Treatment after progression to platinum-based chemotherapy and Immunotherapy : The case of Enfortumab-Vedotin

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My disclosures

- **Advisory Boards:**
  - MSD, BMS, Roche-Genentech, PYCYC, IPSEN, Novartis, Bayer
- **Research Funding:**
  - Roche-Genentech, Astra-Zeneca
- **Travel expenses:**
  - Roche-Genentech, IPSEN, Astra-Zeneca,
- **Clinical Trials:**
  - BMS, Roche-Genentech, PYCYC, EISAI, MSD, Tahio Oncology, Gilead, Exelixis
- **Lectures:**
  - EUSA pharma, MSD, BMS, Roche-Genentech, IPSEN, Jansen, Astellas, Bayer,

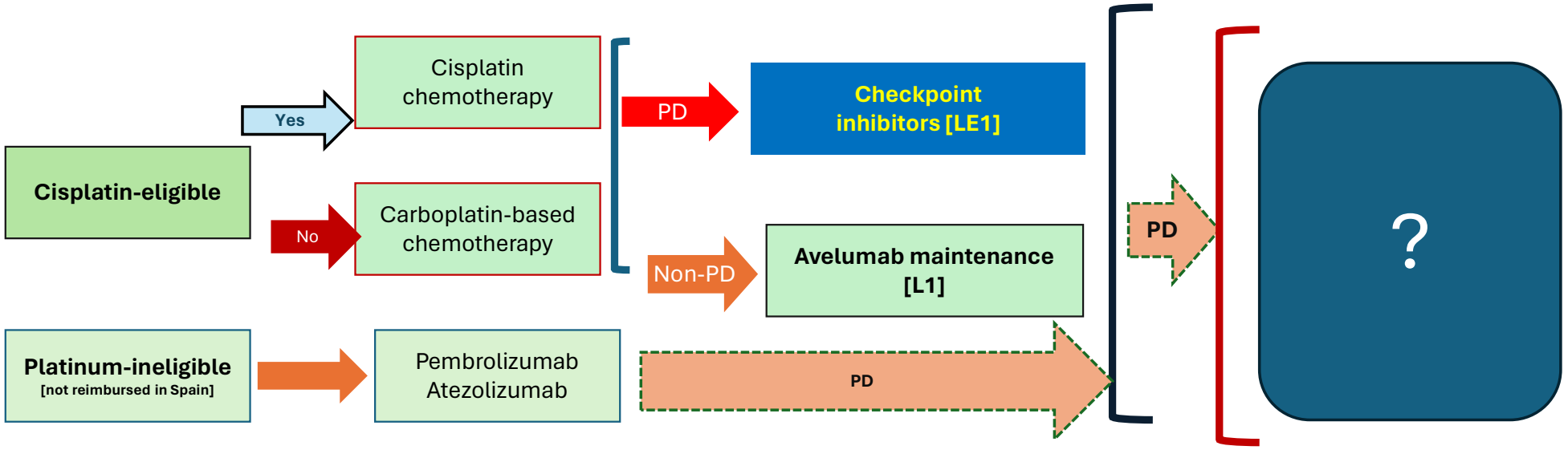
Learning objectives

- To discuss about the most appropriate therapy beyond progression to platinum-based chemotherapy and CPI with an special focus on Enfortumab Vedotin

Outline

- Current treatment scenario in Feb 2024
- The niche after chemo and CPI
- EV as the drug of choice
  - MoA
  - Appropriateness
  - Efficacy
  - Safety
- Alternatives?
- Summary

Current treatment landscape in La-mUC in 2024 [hopefully not for long time]



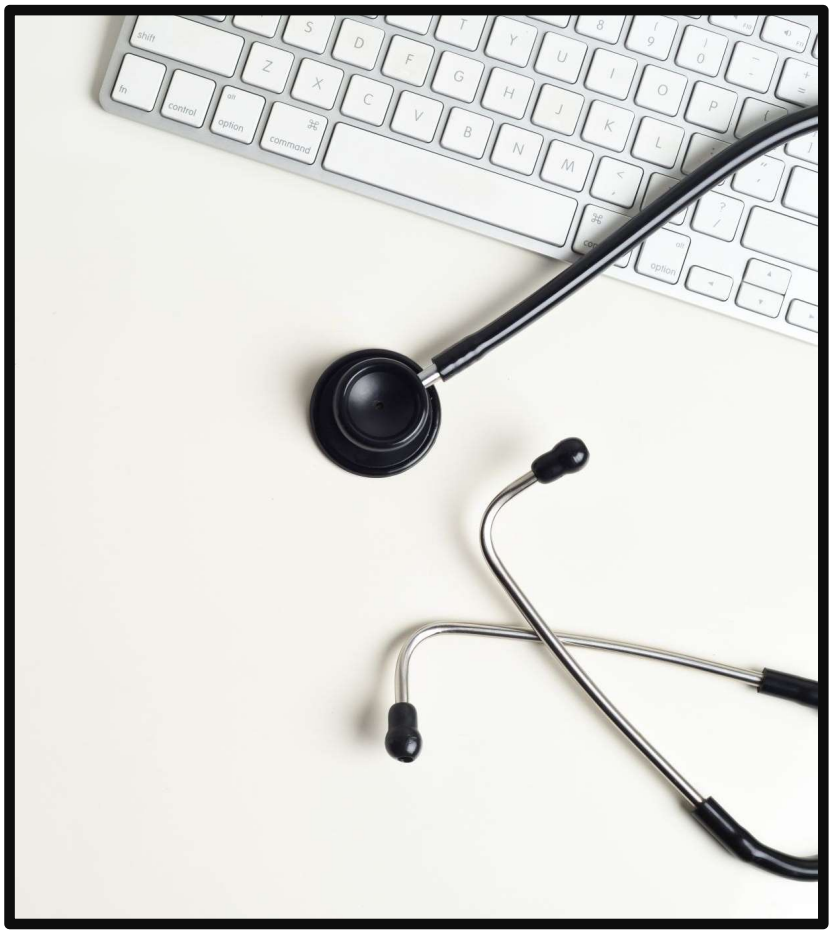
The therapeutic landscape of metastatic urothelial carcinoma (mUC) has dynamically changed with the recent approval of multiple new agents and will hopefully continue to revolve

- Witjes JA, et al. EAU Guidelines muscle-invasive and metastatic bladder cancer. 2021. https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/. Last accessed February 2021.Rosenberg JE, et al. Presentation at ASCO GU 2022; abstract 437. Grivas P, et al. Presentation at ASCO GU 2022; abstract 434. Crabb S, et al. Presentation at ASCO GU 2022; abstract 436. Vignani F, et al. Presentation at ASCO GU 2022; abstract 442. Galsky M, et al. Presentation at ASCO GU 2022; abstract 438. Siefker-Radtke AO, Matsubara N, Park SH, Huddart RA, Burgess EF, Özgüroğlu M, Valderrama BP, Laguerre B, Basso U, Triantos S, Akapame S, Kean Y, Deprince K, Mukhopadhyay S, Loriot Y; THOR cohort 2 investigators. 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. Ann Oncol. 2024 Jan;35(1):107-117. doi: 10.1016/j.annonc.2023.10.003. Epub 2023 Oct 21. PMID: 37871702.

Treatment beyond progression to chemotherapy and CPI

The case of Enfortumab-Vedotin

Why a drug over another option?: My arguments



- **CONFIDENT ABOUT MoA**
- **TREATMENT APPROPRIATENESS**
- **CONFIDENT ABOUT EFFICACY**
- **TREATMENT SAFETY/QOL**
- **ALTERNATIVES**
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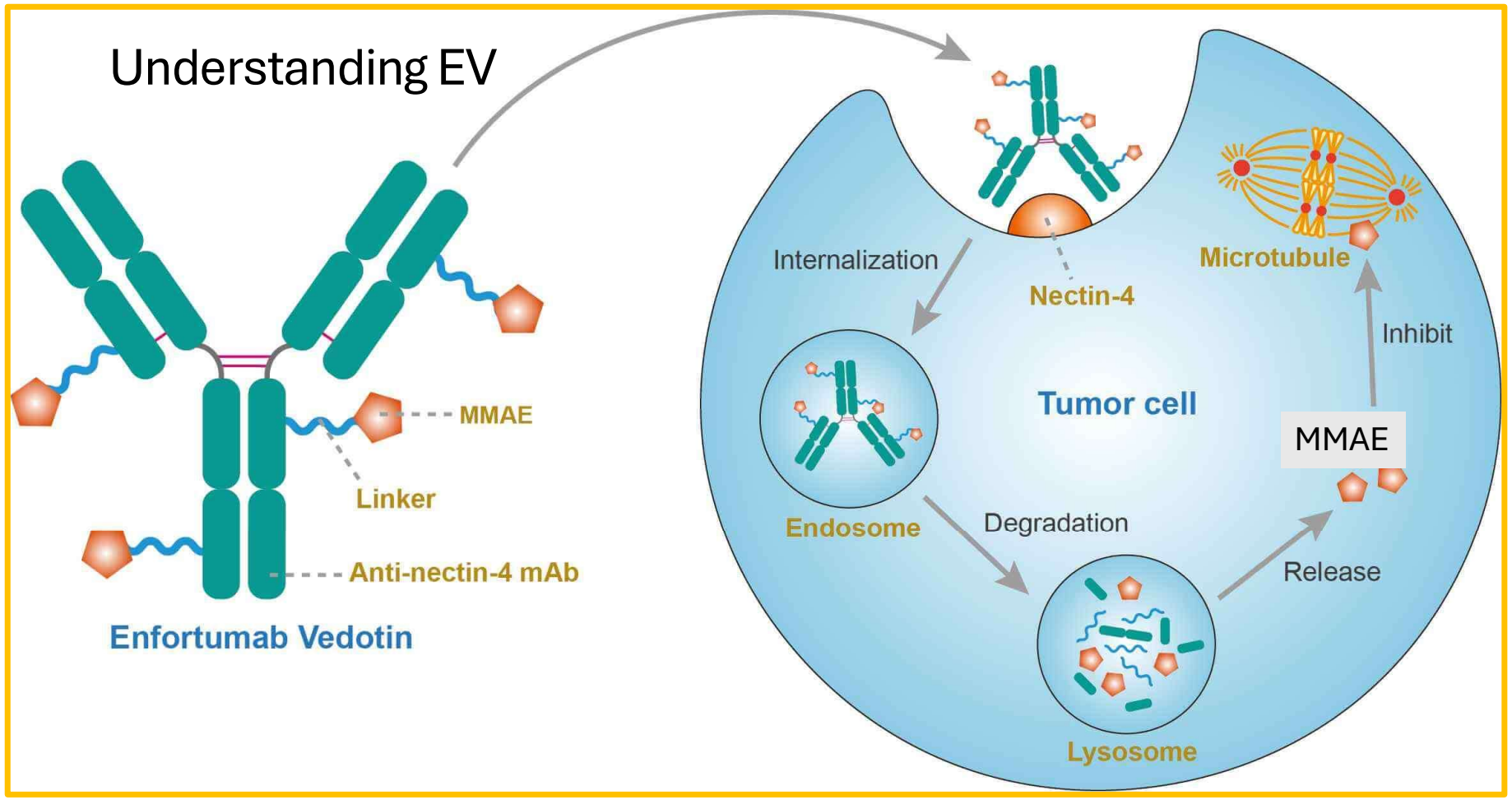


