDATE **2024**

Madrid, 28 de febrero de 2024

MESA 3. CÁNCER DE VEJIGA METASTÁSICO

¿Qué biomarcadores son realmente útiles en la práctica clínica?

Dra. Eugenia García Fernández
Servicio de Anatomía Patológica
Hospital Universitario La Paz
Coordinadora del grupo de Uropatología de la SEAP

OVERVIEW

- INTRODUCCIÓN
- PD1/PDL1 (pembrolizumab, nivolumab, avelumab)
- NECTINA-4 (enfortumab vedotin)
- FGFR (erdafitinib)
- HER2 (trastuzumab)

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Current Treatment Options in Oncology (2023) 24:1870–1888
DOI 10.1007/s11864-023-01151-7

Precision Medicine in Urothelial Carcinoma: Current Markers to Guide Treatment and Promising Future Directions

Eric J. Miller, MD
Matthew D. Galsky, MD[*]

Current guideline-directed precision medicine in urothelial cancer

Indications for molecular testing

Current National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for bladder cancer recommend molecular testing be obtained for patients with stage IVA and IVB disease, and that it be considered in the setting of stage IIIB disease. At the present

PRINCIPLES OF SYSTEMIC THERAPY

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

PRINCIPLES OF SYSTEMIC THERAPY

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]

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]

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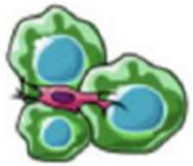
[2] Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
* Correspondence: katimsa@mskcc.org (A.B.K.); kimk1@mskcc.org (K.K.)

ONCOLOGÍA:

% of MIBC	24%	8%	15%	15%	35%	3%
Class Name	Luminal Papillary (LumP)	Luminal Non-Specified (LumNS)	Luminal Unstable (LumU)	Stroma-rich	Basal/Squamous (Ba/Sq)	Neuroendocrine-like (NE-like)
						
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 + PPARG + CDKN2A -	PPARG +	PPARG + E2F3 +, ERBB2 + Genomic instability Cell cycle +		EGFR +	TP53 -, RB1 -, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)*
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology (59%)	Micropapillary variant (36%)			Squamous differentiation (42%)	Neuroendocrine differentiation (72%)
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

* 94% of these tumors present either RB1 mutation or deletion

Current best practice for bladder cancer: a narrative review of diagnostics and treatments

Eva Compérat, Mahul B Amin, Richard Cathomas, Ananya Choudhury, Maria De Santis, Ashish Kamat, Arnulf Stenzl, Harriet C Thoeny, Johannes Alfred Witjes

	Molecular subtype	Possible therapy approaches
Papillary morphology (59%*)	Luminal papillary	NAC or FGFR3 inhibitors
Micropapillary variant (36%*)	Luminal non-specified	Checkpoint inhibitors, anti-PD-L1, PD-1, or CTL4NAC
Micropapillary variant (36%*)	Luminal unstable	Targeted therapies
Micropapillary variant (36%*)	Stroma rich	..
Urothelial carcinoma with divergent differentiation, squamous	Basal or squamous	Checkpoint inhibitors or cisplatin-based combination neoadjuvant chemotherapy
Urothelial carcinoma with divergent differentiation, neuroendocrine	Neuroendocrine-like	Etoposide or cisplatin-based NAC

*Prevalence of this histology in the respective molecular subtype. Adapted from Kamoun and colleagues.[22]

Table 1: **Tumour subtypes**

	Enfortumab vedotin[1,89]	Erdafitinib[3,90] targeting FGFR2 and FGFR3 mutation or fusion	Sacituzumab govitecan[4,5]	RC48 HER2 positive[6]
Cohort size, n	125	99	113	43
Median follow-up, months	22·3	24	..	..
ORR	44%	40% (95% CI 31–50)	27% (95% CI 19–37)	51·2%
ORR, liver metastasis	38%	35%	33·3% (5 of 15)[5]	70% (14 of 20)
ORR in previous immunotherapy responders	56%	59%	23·5%[5]	62·5%
Duration of response, months	7·6	6·03	5·9	..
Progressive disease	23 (18%)	18%	..	..
Progression-free survival, months	5·8	5·5 (95% CI 4·0–6·0)	5·4 (95% CI 3·5– 6·9)	Immature
Median overall survival, months; median overall survival previous immunotherapy, months	12·4 (95% CI 9·46–15·57)	11·3 (95% CI 9·7–15·2);[3] 10·9	10·5 (95% CI 8·2–12·3)	Immature
12-month overall survival rate	50·4%	55%	..	..
18-month overall survival rate	34·2%	..	..	..
24-month overall survival rate	..	31%	..	..
Time to response, months	1·8	1·4	1·6	..

ORR=overall response rate.

Table 2: **Emerging treatments for metastatic muscle-invasive bladder cancer**

OVERVIEW

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- PD1/PDL1 (pembrolizumab, nivolumab, avelumab)
- NECTINA-4 (enfortumab vedotin)
- FGFR (erdafitinib)
- HER2 (trastuzumab)

World Journal of Urology (2021) 39:1345–1355
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

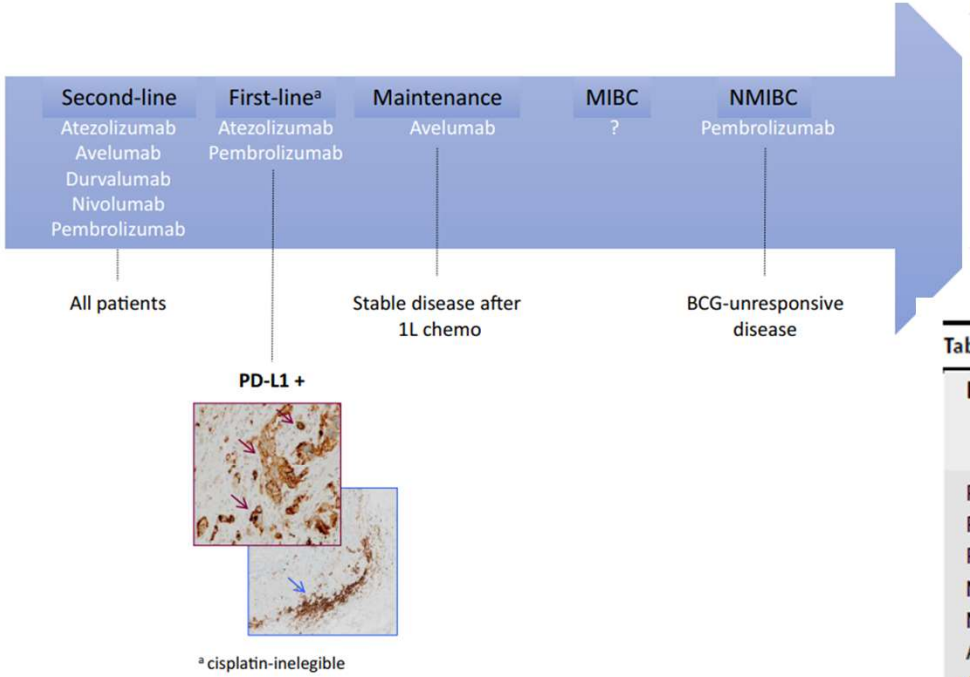

Fig. 3 Indications for anti-PD-L1 monoclonal antibody in UC

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

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TOPIC PAPER

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

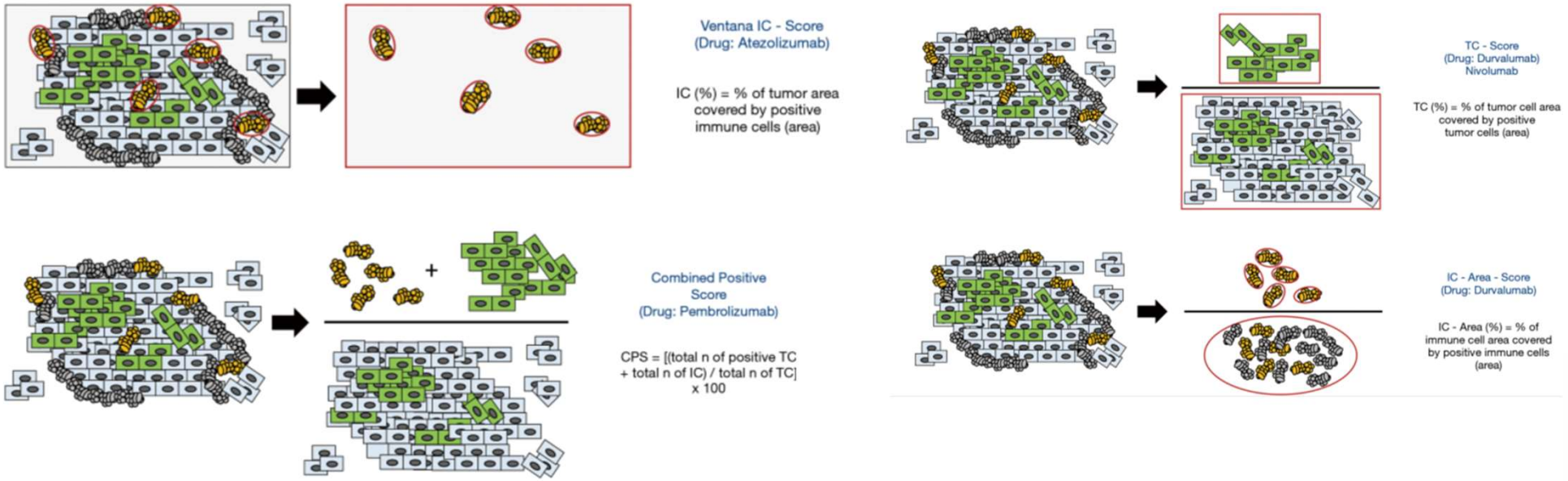
Mathieu Rouanne[1,2] · Camélia Radulescu[3] · Julien Adam[4,5] · Yves Allory[3,6,7]

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

Table 1 Methods for PD-L1 scoring methods across trials and PD-L1 assays

Assay (clone)	28-8	22C3	SP142	SP263
Drug	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Score	Percentage of tumor cells (TC)	Combined positive score (0–100)	Immune cells (IC) score	TC/IC ≥ 25%
Numerator	Number of PD-L1 + tumor cells	Number of PD-L1 + tumor or immune cells	Tumor area occupied by PD-L1 + IC	Number of PD-L1 + tumor cells or immune cells
Denominator	Number of tumor cells	Number of tumor cells	Total viable tumor area	Number of tumor cells or immune cells
Main threshold(s) in UC	≥ 5%	≥ 10	≥ 5% (IC2), ≥ 1% (IC1)	≥ 25% (TC) or ≥ 25% (IC)

TC tumor cells, *IC* immune cells



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

Tabla 2 Recomendaciones de la SEAP para la determinación de PD-L1 en carcinoma urotelial

Pacientes a evaluar

Todos los estadios avanzados y recomendable en pacientes estadio ≥ T2

Recomendaciones sobre la muestra óptima para la determinación de PD-L1

- Seleccionar la muestra más representativa procedente de la RTU, cistectomía o metástasis, siempre que tenga carcinoma infiltrante (> 100 células tumorales invasivas). Se ha demostrado buena/moderada concordancia entre muestras de cistectomía vs. RTU
- Utilizar la muestra más reciente próxima al inicio de la terapia, preferiblemente con antigüedad < 1 año (el 22C3 admite muestras de hasta 5 años). Preferiblemente usar muestra de tumor primario (> expresión que en metástasis)
- Seleccionar microscópicamente el bloque que tenga menor artefacto, sin necrosis y sin excesivo tejido
- Fijación en formol tamponado al 10% y volumen 10 veces más que el tejido. La muestra debe ser fijada de inmediato y lo más rápido posible
- En biopsias de metástasis óseas, aunque se consideran una opción peor, la decalcificación en EDTA es preferible
- En casos de gran heterogeneidad en la expresión de PD-L1, puede hacerse la determinación en más de un bloque. En casos mixtos de carcinoma urotelial convencional y subtipo/s, valorar la expresión de PD-L1 en cada subtipo
- Aunque no se desaconseja volver a valorar la expresión de PD-L1 tras el tratamiento previo, no utilizar muestras obtenidas inmediatamente después de tratamientos de quimioterapia, inmunoterapia o radioterapia

Equivalencia de los anticuerpos anti-PD-L1 disponibles en carcinoma urotelial

- Múltiples estudios de concordancia en carcinoma urotelial avalan el uso equivalente del 22C3 (Dako), 28.8 (Dako) o SP263 (Ventana) a pesar de los anticuerpos utilizados en el CheckMate274 (28.8) y en el JAVELIN Bladder 100 (SP263)
- El SP142 no se considera intercambiable con el resto. En ningún caso se recomienda usar el SP142 (Ventana) para la selección de pacientes para avelumab o nivolumab

¿Qué hacer si es negativo en la primera determinación?

- Si la metodología preanalítica ha sido correcta, no habría en principio motivos para confirmar la negatividad de una tinción utilizando otra sección del mismo bloque ni de otro bloque de la misma muestra
- Aunque no existen datos fiables sobre el valor de repetir la determinación en las metástasis de casos con primarios negativos, en general se podría valorar realizar la determinación en la metástasis para valorar cambios en la expresión de PD-L1

Comunicación del resultado al clínico

En el informe de resultado de PD-L1 debe constar:

- Tipo histológico del tumor, si la muestra procede del primario o la metástasis, especificar localización anatómica y los controles ± pertinentes
- El tipo de anticuerpo
- Plataforma de IHQ (Dako, Ventana)
- Porcentaje de células tumorales e inmunes positivas, y también CPS si se considera oportuno
- Si se observa expresión se recomienda indicar: «tumor con expresión proteica positiva en células tumorales y/o células inmunes» según proceda

Elección de la muestra

Equivalencias

Informe

Revista Española de Patología 56 (2023) 261–270

SEAP-IAP

Patología

www.elsevier.es/patologia

REVISIÓN

Aspectos prácticos sobre la determinación de PD-L1 en el tratamiento de carcinoma urotelial. Consenso del [illegible] de la SEAP

[illegible] González-Peramato[b], Julián Sanz-Ortega[c], Juan Daniel Prieto Cuadra[d], Isabel Trias[e], Rafael J. Luque Barona[f], María Eugenia Semidey[g], Pablo Maroto[h] y Ferran Algaba[i,*]

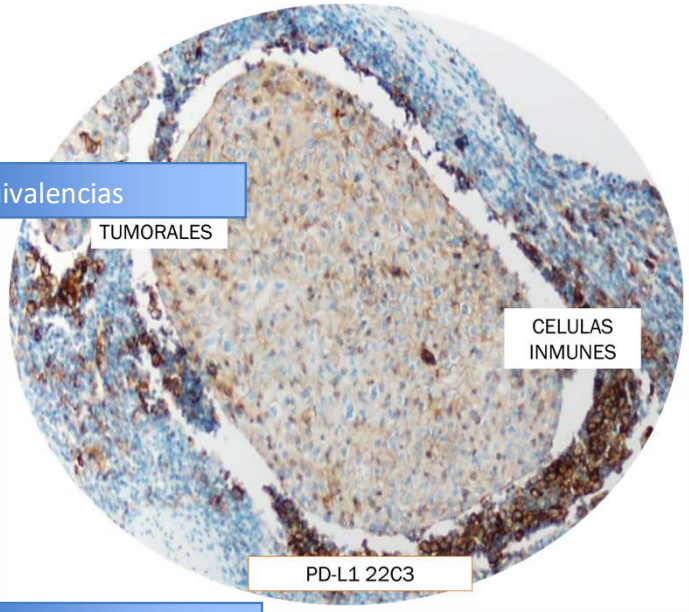


Tabla 1 Fármacos de inmunoterapia en carcinoma urotelial aprobados, asociados a PD-L1 como biomarcador y algoritmos de utilización en ensayos clínicos