ENFORTUMAB

- mAB that binds a target **(NECTIN-4**

VEDOTIN

- Microtubule-disrupting agent, **monomethyl auristatin E** (MMAE) and the linker. Very potent synthetic **<u>antimicrotubule agent</u>**

Image modified from https://www.creativebiolabs.net/enfortumab-vedotin-overview.htm Accessed Sept 19th 2023

Nectin-4

- Nectin-4, expressed by gene pvr14, **is a type I transmembrane glycoprotein,**
- As a **cell adhesion molecule**, Nectin-4 is **involved in the connection between epithelial cells and endothelial cells.**
- Nectin-4 plays a role in **oncogenesis** by mediating **cell adhesion, migration, proliferation, differentiation,** and **survival.**
- Nectin-4 expression, primarily reported by immunohistochemistry H-score reported **in nearly all UC tumor samples,** with median **H-scores** from 275 to 290 (range 0–300)

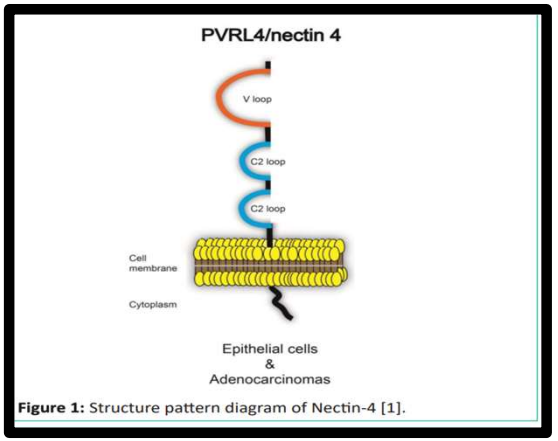


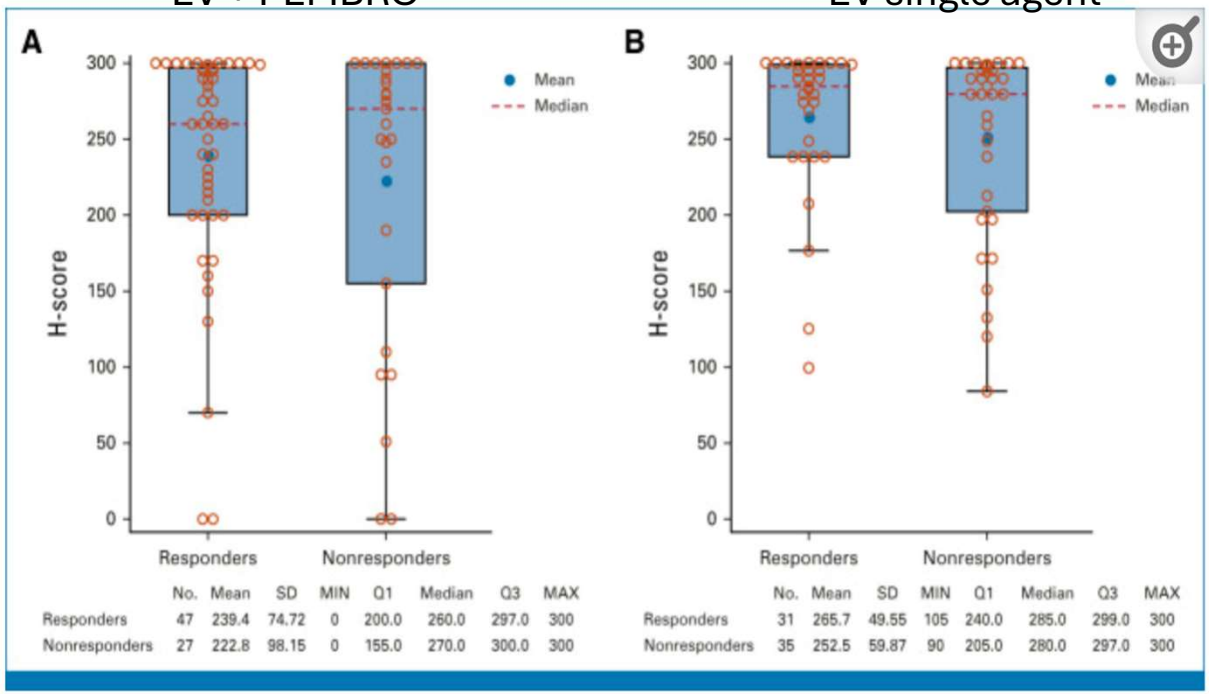
Figure 1: Structure pattern diagram of Nectin-4 [1].

Challita-Eid PM, Satpayev D, Yang P, et al: Enfortumab vedotin antibody-drug conjugate targeting Nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer Res 76:3003-3013, 2016

Nectin-4 does NOT seem to be predictive of Benefit: EV-103 K

EV + PEMBRO

EV single agent



	No.	Mean	SD	MIN	Q1	Median	Q3	MAX
Responders	47	239.4	74.72	0	200.0	260.0	297.0	300
Nonresponders	27	222.8	98.15	0	155.0	270.0	300.0	300

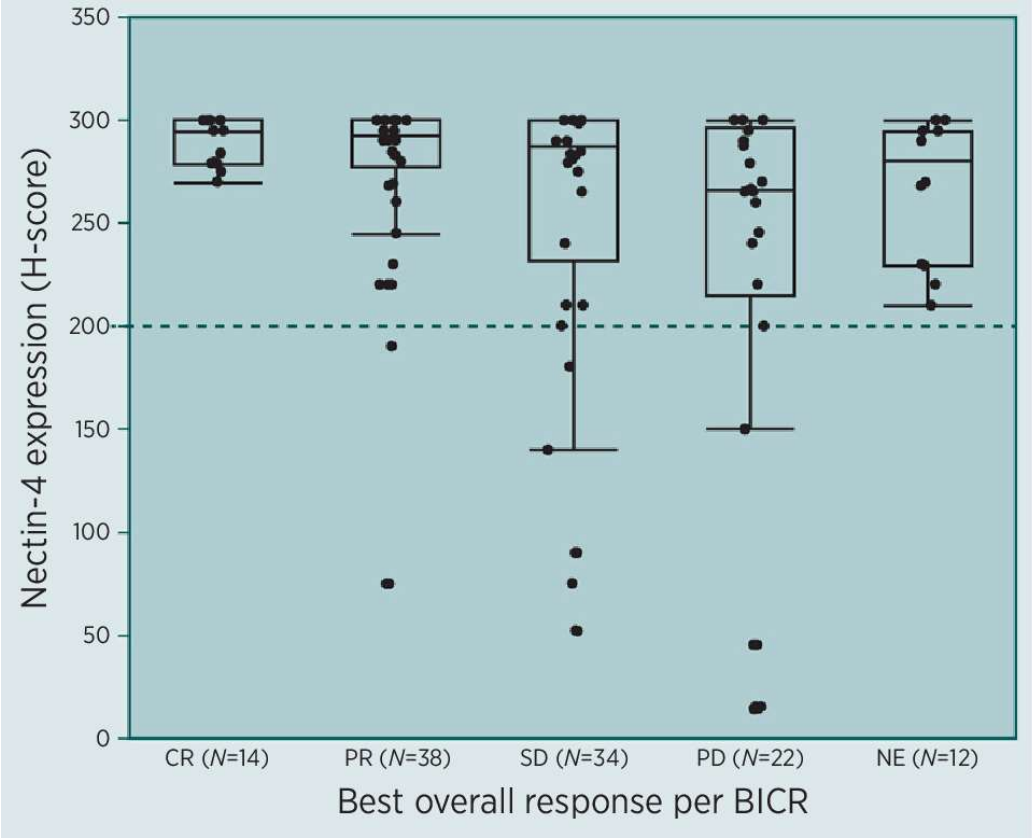
	No.	Mean	SD	MIN	Q1	Median	Q3	MAX
Responders	31	265.7	49.55	105	240.0	285.0	299.0	300
Nonresponders	35	252.5	59.87	90	205.0	280.0	297.0	300

EV-103 COHORT K

Nectin-4 expression was generally high as indicated by median H-score in the combination arm, and the distribution was similar between responders (median, 260.0; IQR, 200.0-297.0) and nonresponders (270.0; 155.0-300.0;

O'Donnell PH, Milowsky MI, Petrylak DP, Hoimes CJ, Flaig TW, Mar N, Moon HH, Friedlander TW, McKay RR, Bilen MA, Srinivas S, Burgess EF, Ramamurthy C, George S, Geynisman DM, Bracarda S, Borchiellini D, Geoffrois L, Maroto Rey JP, Ferrario C, Carret AS, Yu Y, Guseva M, Homet Moreno B, Rosenberg JE. Enfortumab Vedotin With or Without Pembrolizumab in Cisplatin-Ineligible Patients With Previously Untreated Locally Advanced or Metastatic Urothelial Cancer. J Clin Oncol. 2023 Sep 1;41(25):4107-4117. doi: 10.1200/JCO.22.02887. Epub 2023 Jun 27. PMID: 37369081; PMCID: PMC10852367.