Inhibidor del punto de control inmunitario Ensayo clínico (año)	Escenario	Ensayo diagnóstico (fabricante)	Definición de positividad para la expresión de PD-L1 (algoritmo)	Indicación EMA
Atezolizumab				
IMvigor 210 (2016)[41]	Primera línea	SP142 (Ventana)	> 5% de CI	Tecentriq® en monoterapia está indicado para el tratamiento de pacientes adultos con CU localmente avanzado o metastásico: en los que no son considerados aptos para el tratamiento con cisplatino cuyos tumores tengan una expresión de PD-L1 > 5%
Nivolumab				
CheckMate274 (2021)[9]	Adyuvancia	28.8 (Dako)	≥ 1% de CT	Opdivo® en monoterapia está indicado para el tratamiento adyuvante de adultos con carcinoma urotelial músculo invasivo (CUMI) con expresión de PD-L1 en células tumorales ≥ 1%, con alto riesgo de recurrencia después de someterse a resección radical del CU
Pembrolizumab				
KEYNOTE-052 (2017)[42]	[illegible] línea	22C3 [illegible]	CPS ≥ 10	[illegible] en monoterapia está indicado para el tratamiento del CU localmente avanzado o metastásico en adultos que no son candidatos a quimioterapia basada en cisplatino y cuyos tumores expresen PD-L1 con un CPS ≥ 10
Avelumab				
JAVELIN Bladder 100 (2020)[4]	Mantenimiento en primera línea en ausencia de progresión a quimioterapia	SP263 (Ventana)	≥ 25% de CT; o ≥ 25% de CI si > 1% del área del tumor contenía CI; o 100% de las CI si ≤ 1% del área del tumor contenía CI Análisis exploratorio adicional[a]	Bavencio® está indicado en monoterapia para el tratamiento de mantenimiento de primera línea de los pacientes adultos con CU localmente avanzado o metastásico libres de progresión después de recibir quimioterapia basada en platino independientemente de la expresión de PD-L1 *En España, Bavencio® está financiado en monoterapia para el tratamiento de mantenimiento en primera línea de los pacientes adultos con tumores PD-L1 positivos*[b]

CI: células inmunitarias; CPS: combined positive score (puntuación positiva combinada); CT: células tumorales; CU: carcinoma urotelial; CUMI: carcinoma urotelial músculo invasivo; EMA: Agencia Europea del Medicamento.

[a] Adicionalmente, se revisan los datos de un análisis exploratorio de eficacia del JAVELIN Bladder 100 con un corte de positividad para PD-L1 de ≥ 1% de las CT positivas o ≥ 1% de las CI positivas.

[b] Resolución de financiación para la indicación de Bavencio® de la Dirección General de Cartera Común de Servicios del SNS y Farmacia.

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REVISIÓN

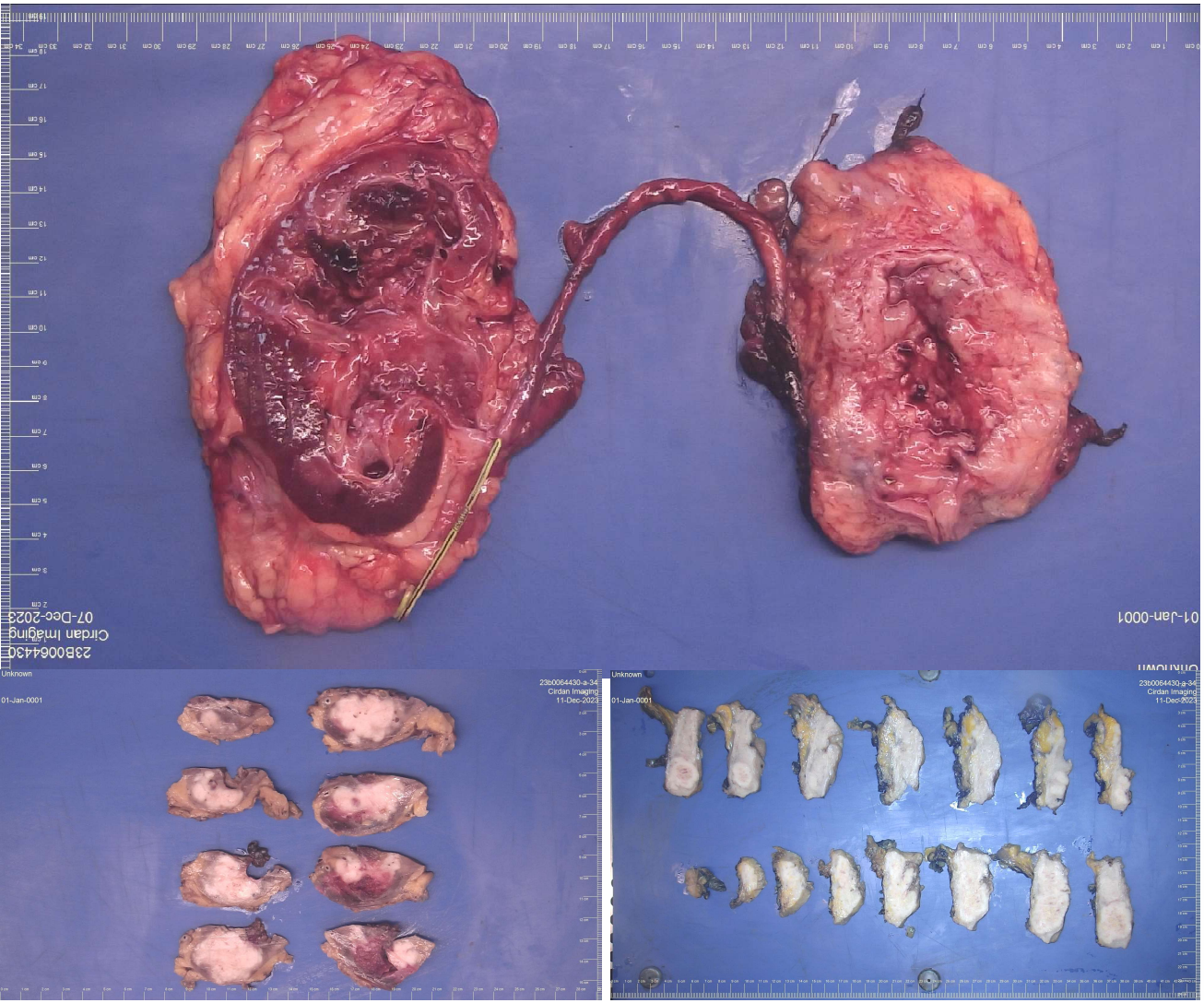
Aspectos prácticos sobre la determinación de PD-L1 en el tratamiento de carcinoma urotelial. Consenso del grupo de uropatología de la SEAP

Antonio López-Beltrán[a], Pilar González-Peramato[b], Julián Sanz-Ortega[c], Juan Daniel Prieto Cuadra[d], Isabel Trias[e], Rafael J. Luque Barona[f], María Eugenia Semidey[g], Pablo Maroto[h] y Ferran Algaba[i,*]

A petición del Servicio de Oncología Médica del Hospital Universitario La Paz se ha realizado determinación de PD-L1 en el bloque 23B-bloque 1 (RTU de VEJIGA) con los siguientes resultados:

Anticuerpo: 28-8.

- Plataforma de inmunohistoquímica: DAKO.
- Porcentaje de células tumorales positivas (TPS): 8%
- Porcentaje de células inmunes positivas: 2%
- CPS: 10



Se ha realizado determinación de PD-L1 en el bloque 23B64430-bloque 59 (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

Se ha realizado determinación de PD-L1 en el bloque 23B64430-bloque 44 (carcinoma urotelial en riñon) con

los siguientes resultados:

Anticuerpo: 28-8.