Nectin-4 does NOT seem to be predictive of Benefit: EV-201



- Nectin-4 expression (H-score) by best overall response per BICR in **EV-201, Cohort 1**

- There is a biomarker análisis from **EV-301** that will add light to this field (manuscript in preparation)

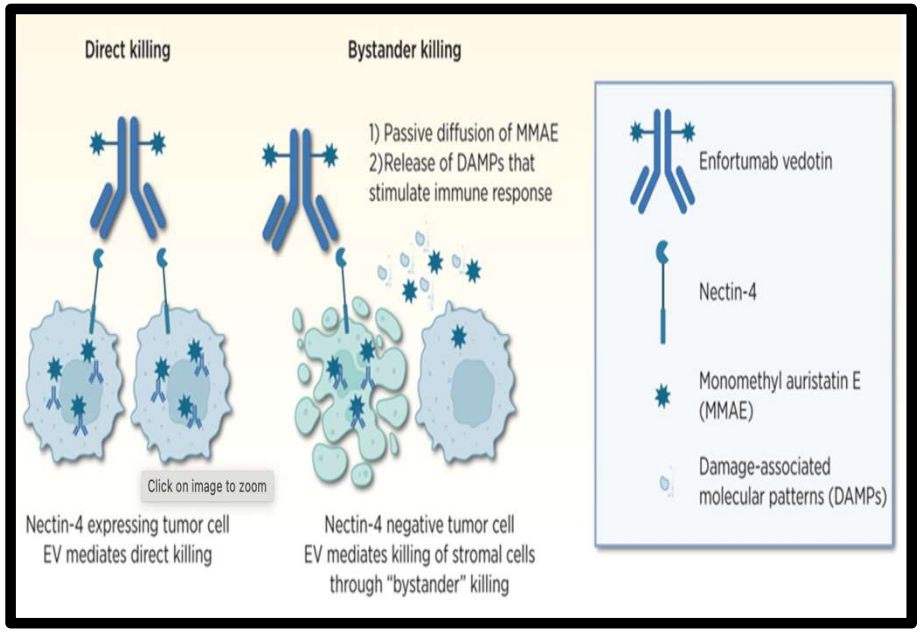
•DOI:10.1158/1078-0432.CCR-20-2275

Nectin-4 does NOT clearly seem to be a predictive biomarker of response?

- **NECTIN-4** expression **alone, MAY NOT completely identify** the universe of patients who **may benefit from EV therapy.**

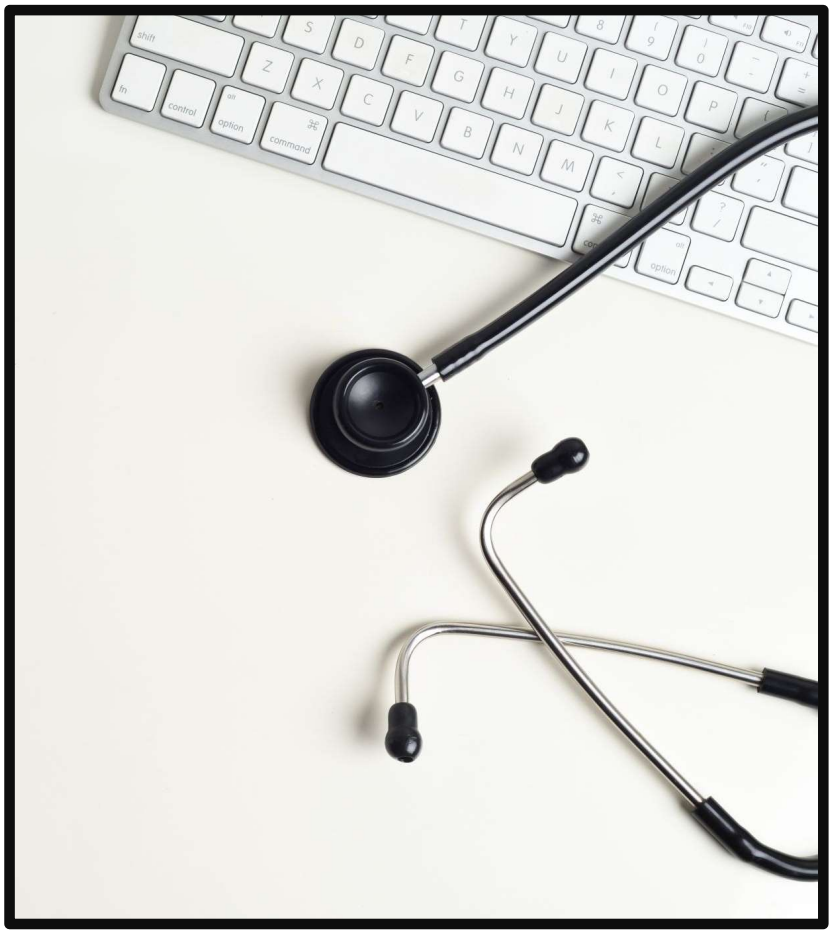
- **NECTIN-4** is potentially **a dynamic biomarker** subject to intralesional heterogeneity and temporal expression changes that may not be adequately captured by IHC from a single biopsy.

- It is possible that **some NECTIN-4 low tumors by IHC are still EV responsive,** and there has **NOT yet been defined** a **minimum threshold** of NECTIN-4 expression that is required to induce a treatment response.



Aggen DH, Chu CE, Rosenberg JE. Scratching the Surface: NECTIN-4 as a Surrogate for Enfortumab Vedotin Resistance. Clin Cancer Res. 2023 Apr 14;29(8):1377-1380.

Why a drug over another option?: My arguments



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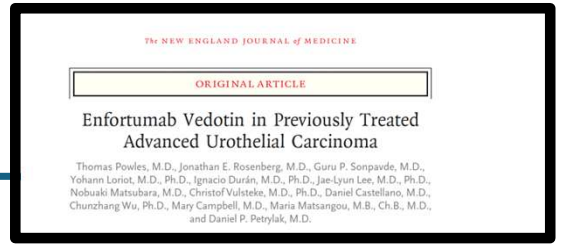
Is the population of the pivotal study representative of the niche?


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Thomas Powles, M.D., Jonathan E. Rosenberg, M.D., Guru P. Sonpavde, M.D., Yohann Loriot, M.D., Ph.D., Ignacio Durán, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Nobuaki Matsubara, M.D., Christof Vulsteke, M.D., Ph.D., Daniel Castellano, M.D., Chunzhang Wu, Ph.D., Mary Campbell, M.D., Maria Matsangou, M.B., Ch.B., M.D., and Daniel P. Petrylak, M.D.

An international, open-label, randomised, Phase III study[1]

Adult patients with unresectable LA/mUC (N=608)

- Histologically/cytologically confirmed urothelial carcinoma
- ECOG PS 0 or 1
- Disease **progression or relapse during or after PD-1/L1 inhibitor** treatment
- **Prior platinum-based chemotherapy** (including as adjuvant or neoadjuvant therapy*)

R 1:1

EV 1.25 mg/kg (n=301)

30-minute IV infusion on Days 1, 8, and 15 of a 28-day cycle

Premedication not required

Investigator-chosen chemotherapy (n=307)

Either of the following as an IV infusion on Day 1 of a 21-day cycle:

- Docetaxel 75 mg/m^2 over 1 hour (n=117) (+ premedication)
- Paclitaxel 175 mg/m^2 over 3 hours (n=112) (+ premedication)
- Vinflunine 320 mg/m^2 over 20 minutes (n=78)

Premedication administered to patients receiving docetaxel or paclitaxel to prevent hypersensitivity reactions and fluid retention

Primary endpoint:
OS

Secondary endpoints:
PFS, ORR, DCR,CRR, DOR, QOL/PROs, and safety and tolerability

EV-301 was conducted to investigate the efficacy and safety of EV in patients with LA/mUC previously treated with platinum-based chemotherapy and a PD-1/L1 inhibitor[1]

1. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 2. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (protocol); 3. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (supplementary appendix).

EV-301 included patients with LA/mUC reflective of real world [1,2*]

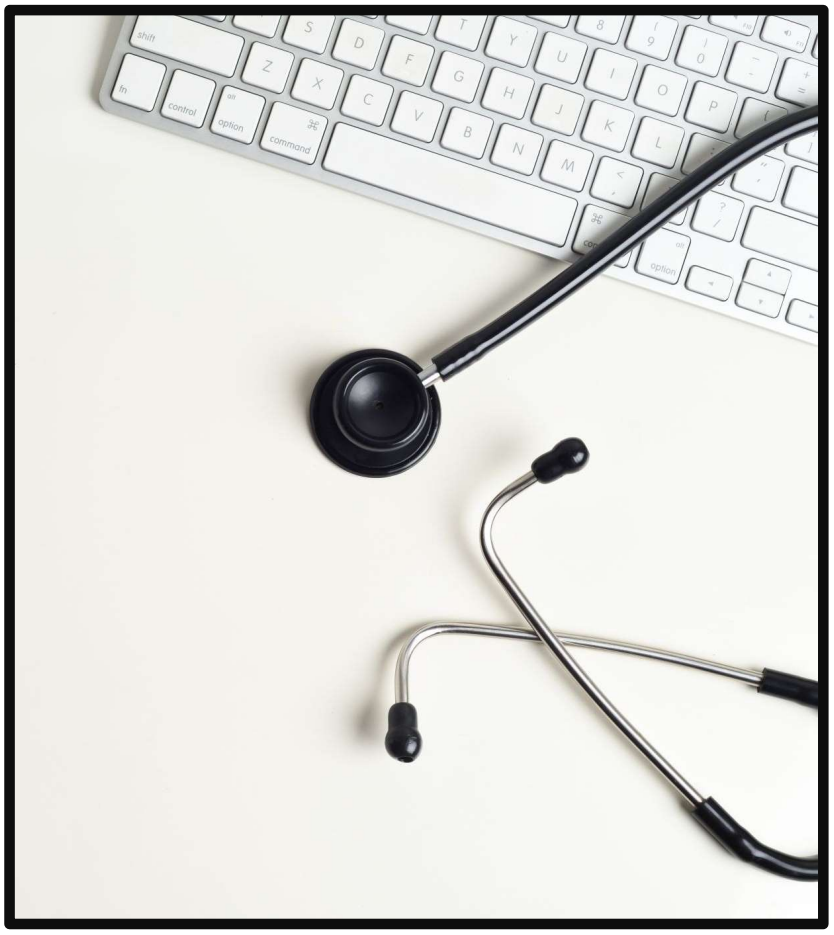
Characteristic	Subgroup	EV (n=301)	Chemotherapy (n=307)
Median age (range), years	–	68.0 (**34.0–85.0**)	68.0 (**30.0–88.0**)
Male sex, n (%)	–	238 (**79.1**)	232 (**75.6**)
ECOG PS, n (%)	1	181 (**60.1**)	183 (**59.6**)
Bellmunt risk score, n (%)	0–1	201 (**66.8**)	208 (**67.8**)
	≥2	90 (**29.9**)	96 (**31.3**)
	Not reported	10 (**3.3**)	3 (**1.0**)
Origin site of primary disease, n (%)	Upper urinary tract	98 (**32.6**)	107 (**34.9**)
	Bladder or other site	203 (**67.4**)	200 (**65.1**)
Histologic type at initial diagnosis, n/N (%)	Urothelial or transitional cell carcinoma	229/301 (**76.1**)	230/305 (**75.4**)
	Urothelial carcinoma, mixed types	45/301 (**15.0**)	42/305 (**13.8**)
	Other[†]	27/301 (**9.0**)	33/305 (**10.8**)
Metastatic sites, n/N (%)	Lymph node only	34/301 (**11.3**)	28/306 (**9.2**)
	Visceral disease	234/301 (**77.7**)	250/306 (**81.7**)
	Liver metastasis	93/301 (**30.9**)	95/307 (**30.9**)
Prior lines of systemic therapy, n (%)	1–2	262 (**87.0**)	270 (**87.9**)
	≥3	39 (**13.0**)	37 (**12.1**)
Best response to prior CPI, n (%)	Responder (CR or PR)	61 (**20.3**)	50 (**16.3**)
	Non-responder (SD or PD)	207 (**68.8**)	215 (**70.0**)
Median time since diagnosis of LA/mUC (range), months	–	**14.8** (0.2–114.1)	**13.2** (0.3–118.4)