- Plataforma de inmunohistoquímica: DAKO.
- Porcentaje de células tumorales positivas (TPS): 0%
- Porcentaje de células inmunes positivas: 0%
- CPS: 0

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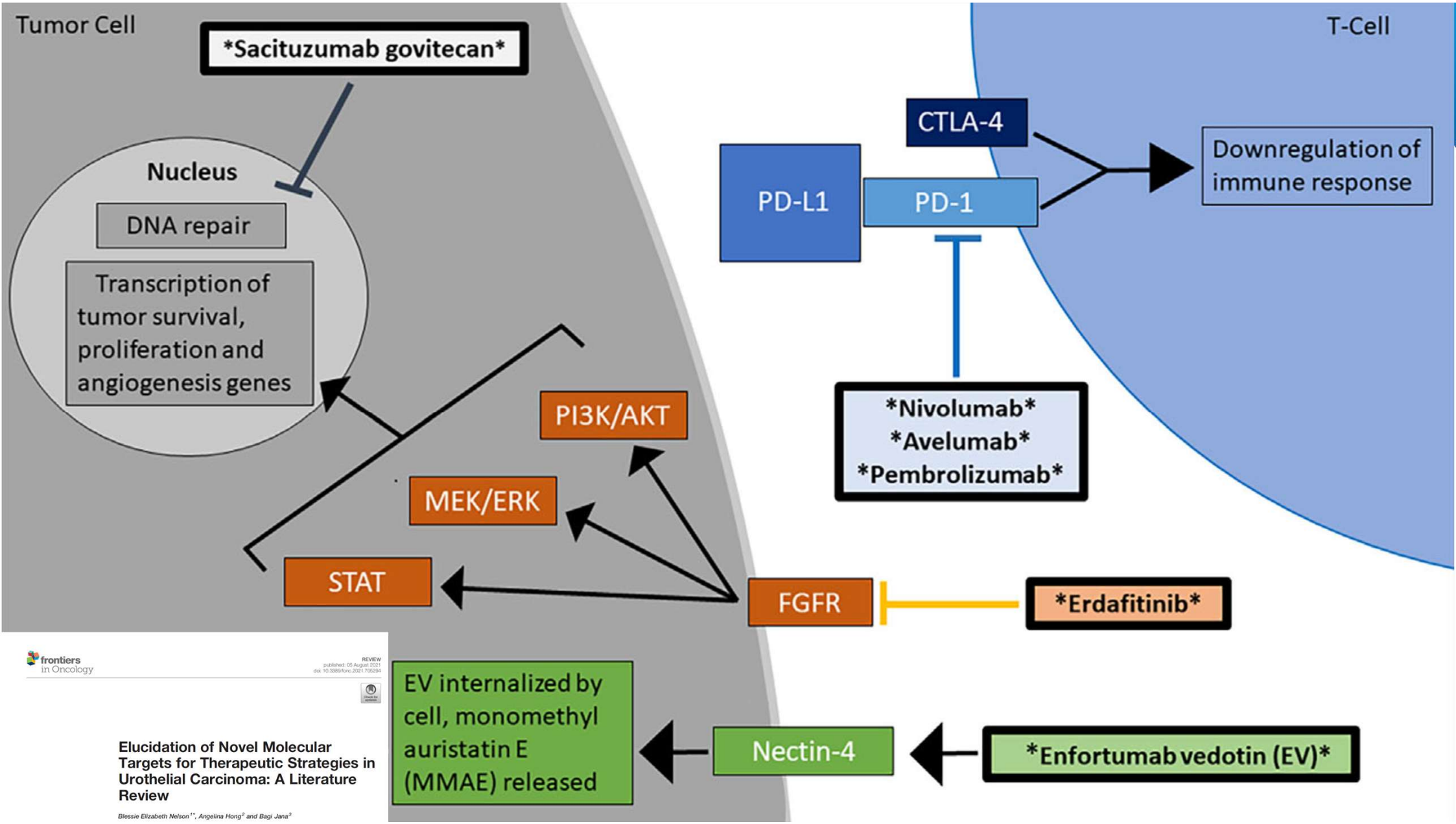
- NECTINA-4 (enfortumab vedotin)
- FGFR (erdafitinib)
- HER2 (trastuzumab)



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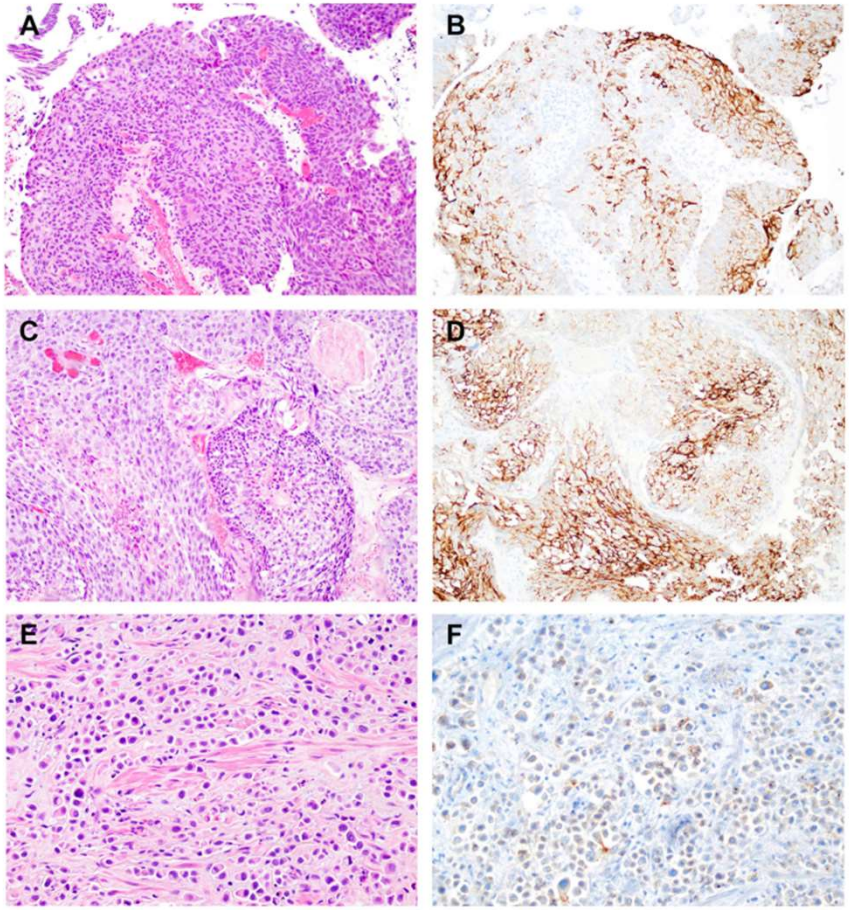
Elucidation of Novel Molecular Targets for Therapeutic Strategies in Urothelial Carcinoma: A Literature Review

Blessie Elizabeth Nelson[1], Angelina Hong[2] and Bagi Jana[3]*

ACTUALIZACIÓN EN **URO-ONCOLOGÍA:** UPDATE **2024**

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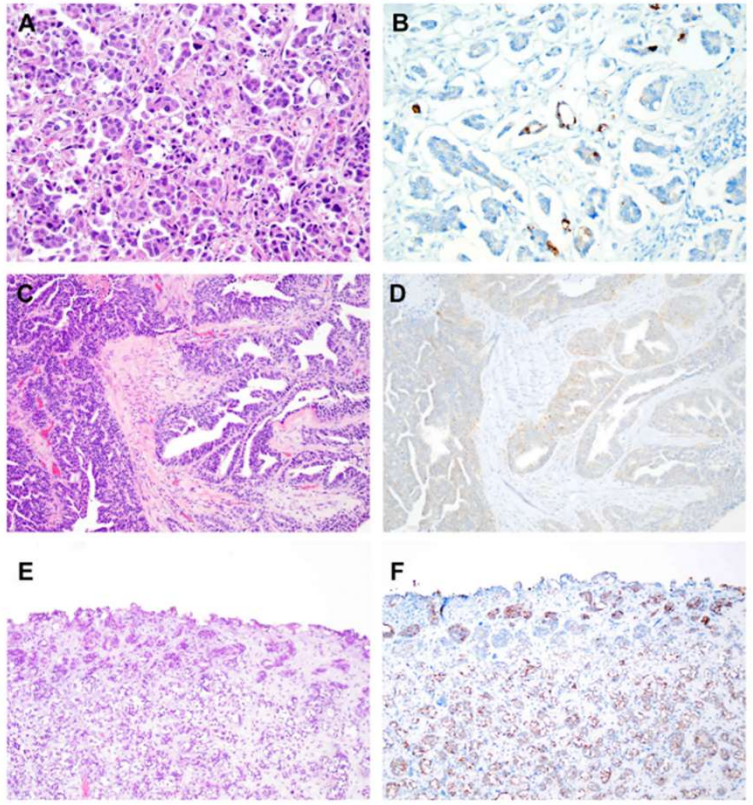
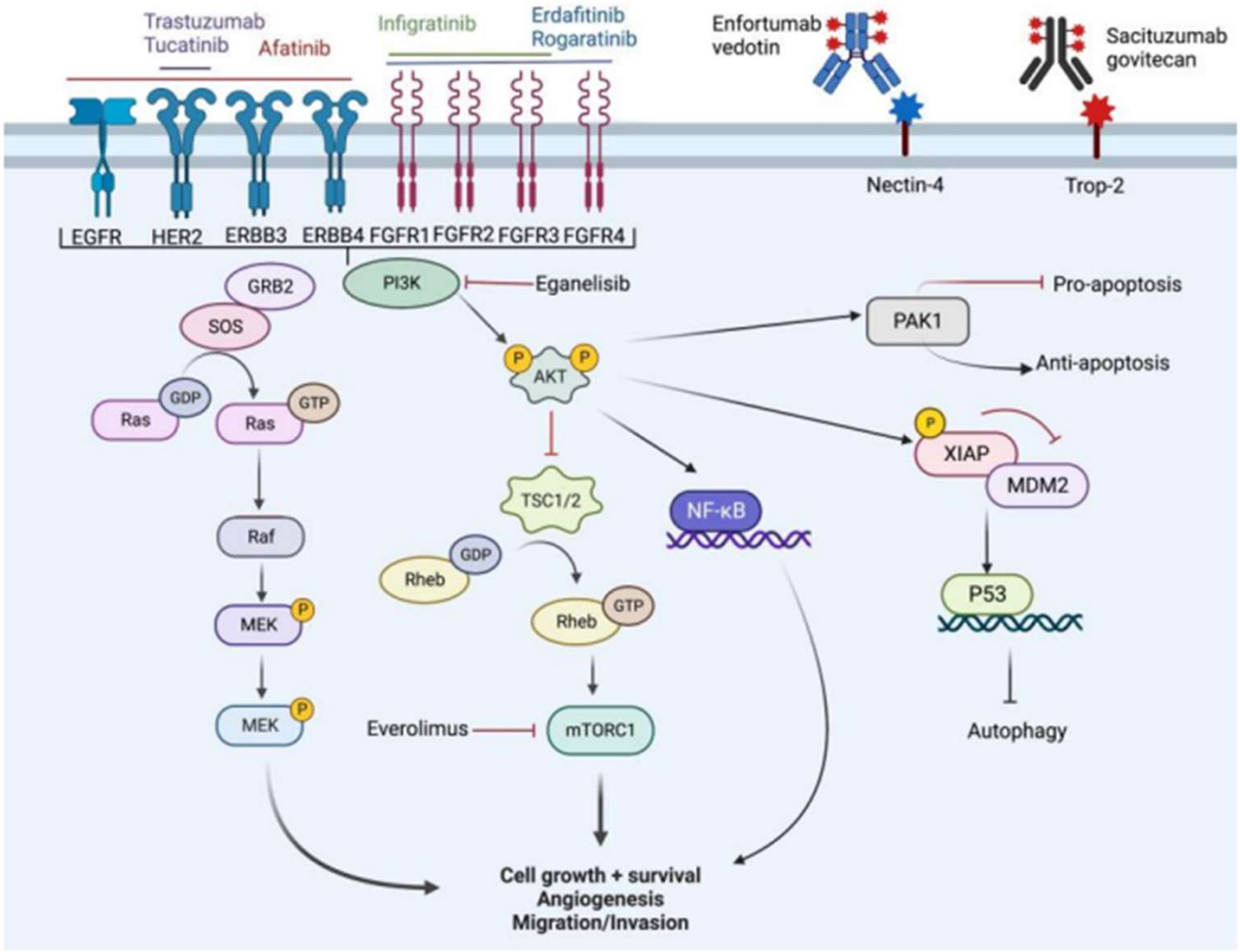
Expression of Nectin-4 in Bladder Urothelial Carcinoma and in Morphologic Variants and Non-Urothelial Histotypes