119 Centres
19 Countries
4 continents

Similar to real life

1. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 2. Rosenberg JE et al. Presented at ESMO 2021. P698.

Why a drug over another option?: My arguments



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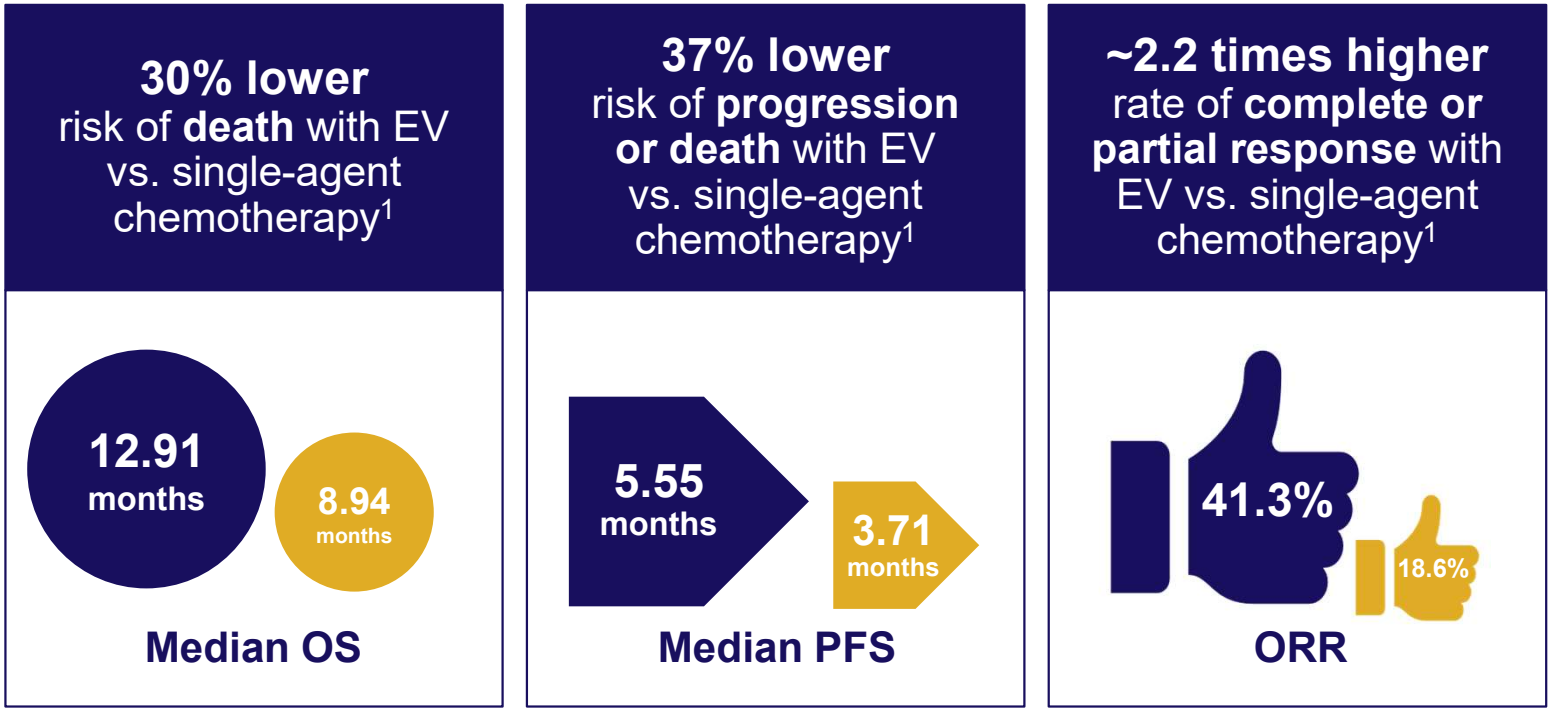
Summary of the efficacy

Key outcomes from EV-301



Median follow-up: 23.8 months.[1]
*Data at Week 12.[2]
EORTC, European Organisation for Research and Treatment of Cancer; EV, enfortumab vedotin; ORR, objective response rate; OS, overall survival; PD-1/L1, programmed cell death protein 1/ligand 1; PFS, progression-free survival; QLQ-C30, Quality of Life Questionnaire Core 30.
1. Rosenberg JE et al. Presented at ASCO 2022. P4516; 2. Mamtani R et al. Presented at ASCO 2021. P4539.

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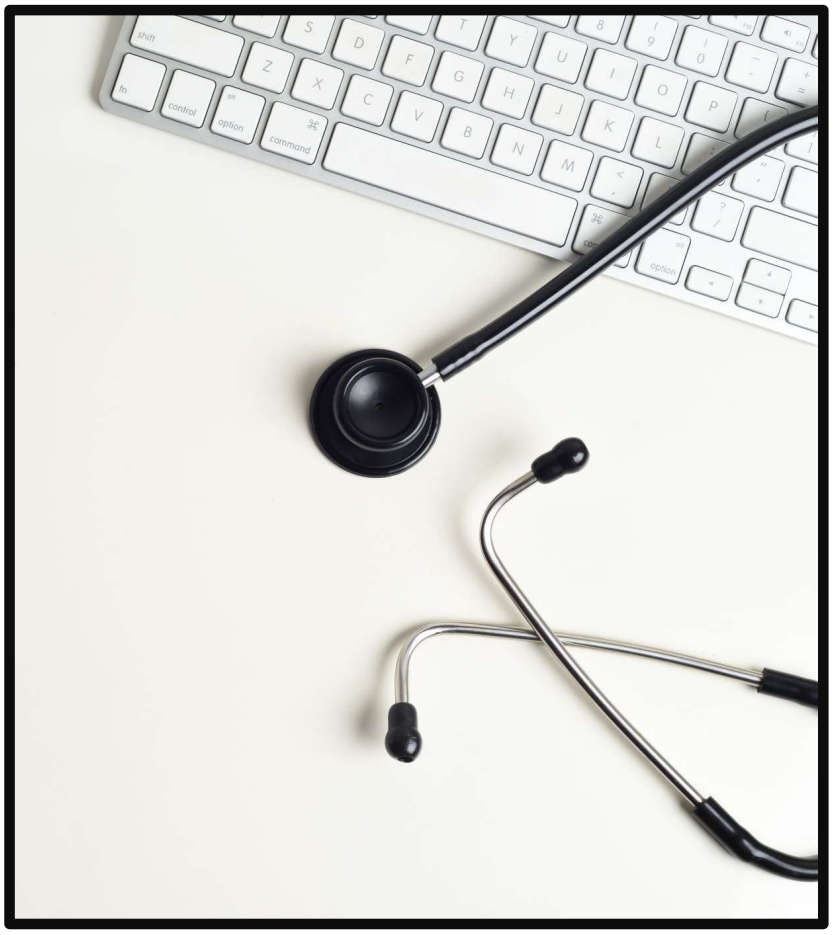

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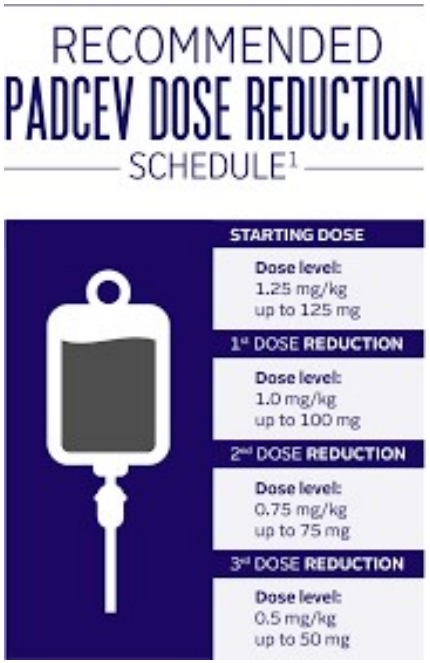
TWO
SIDES
OF THE
SAME COIN

Be ready to adjust the drug

51% of patients in EV-301 experienced EV-related AEs leading to **dose interruption** (151/296)[1]

32% of patients in EV-301 experienced EV-related AEs leading to **dose reduction** (96/296)[1]

14% of patients in EV-301 experienced EV-related AEs leading to **treatment withdrawal** (40/296)[1]