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



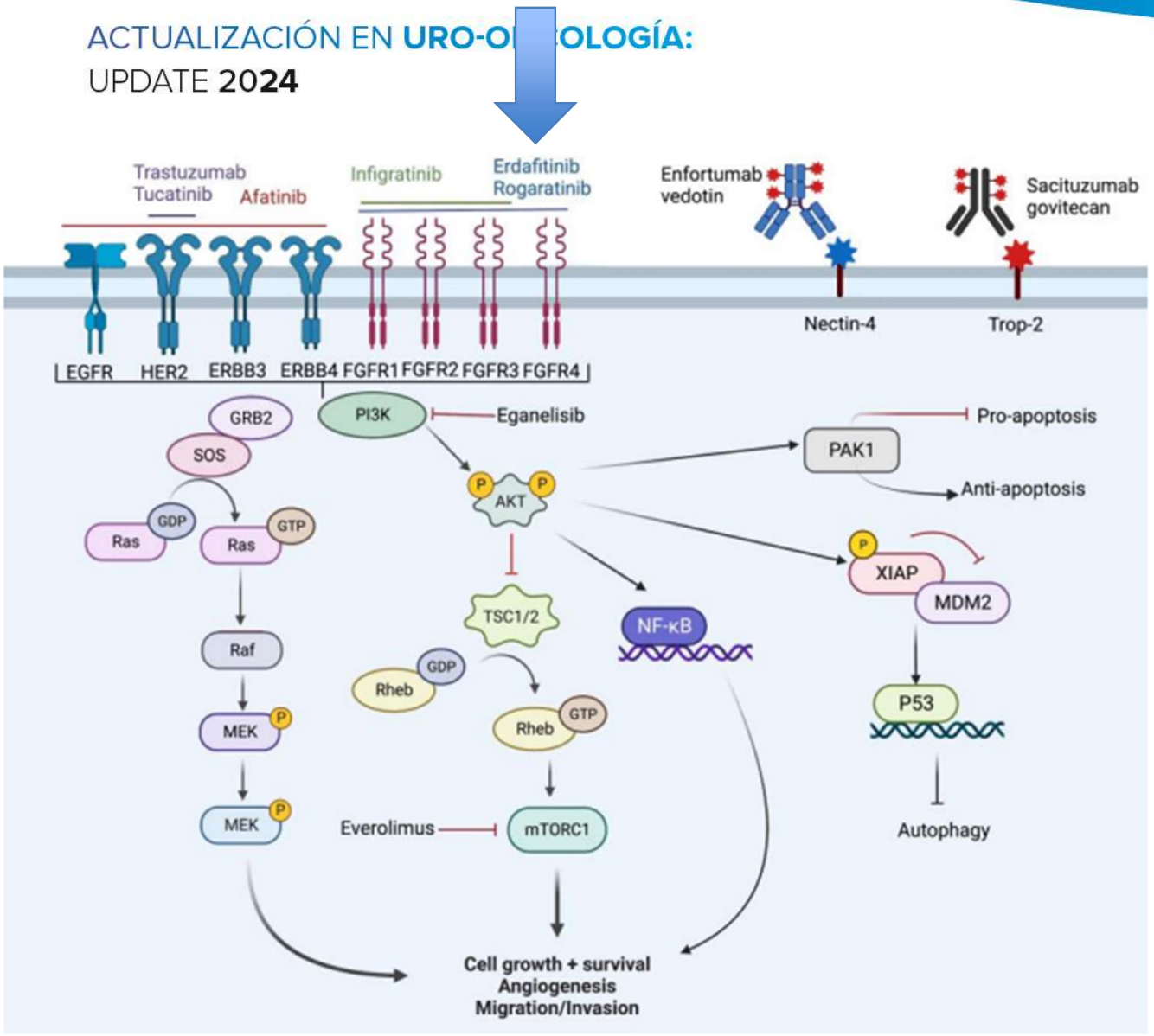


- Trop-2 (antígeno de superficie del trofoblasto). Aumentada en el CU y se correlaciona con empeoramiento de la enfermedad.
- SG es un anticuerpo anti Trop2 que se encuentra en la superficie de la célula tumoral e incorpora el inhibidor de la topoisomerasa I que rompe el DNA en la fase S de la mitosis.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

OVERVIEW

- INTRODUCCIÓN
- PD1/PDL1 (pembrolizumab, nivolumab, avelumab)
- NECTINA-4 (enfortumab vedotin)
- FGFR (erdafitinib)
- HER2 (trastuzumab)

ACTUALIZACIÓN EN URO-ONCOLOGÍA:
UPDATE 2024



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]

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- Los receptores de FGFR son codificados por 4 genes que, al activarse , activan vías de transducción.
- Normalmente la activación de estos receptores FGFR, son importantes en el desarrollo embrionario, metabolismo y reparación tisular. 7% de los tumores tienen alteraciones genéticas en el eje FGF y FGFR. Amplificaciones de FGFR1 se observa en 10% de los uroteliales, 3-5% en FGFR3 y FGFR2
- Mutaciones activadoras en FGFR3 en el 38-66% de los no invasivos y 15-20% de los invasivos

Table 1 – Patient and tumor characteristics of the 1000 patients (cT1-4aN0M0) who underwent radical cystectomy.

Age (yr), median (IQR)		68	58–73
Sex	Female	200	20%
pT stage at cystectomy	pTa/is/1	31/7/44	8.2%
	pT2	247	25%
	pT3	474	47%
	pT4	197	20%
Grade (WHO 1973)	G1	4	0.4%
	G2	81	8.1%
	G3	915	92%
Carcinoma in situ		347	35%
pN stage	pN0	621	62%
	pN+	379	38%
Lymph nodes removed, median (IQR)		12	7.3–18
Adjuvant radiotherapy	No	872	87%
	Yes	54	5.4%
	Unknown[a]	74	7.4%
Adjuvant chemotherapy	No	725	73%
	Yes	275	28%
FGFR3 mutation	All	107	11%
	S249C	67	6.7%//63%
	Other mutations	40	4.0%//37%
FGFR3 expression	Overexpression	279	28%
	Normal	721	72%
p53 expression	Overexpression	638	64%
	Low level	288	29%
	Unknown[a]	74	7.4%
City/hospital/laboratory	Regensburg	156	16%
	Toronto	104	10%
	Turku[b]	54	5.4%
	Rotterdam	147	15%
	Amsterdam	195	20%
	Erlangen	98	9.8%
	Paris	172	17%
	Madrid	74	7.4%
Total		1000	100%

EUROPEAN UROLOGY 78 (2020) 682–687

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journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority Brief Correspondence

Editorial by Ronan Flippot and Yohann Loriot on pp. 688–689 of this issue

FGFR3 Mutation Status and FGFR3 Expression in a Large Bladder Cancer Cohort Treated by Radical Cystectomy: Implications for Anti-FGFR3 Treatment?†

Bas W.G. van Rhijn[a,b,c,‡,], Laura S. Mertens[b,†], Roman Mayr[c,†], Peter J. Bostrom[a,d,‡], Francisco X. Real[e,f], Ellen C. Zwarthoff[g], Joost L. Boormans[h], Cheno Abas[g], Geert J.L.H. van Leenders[g,h], Stefanie Götz[c], Katrin Hippe[i], Simone Bertz[j], Yann Neuzillet[b], Joyce Sanders[k], Annegien Broeks[k], Michiel S. van der Heijden[l], Michael A.S. Jewett[a], Mirari Marquez[m], Robert Stoehr[j], Alexandre R. Zlotta[a], Markus Eckstein[j], Yanish Soorojebally[n], Hossain Roshani[o], Maximilian Burger[c], Wolfgang Otto[c], François Radvanyi[n], Nanor Sirab[n], Damien Pouessel[n,p], Bernd Wullich[q], Theo H. van der Kwast[r,§], Núria Malats[m,§], Arndt Hartmann[j,§], Yves Allory[n,s,§], Tahlita C.M. Zuiverloon[g,h,§,**]*

In conclusion, FGFR3 mutations identify patients with favorable BC at RC, regardless of FGFR3 expression. FGFR3 overexpression is not associated with prognosis in FGFR3 wild-type tumors. This suggests that FGFR3 mutations have a distinct functional role compared with FGFR3 overexpression. Ideally, the hypothesis that patients with FGFR3 mutations are more likely to benefit from anti-FGFR3 therapy than patients with FGFR3 overexpression only should be tested in further research.

FGFR + IT
Puede mejorar los efectos antitumorales de los inhibidores de FGFR y prevenir o retrasar la aparición de resistencia

4504 **Oral Abstract Session**

Erdafitinib (ERDA) vs ERDA plus cetrelimab (ERDA+CET) for patients (pts) with metastatic urothelial carcinoma (mUC) and fibroblast growth factor receptor alterations (FGFRa): Final results from the phase 2 Norse study.

Arlene O. Siefker-Radtke, Thomas Powles, Victor Moreno, Taek Won Kang, Irfan Cicin, Angela Girvin, Sydney Akapame, Spyros Triantos, Anne O'Hagan, Wei Zhu, Meggan Tammaro, Yohann Loriot; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St. Bartholomew's Hospital, London, United Kingdom; START Madrid-FJD, Fundación Jiménez Díaz, University Hospital, Madrid, Spain; Department of Urology, Chonnam National University Medical School, Gwangju, South Korea; Department of Medical Oncology, Trakya University Faculty of Medicine, 22030, Edirne, Turkey; Janssen Research & Development, Spring House, PA; Janssen Research & Development, Raritan, NJ; Gustave Roussy and Paris Saclay University, Villejuif, France