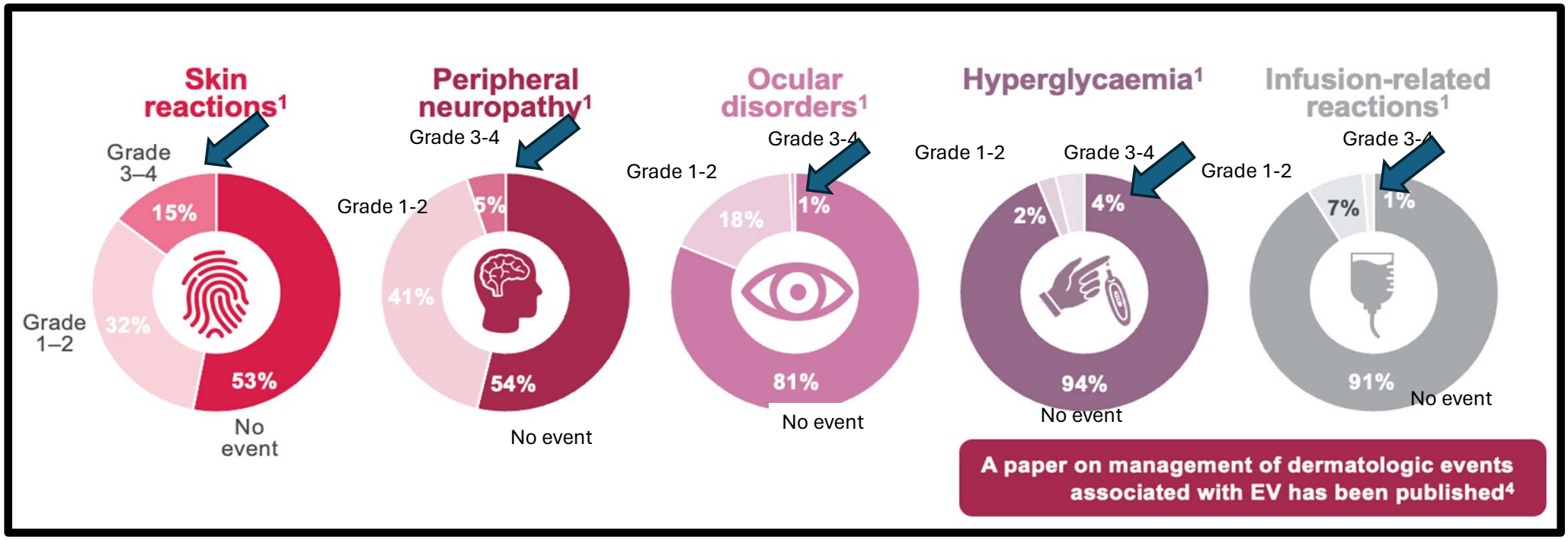
Median follow-up: 11.1 months. Analysis of the safety population (all patients who received any amount of study drug). Data presented are TRAEs (adverse events for which there is a reasonable possibility that the event was caused by study treatment, according to the study investigator).[2]

AE, adverse event; EV, enfortumab vedotin; TRAE, treatment-related adverse event.

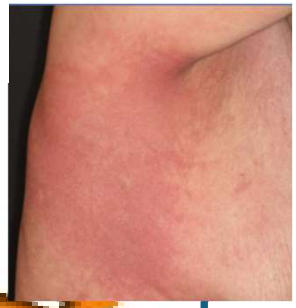
1. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (supplementary appendix); 2. Powles T et al. *N Engl J Med* 2021;384:1125–1135.

SPECIAL INTEREST

SEVERE TOXICITIES ARE RARE



Note: Adverse events of interest for EV are based on current safety data from clinical studies and known risks with similar ADCs.[3]
Median follow-up: 11.1 months. Analysis of the safety population (all patients who received any amount of study drug). Data presented are TRAEs (adverse events for which there is a reasonable possibility that the event was caused by study treatment, according to the study investigator).[2] Percentages may not total 100% due to rounding.
ADC, antibody–drug conjugate; AESI, adverse events of special interest; EV, enfortumab vedotin; TRAE, treatment-related adverse event.
1. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (supplementary appendix); 2. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 3. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (protocol);
4. Lacouture ME et al. *Oncologist* 2022;27:e223–e232.

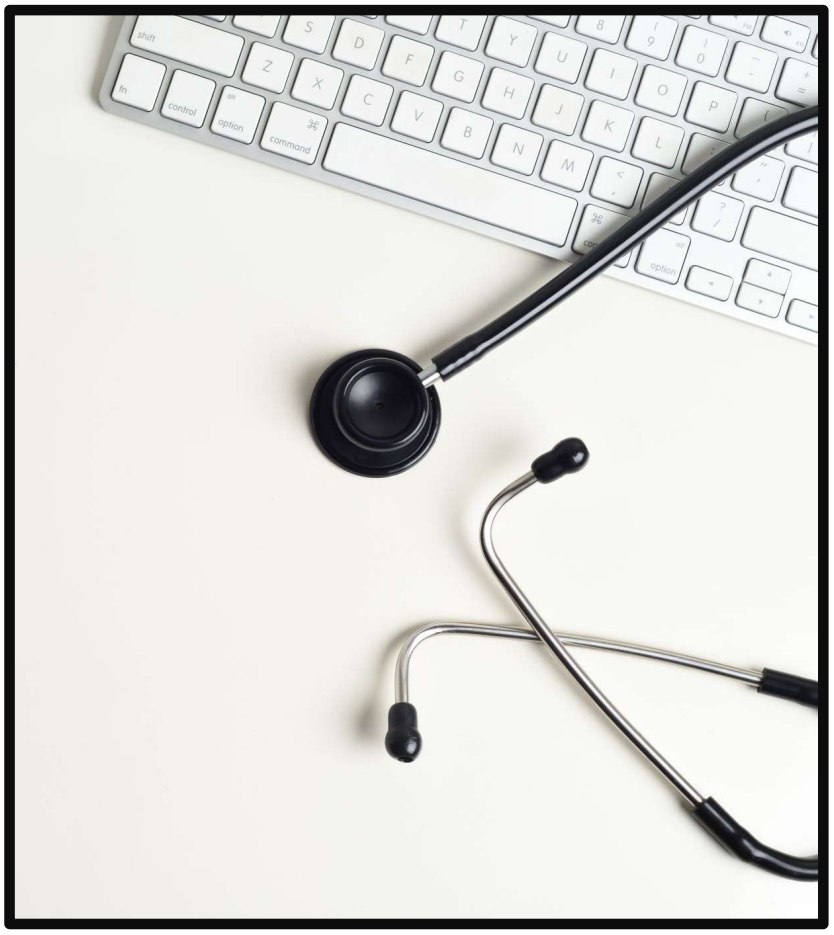


Event,* n (%)[1]	EV (n=296) n	EV (n=296) Months, median (range)
Skin reactions	139	0.43 (0.03–12.68)
Peripheral neuropathy	137	2.69 (0.03–11.99)
Corneal disorders	2	4.34 (1.91–6.77)
Dry eye	47	1.91 (0.30–9.66)
Blurred vision	12	2.45 (0.07–5.09)
Infusion-related reactions	26	0.51 (0.03–9.40)
Hyperglycaemia	19	0.56 (0.26–5.78)

Most relevant Toxicities if appears
it appears
in the first few months
Specially **the skin toxicity**

Median follow-up: 11.1 months. Analysis of the safety population (all patients who received any amount of study drug).[2]
*TRAEs are adverse events for which there is a reasonable possibility that the event was caused by study treatment, according to the study investigator.[2]
AESI, adverse event of special interest; EV, enfortumab vedotin; NA, not applicable; TRAE, treatment-related adverse event.
1. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (supplementary appendix); 2. Powles T et al. *N Engl J Med* 2021;384:1125–1135.

Why a drug over another option?: My arguments



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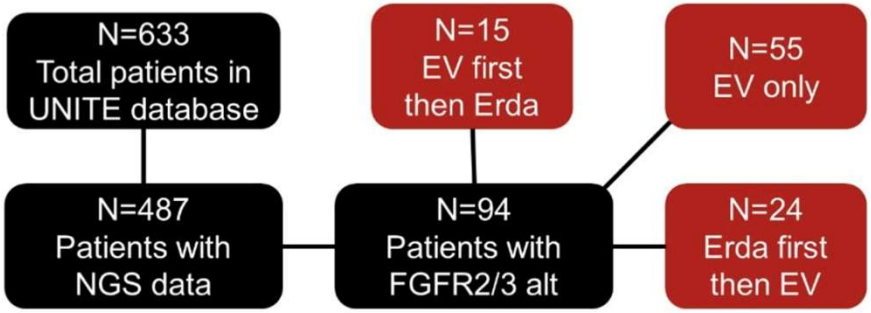
- There are other alternatives with LE-1 such as targeted therapies with FGFR inhibitors [ERDAFITINIB] in those tumors with FGFR fusions or mutations
- How frequent are these molecular alterations?
- What is the safety profile of these drugs? Can we maintain dose intensity for a long time? What is the therapeutic window?
- Why these treatment fail when compared with something stronger than "old chemo" [THOR Cohort 2]
- More importantly, DO WE HAVE ACCESS TO THESE DRUGS? ARE THEY GOING TO BE EASILY ACCESIBLE AND REIMBURSED?

Loriot Y, et al. THOR Cohort 1 Investigators. Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2023 Nov 23;389(21):1961-1971..

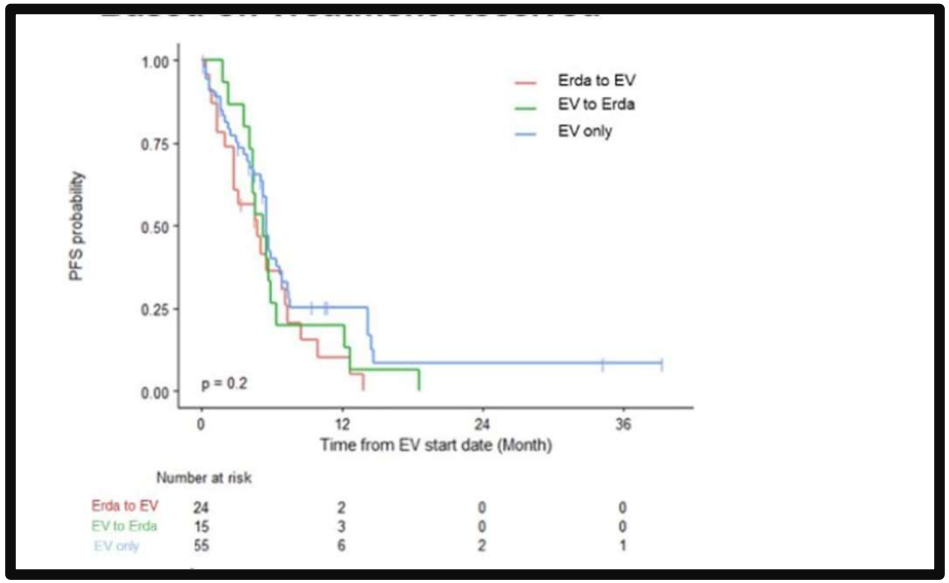
Sequencing agents: The order matters?

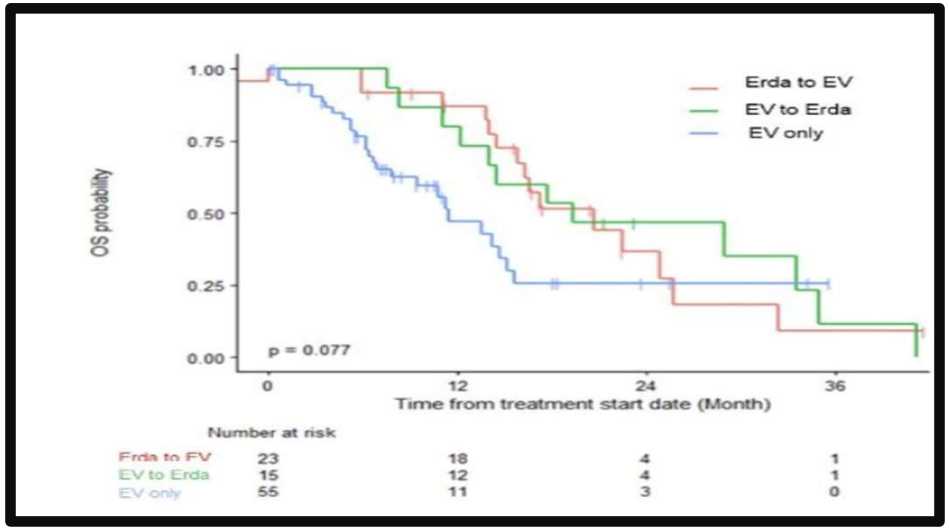


On multivariable analysis, there was no difference in overall survival between the two treatment combination sequences.

Table 2. Univariate and Multivariate Analysis of OS and PFS Based on Clinical Characteristics

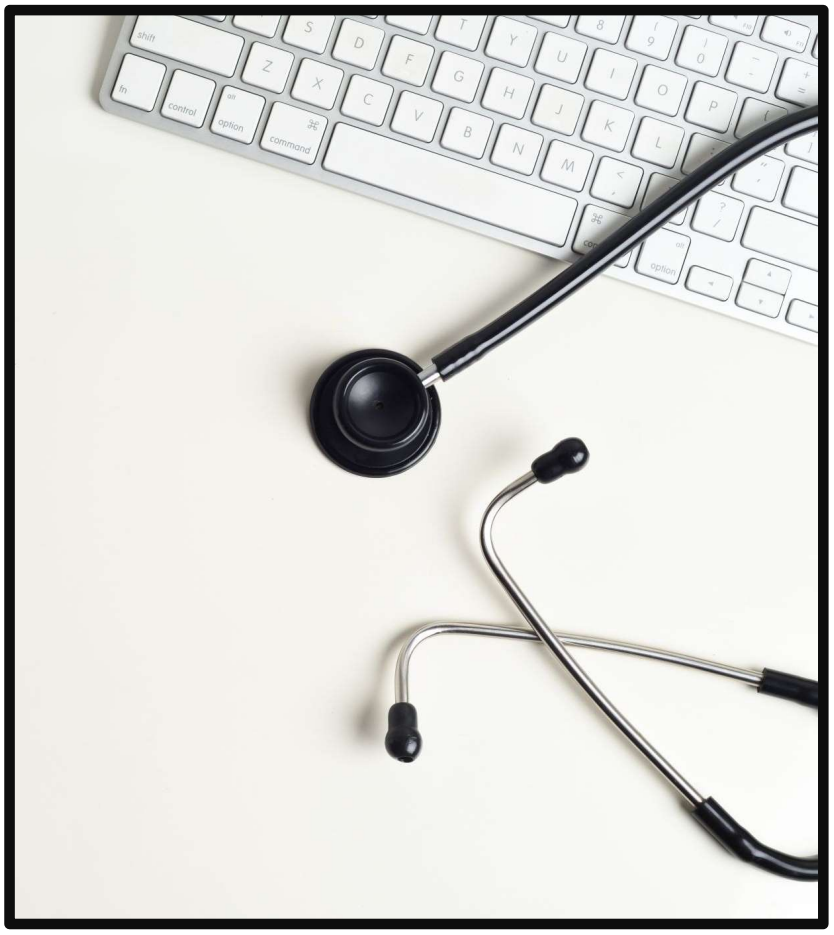
Characteristic	UVA OS: HR (95% CI)	p	MVA OS: HR (95% CI)	p	UVA PFS: HR (95% CI)	p	MVA PFS: HR (95% CI)	p
Visceral Metastases (yes vs no)	1.49 (0.83-2.68)	0.18	1.56 (0.86-2.83)	0.14	1.49 (0.92-2.4)	0.10	1.46 (0.87-2.44)	0.15
EV then Erda vs EV only	0.54 (0.26-1.09)	0.08	0.51 (0.25-1.02)	0.06	1.32 (0.73-2.4)	0.36	1.49 (0.79-2.81)	0.22
Erda then EV vs EV only	0.53 (0.27-1.01)	0.05	0.52 (0.27-1.01)	0.05	1.61 (0.94-2.76)	0.08	1.64 (0.91-2.96)	0.10
EV <-> Erda (regardless of sequence) vs EV only	**0.53 (0.3-0.93)**	**0.03**	**0.52 (0.3-0.9)**	**0.02**	1.47 (0.93-2.33)	0.10	1.57 (0.97-2.55)	0.07
Prior anti-PD(L)1 (yes vs no)	1.12 (0.35-3.62)	0.85	-	-	0.4 (0.18-0.88)	0.02	0.48 (0.19-1.21)	0.12
BMI at EV start (>30 vs <19)	0.7 (0.09-5.54)	0.74	-	-	**0.3 (0.09-1.09)**	**0.07**	**0.23 (0.06-0.86)**	**0.03**





Cindy Y. Jiang Sequencing of Erdafitinib and Enfortumab Vedotin in Patients with FGFR2/3 Altered Advanced Urothelial Cancer: Analysis of UNITE Database. ASCO GU 2024

Why a drug over another option?: My arguments



- CONFIDENT ABOUT MoA
- TREATMENT APPROPRIATENESS
- CONFIDENT ABOUT EFFICACY
- TREATMENT SAFETY/QOL
- ALTERNATIVES
- **SUMMARY**

Summary and conclusions

- Enfortumab Vedotin has a consistent **biological rationale**, **efficacy data** and **solid clinical development** in the post chemo post CPI context with a and therefore seems a valid option to consider in this context

- With an **appropriate training management** safety should NOT result an absolute limitation to the use of EV **although caution and further studies** to potentially anticipate toxicity are highly needed

- **Other alternatives with also LE-1** [i.e Erdafitinib] **can be considered** and might have comparable outcomes although its access, safety and dose intensity maintenance seem a bit more challenging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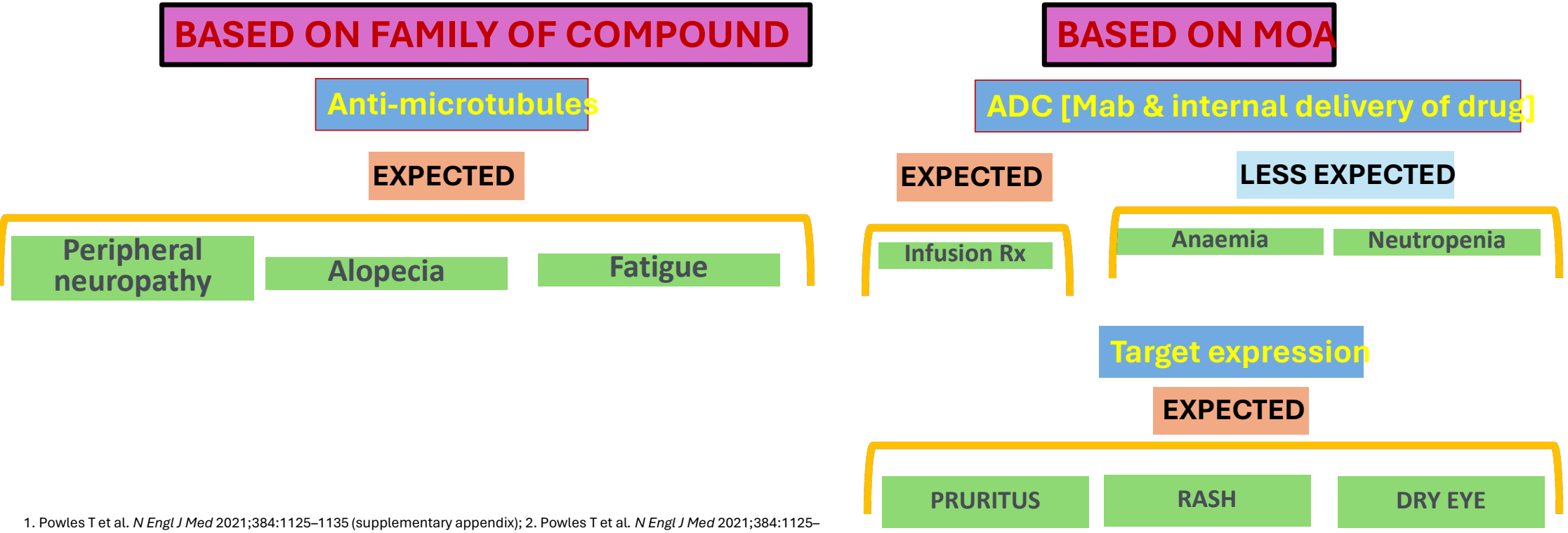
BACK UP SLIDES

Understanding toxicity: Understanding EV

- By knowing the drug and the MOA we could somehow anticipate some of the major side effects related to this drug



1. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (supplementary appendix); 2. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 3. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (protocol); 4. Lacouture ME et al. *Oncologist* 2022;27:e223–e232.