Background: First-line (1L) therapy for cisplatin (cis)-ineligible pts with mUC remains an unmet need and includes alternative chemotherapy or anti-PD-(L)1 monotherapy for PD-L1 positive tumors. FGFRa tumors are enriched for the luminal 1 subtype with lower immune cell infiltrate and potential lower benefit from anti-PD-(L)1 monotherapy. We studied ERDA+CET in 1L, FGFRa, mUC to determine the potential impact in this setting (NCT03473743). **Methods:** Pts aged ≥ 18 y with mUC, susceptible FGFRa and measurable disease (no prior systemic therapy for mUC, cis-ineligible) were randomized 1:1 to once-daily ERDA 8 mg (with pharmacodynamically guided uptitration (UpT) to 9 mg) or ERDA 8 mg (no UpT) + IV CET 240 mg every 2 weeks (wks) at cycles 1-4 and 480 mg every 4 wks thereafter. Primary endpoints were investigator-assessed overall response rate (ORR) per RECIST 1.1 and safety; secondary included duration of response (DOR), time to response (TTR), progression free survival (PFS) and overall survival (OS). There were no pre-planned statistical comparisons between treatment arms. **Results:** As of the data cutoff, 87 pts were randomized and treated; 44 to ERDA+CET and 43 to ERDA: median age was 69 vs 72 y; visceral metastases were present in 60.0 vs 63.6%. Median follow-up time was 14.2 months (mo). ORR for ERDA+CET was 54.5% with 6 (13.6%) CRs and 12 mo OS 68%. 11/24 responders were ongoing. ORR for ERDA was 44.2% with 1 CR and 12 mo OS 56%. 9/19 responders were ongoing. 4 pts in each arm were PD-L1 positive. 3/4 (75%) PD-L1 positive pts responded to ERDA+CET vs 0 for ERDA. The most frequent treatment-emergent AEs (any grade) were hyperphosphatemia (68.9 vs 83.7%), stomatitis (59.1 vs 72.1%) and diarrhea (45.5 vs 48.8%) for ERDA+CET and ERDA respectively. Grade ≥3 treatment-related AEs occurred in 45.5 (ERDA+CET) and 46.5% (ERDA) of pts. There was one CET-related death in ERDA+CET secondary to pulmonary failure. **Conclusions:** Combination ERDA+CET demonstrated clinically meaningful activity and was well tolerated. These results, in 1L cis-ineligible pts, support previously described activity of ERDA monotherapy in FGFRa mUC. The safety profile was consistent with the known profile for ERDA and CET with no additive toxicity for the combination. Clinical trial information: NCT03473743. Research Sponsor: Janssen Research & Development.

	ERDA+CET (n=44)	ERDA (n=43)
ORR, % (95% CI)	54.5 (38.8, 69.6)	44.2 (29.1, 60.1)
Confirmed CR, n (%)	6 (13.6)	1 (2.3)
DCR, % (95% CI)	79.5 (64.7, 90.2)	88.4 (74.9, 96.1)
Median DOR (95% CI), mo	11.10 (8.77, NE)	9.72 (4.60, NE)
Median PFS (95% CI), mo	10.97 (5.45, 13.63)	5.62 (4.34, 7.36)

OVERVIEW

- INTRODUCCIÓN
- PD1/PDL1 (pembrolizumab, nivolumab, avelumab)
- NECTINA-4 (enfortumab vedotin)
- FGFR (erdafitinib)
- HER2 (trastuzumab)

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

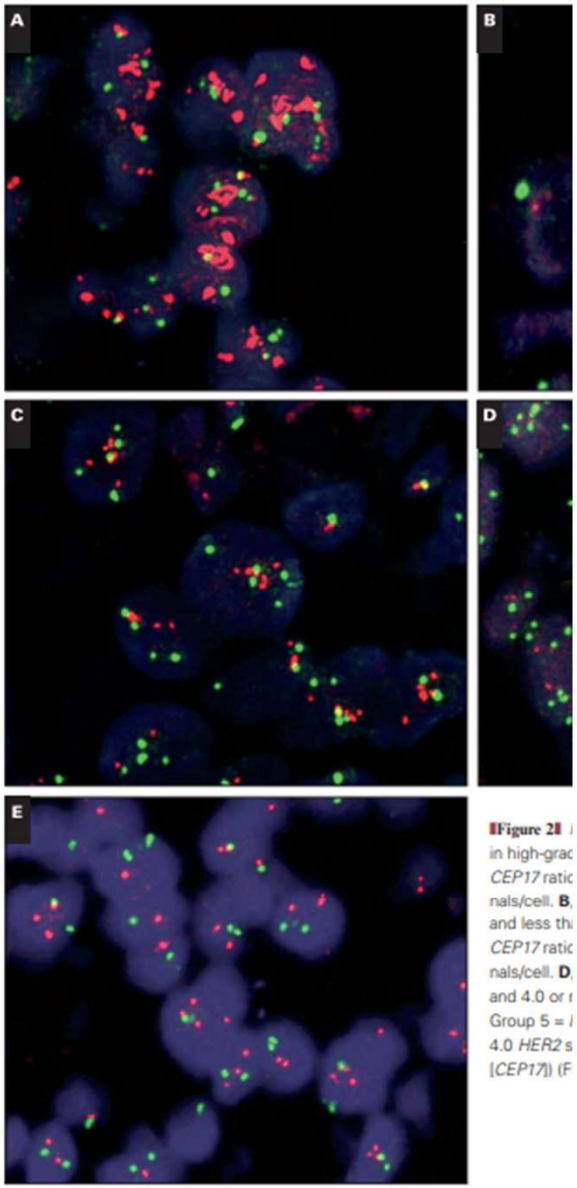
Table 6. Reporting Results of *HER2* Testing by In Situ Hybridization (dual-probe assay)

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”.



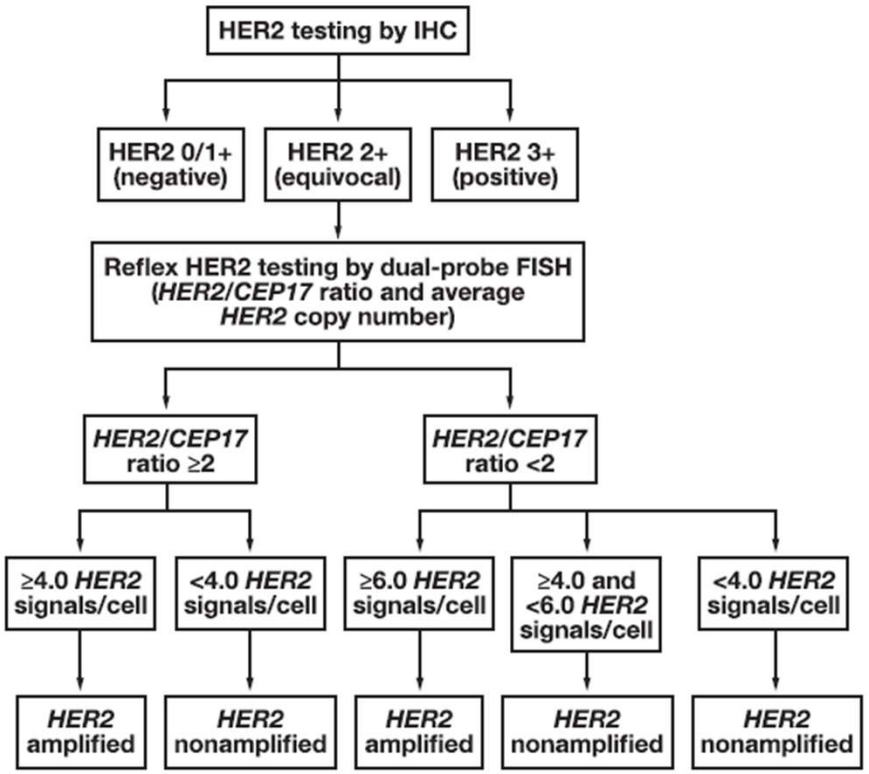


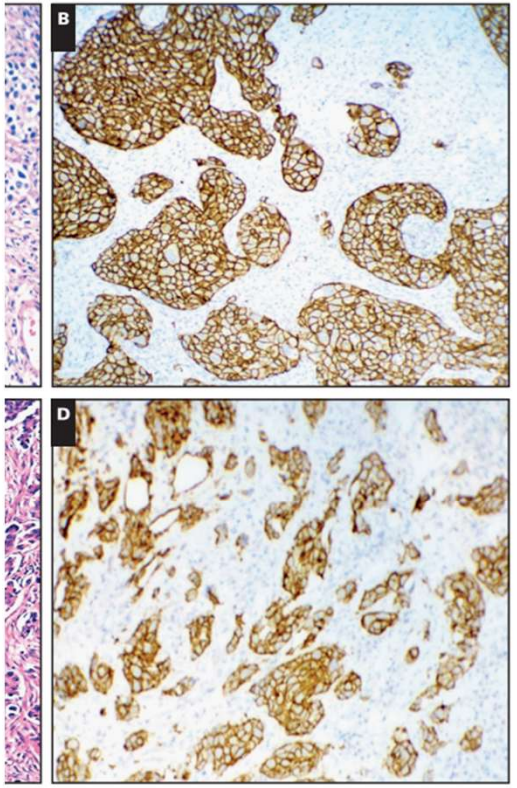
Figure 4 Algorithm for human epidermal growth factor receptor 2 (HER2) testing in high-grade urothelial carcinoma. First, immunohistochemistry (IHC) testing for HER2 should be performed. A fluorescence in situ hybridization (FISH) test is not required if the HER2 IHC test results are either negative (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