Understanding toxicity: Understanding EV

Event, n (%)[1]	Any grade	
	EV (n=296)	Chemotherapy (n=291)
Any TRAE*	278 (**93.9**)	267 (**91.8**)
Most common TRAEs†		
Alopecia	135 (**45.6**)	108 (**37.1**)
Peripheral sensory neuropathy‡	103 (**34.8**)	63 (**21.6**)
Pruritus	96 (**32.4**)	14 (**4.8**)
Fatigue	93 (**31.4**)	66 (**22.7**)
Decreased appetite	92 (**31.1**)	69 (**23.7**)
Diarrhoea	74 (**25.0**)	49 (**16.8**)
Dysgeusia	73 (**24.7**)	22 (**7.6**)
Nausea	71 (**24.0**)	64 (**22.0**)
Maculopapular rash	50 (**16.9**)	5 (**1.7**)
Anaemia	34 (**11.5**)	63 (**21.6**)
Decreased neutrophil count	31 (**10.5**)	51 (**17.5**)
Neutropenia	20 (**6.8**)	25 (**8.6**)
Decreased white cell count	15 (**5.1**)	32 (**11.0**)
Febrile neutropenia	2 (**0.7**)	16 (**5.5**)

Alopecia, Neuropathy, Pruritus and Fatigue were more common with EV vs Chemo in EV 301

Haematological toxicity was less common in EV vs Chemo
Low rates of FN

Median follow-up: 23.75 months. Analysis of the safety population (all patients who received any amount of study drug).
*TRAEs are ‡A total of 113 patients AEs for which there is a reasonable possibility that the event was caused by the study treatment, according to the study investigator;[2] †TRAEs that occurred in ≥20% of patients in either treatment group or Grade ≥3 TRAEs that occurred in ≥5% of patients in either treatment group;[1]
(55 in the EV group and 58 in the chemotherapy group) had pre-existing peripheral neuropathy.[2]
AE, adverse event; EV, enfortumab vedotin; NR, not reported; TRAE, treatment-related adverse event, FN, Febrile Neutropenia.
1. Rosenberg JE et al. Presented at ASCO 2022. P4516 . 2. Powles T et al. N Engl J Med 2021;384:1125–1135.

Understanding toxicity: Understanding EV

Event, n (%)[1]	Any grade		Grade ≥3	
	EV (n=296)	Chemotherapy (n=291)	EV (n=296)	Chemotherapy (n=291)
Any TRAE*			155 (**52.4**)	147 (**50.5**)
Most common TRAEs†				
Alopecia			NR	NR
Peripheral sensory neuropathy‡			15 (**5.1**)	6 (**2.1**)
Pruritus			4 (**1.4**)	1 (**0.3**)
Fatigue			20 (**6.8**)	13 (**4.5**)
Decreased appetite			9 (**3.0**)	5 (**1.7**)
Diarrhoea			10 (**3.4**)	5 (**1.7**)
Dysgeusia			NR	NR
Nausea			3 (**1.0**)	4 (**1.4**)
Maculopapular rash			22 (**7.4**)	NR
Anaemia			8 (**2.7**)	23 (**7.9**)
Decreased neutrophil count			18 (**6.1**)	41 (**14.1**)
Neutropenia			14 (**4.7**)	18 (**6.2**)
Decreased white cell count			4 (**1.4**)	21 (**7.2**)
Febrile neutropenia	2 (**0.7**)	16 (**5.5**)	2 (**0.7**)	16 (**5.5**)

Grade≥3 toxicities with **EV** had to do with **SKIN, NEUROPATHY** and **FATIGUE**

Grade≥3 toxicities with **CHEMO** had to do with **HEMATOLOGICAL, TOX**

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‡A total of 113 patients (55 in the EV group and 58 in the chemotherapy group) had pre-existing peripheral neuropathy.[2]
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Efficacy in a consistent fashion

Investigator-assessed clinical response rate in patients previously treated with chemotherapy and a PD-1/L1 inhibitor*

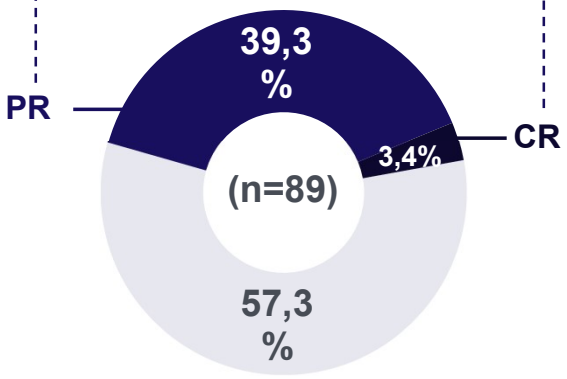
EV-101[1]

Phase I dose-escalation/ dose-expansion study

ORR (CR + PR):

42.7%

(95% CI: 32.3–53.6)



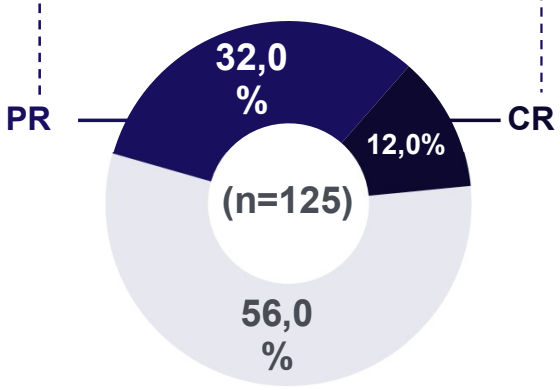
EV-201 Cohort 1[2]

Phase II, single-arm, open-label study

ORR (CR + PR):

44.0%

(95% CI: 35.1–53.2)



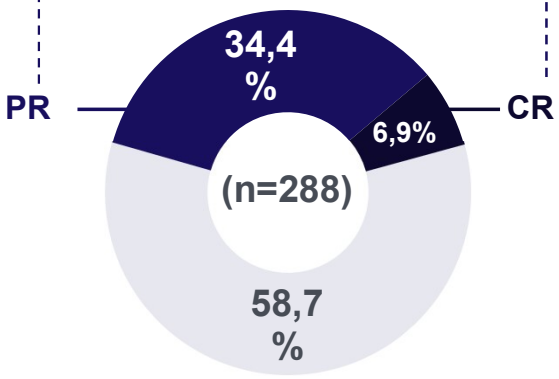
EV-301[3]

Phase III, randomised, active-controlled study

ORR (CR + PR):

41.3%

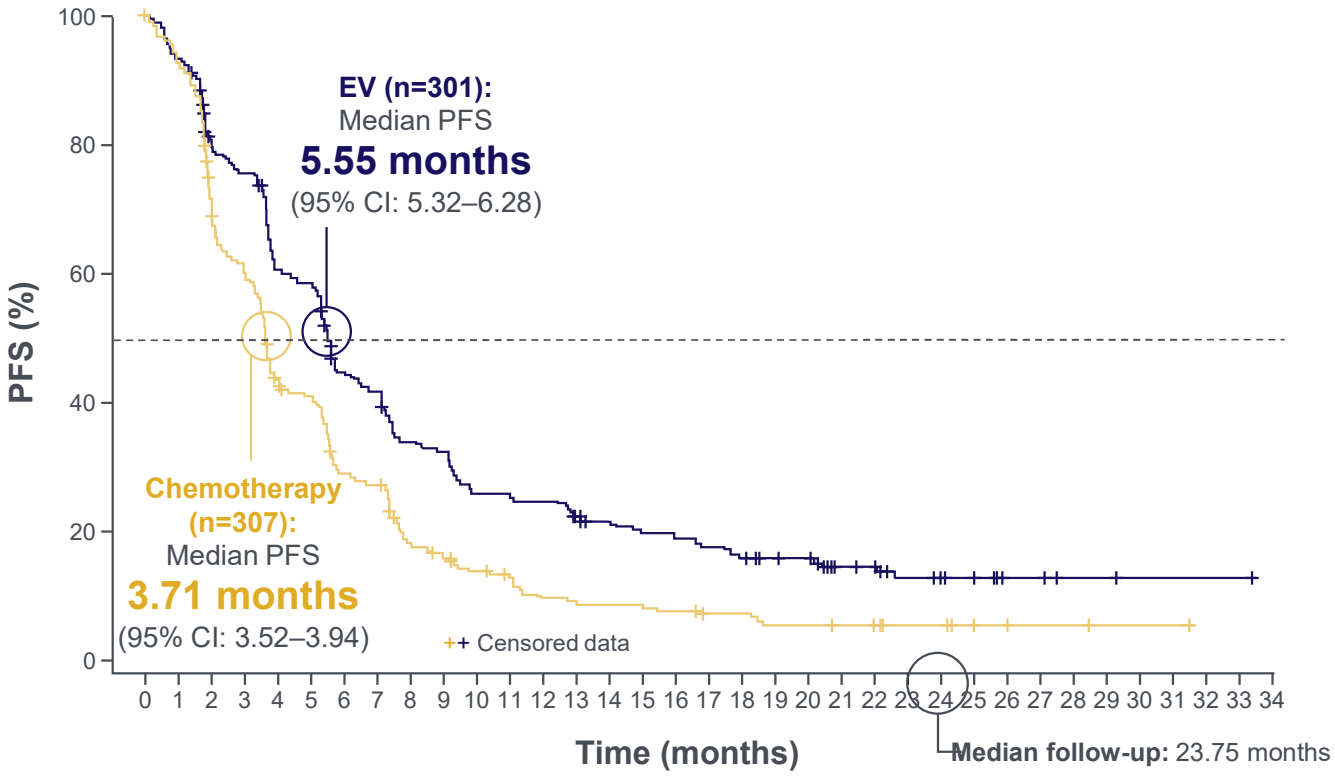
(95% CI: 35.6–47.3)



*Best confirmed responses according to RECIST v1.1.[1–3]
CI, confidence interval; CR, complete response; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; ORR, overall response rate; PD-1/L1, programmed cell death protein 1/ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Rosenberg J et al. *J Clin Oncol* 2020;38:1041–1049; 2. Rosenberg JE et al. *J Clin Oncol* 2019;37:2592–2600; 3. Rosenberg JE et al. Presented at ASCO 2022. P4516.