Ankit Tiwari, PhD,[1] Niharika Pattnaik, MD,[1] Sunil Jaiswal, MS, DNB,[4] anas R. Pradhan, MS, MCh,[6] Tapas R. Swain, DMLT,[1] MD,[8,☐] and Anil V. Parwani, MD, PhD[9]

l Oncology, [4]Surgical Oncology, and [6]Urology, Advanced Medical aboratory Medicine, CORE Diagnostics, Gurgaon, India; [1]Department r, India; [8]Department of Urology, Kalinga Hospital, Bhubaneswar, India; Department of Pathology, Wexner Medical Center, Ohio State University,

practice guidelines



- 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				
Laé 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-CD11 (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)
Naruse 2010	Observational	46	21.7%	IHC 3+; Dako HercepTest (IHC)
Kossai 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	26.1%	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)
Røtterud 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)
Chakravati 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

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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)
Necchi 2015	Observational	52	46.2%	IHC 2+ or 3+; N/A
Soria 2017	Observational	252	47.6%	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)

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Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

Funda Meric-Bernstam, MD[1]; Vicky Makker, MD[2,3]; Ana Oaknin, MD[4]; Do-Youn Oh, MD[5]; Susana Banerjee, PhD[6]; Antonio González-Martín, MD[7]; Kyung Hae Jung, MD[8]; Iwona Ługowska, MD[9]; Luis Manso, MD[10]; Aránzazu Manzano, MD[11]; Bohuslav Melichar, MD[12]; Salvatore Siena, MD[13]; Daniil Stroyakovskiy, MD[14]; Anitra Fielding, MBChB[15]; Yan Ma, MSc[16]; Soham Puvvada, MD[15]; Norah Shire, PhD[15]; and Jung-Yun Lee, MD[17]

DOI https://doi.org/10.1200/JCO.23.02005

CONTEXT

Key Objective

What is the efficacy and safety of trastuzumab deruxtecan (T-DXd; 5.4 mg/kg once every 3 weeks) in previously treated patients with locally advanced or metastatic human epidermal growth factor 2 (HER2)–expressing (immunohistochemistry [IHC] 3+/2+) solid tumors?

Knowledge Generated

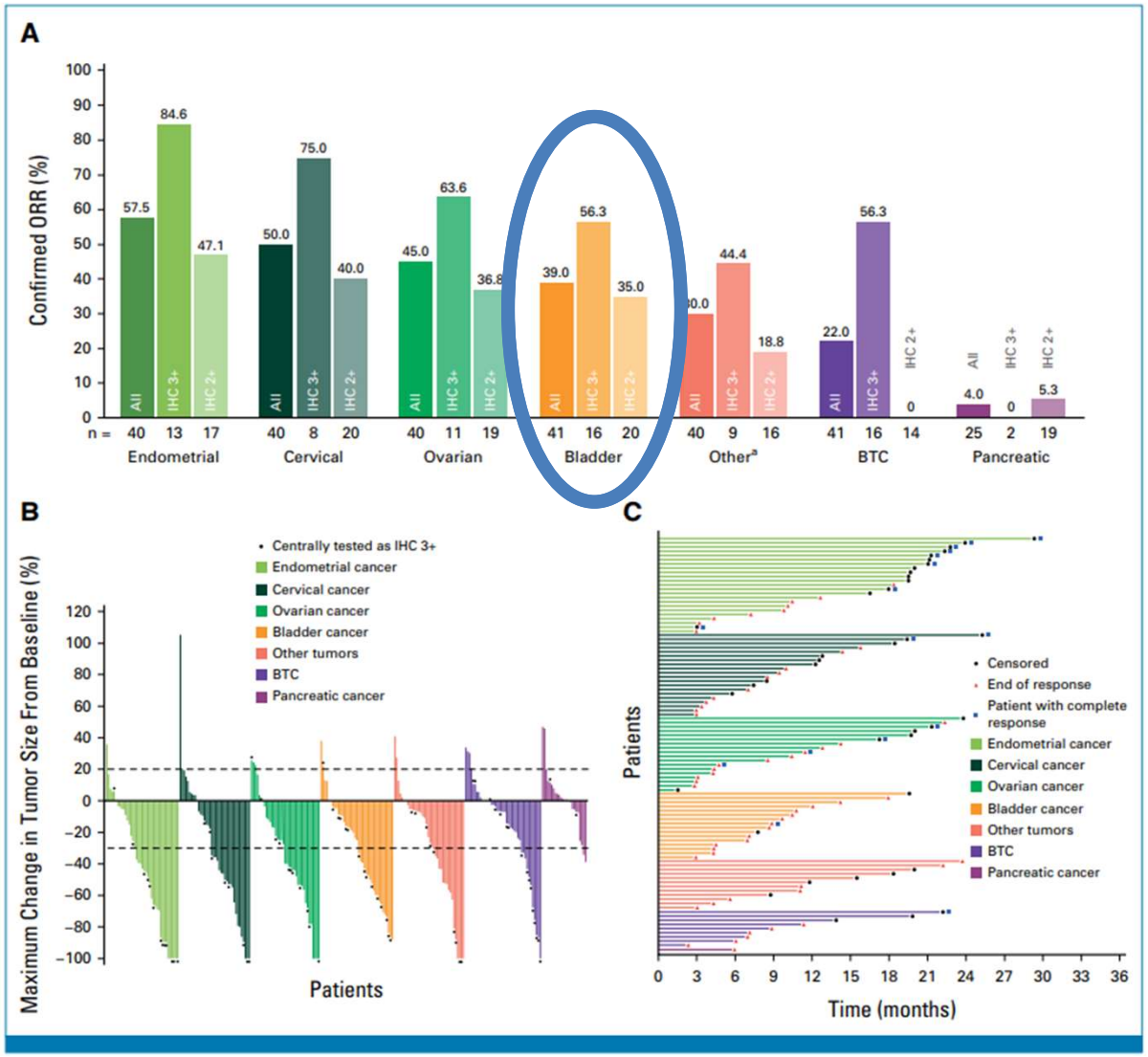
DESTINY-PanTumor02 demonstrated that treatment with T-DXd resulted in durable responses across multiple tumor types, alongside clinically meaningful rates of progression-free survival and overall survival, with the greatest benefit observed in the HER2 IHC 3+ population. The safety profile was consistent with the known profile for T-DXd, including the incidence of interstitial lung disease (ILD).

Relevance *(G.F. Fleming)*

T-DXd provides meaningful benefit for patients with multiple types of solid tumors that express HER2, particularly for those whose tumors express HER2 at the 3+ level on central review.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD.

Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate composed of a humanized immunoglobulin G1 anti-HER2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a potent topoisomerase I inhibitor payload



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 Nectina4 ni de Trop-2.
- Pacientes en los que se plantea tratamiento con inhibidores de FGFR (erdafitinib) es necesario el estudio molecular.
- Habrá una mayor demanda de determinación de HER2 en vejiga .
- Cuando deberíamos realizar las pruebas moleculares/inmunohistoquímica, al diagnóstico de la RTU (T2) o cuando se ha confirmado la metástasis?.

MUCHAS GRACIAS