Efficacy in delaying progression



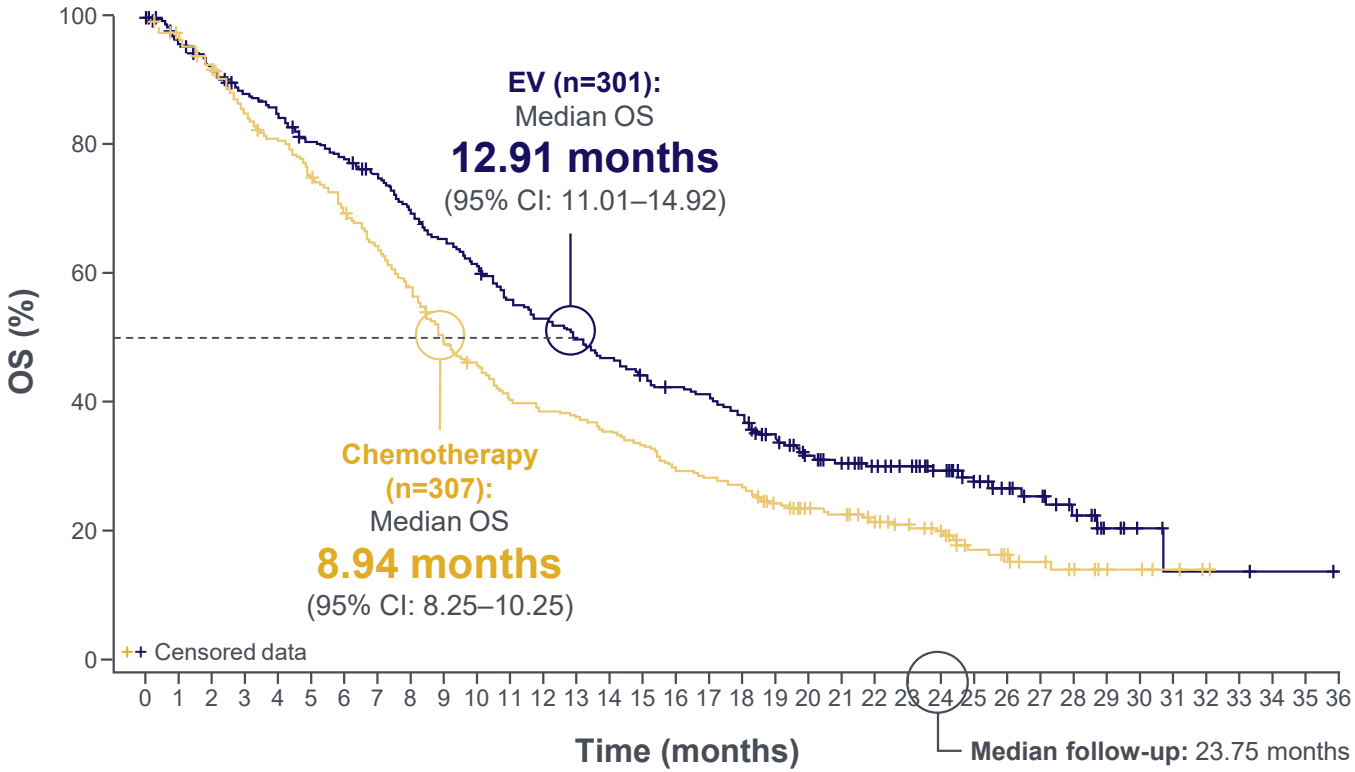
37% lower

risk of **progression or death** with EV vs. single-agent chemotherapy in the 2-year analysis

Median PFS: 5.55 vs. 3.71 months;
HR: 0.63
(95% CI: 0.53–0.76; p=0.00001)

Figure adapted from Rosenberg JE et al. 2022.
Analysis of the intention-to-treat population (all randomised patients).
CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; PFS, progression-free survival.
Rosenberg JE et al. Presented at ASCO 2022. P4516.

Efficacy in improving overall survival



30% lower

risk of **death** with EV vs. single-agent chemotherapy in the **2-year analysis**

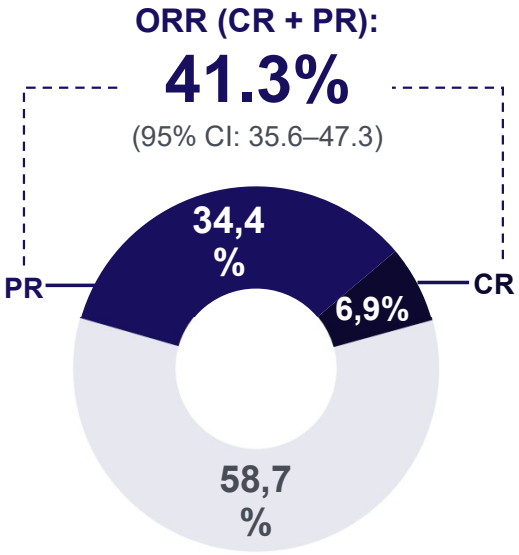
Median OS: 12.91 vs. 8.94 months;
HR 0.70
(95% CI: 0.58–0.85; p<0.001)

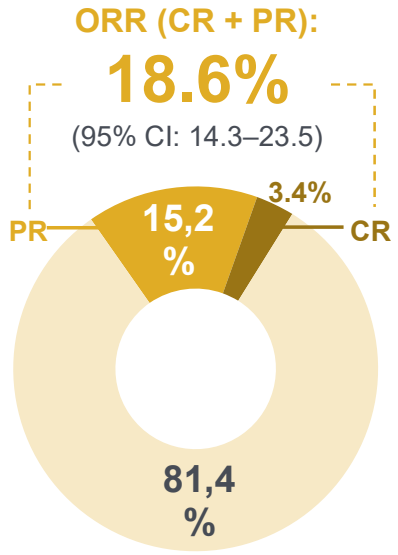
Figure adapted from Rosenberg JE et al. 2022.
Analysis of the intention-to-treat population (all randomised patients).
CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; OS, overall survival.
Rosenberg JE et al. Presented at ASCO 2022. P4516.

Efficacy in decreasing tumor burden

Response

Investigator-assessed clinical response rate*

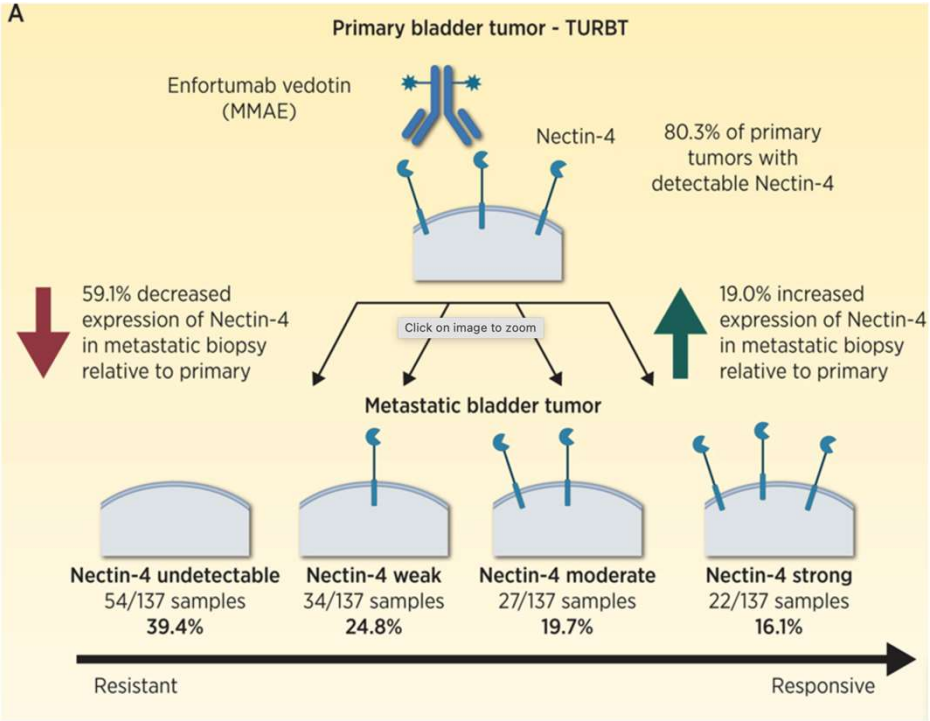




The confirmed ORR was **~2.2 times higher in the EV group** than the chemotherapy group (41.3% vs. 18.6%; p<0.001)

Median follow-up: 23.8 months. Analysis of the intention-to-treat population (all randomised patients).
*Responses according to RECIST v1.1, response evaluable population.
CI, confidence interval; CR, complete response; EV, enfortumab vedotin; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
Rosenberg JE et al. Presented at ASCO 2022. P4516.

Nectin-4: Is it clearly predictive?



- Variability of expression of Nectin-4 across settings and studies in bladder cancer [Different antibodies?]
- Still undefined role of NECTIN-4 in mechanisms of resistance
- Some studies revealed high expression of NECTIN-4 in progressors [not involved in res]
- Others suggest downregulation of NECTIN-4 as mechanism of resistance/progression

Reymond N, Fabre S, Lecocq E, Adelaïde J, Dubreuil P, Lopez M. Nectin4/PRR4, a new afadin-associated member of the nectin family that trans-interacts with nectin1/PRR1 through V domain interaction. *J Biol Chem* 2001;276(46):43205–15Brancati F, Fortugno P, Bottillo I, Lopez M, Josselin E, Boudghene-Stambouli O, et al. Mutations in PVRL4, encoding cell adhesion molecule nectin-4, cause ectodermal dysplasia-syndactyly syndrome. Am J Hum Genet 2010;87(2):265–73Chu CE, Sjöström M, Egusa EA, Gibb EA, Badura ML, Zhu J, et al. Heterogeneity in NECTIN4 Expression Across Molecular Subtypes of Urothelial Cancer Mediates Sensitivity to Enfortumab VedotinNECTIN4 Expression Mediates Sensitivity to EV. Clinical Cancer Research 2021;27(18):5123–30Hoffman-Censits J, Lombardo K, McConkey D, Hahn NM, Bashir B, Kelly WK, et al. New and topics: enfortumab vedotin mechanisms of response and resistance in urothelial cancer - What do we understand so far? Urol Oncol 2021;39(10):619–22

H-Score System

- H-score system, which is the product of **intensity** (score, 0–3), and **percentage** of stained cells (0–100)

- Specimens are classified as **negative** (0; H-score, 0–14), **weak** (1+; H-score, 15–99), **moderate** (2+; H-score, 100–199), and **strong** (3+; H-score, 200–300).

Challita-Eid PM, Satpayev D, Yang P, et al. Enfortumab Vedotin Antibody-Drug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models. *Cancer Res.* 2016;76:3003–3013.