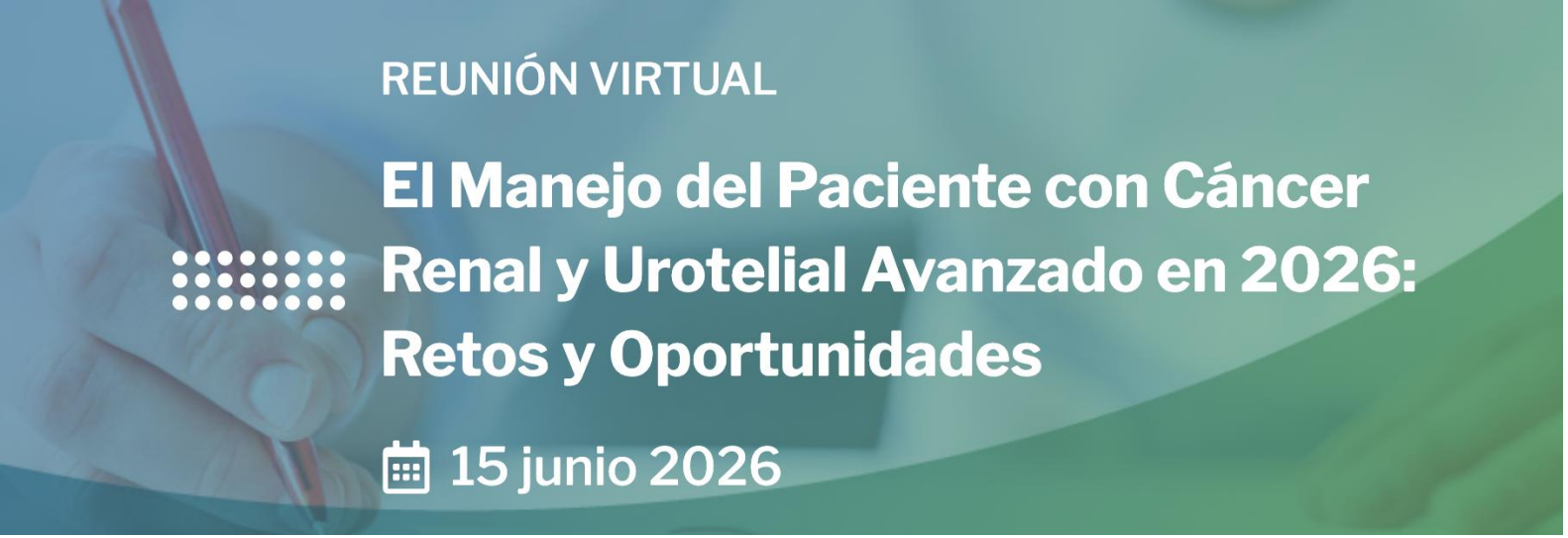


Advanced Bladder Cancer: A global review

Ignacio Duran, MD, PhD

Hospital Universitario Marques de Valdecilla. IDIVAL

Santander

My disclosures

- **Compensated Advisory Boards:**
  - MSD, BMS, Roche-Genentech, Astellas, PYCYC, IPSEN, Novartis, Bayer, Astra-Zeneca
- **Research Funding [institution]:**
  - Roche-Genentech, Astra-Zeneca
- **Cover of Travel expenses:**
  - Roche-Genentech, IPSEN, Astra-Zeneca, Bayer
- **Clinical Trials [collaboration]:**
  - BMS, Roche-Genentech, PYCYC, EISAI, MSD, Tahio Oncology, Gilead, Exelixis, Bicycle Therapeutics,
- **Compensated Lectures:**
  - EUSA pharma, MSD, BMS, Roche-Genentech, IPSEN, Jansen, Astellas, Bayer, Astra-Zeneca
- **Clinical trial [lead]:** Gilead [PI of PRISMA-1 study]

Learning objectives

- To briefly review mUC therapeutics with a historical approach and understand current standard of care in June 2026 in Spain as an introduction to the case/s to be discussed

Outline

- Epidemiology
- Introduction
- Historical treatment data
- Current treatment options
- Take home message
- Q&A

Epidemiology: How relevant is BC?

- **614,298** new diagnoses of bladder cancer worldwide in 2022 and over 220.000 deaths
- Age primary risk factor, **median diagnosis age of 73** in USA [68 y/o in Spain (Ebano)]
- Long-term exposure to carcinogens, **especially tobacco smoke**, accounts for >50% of cases, followed by occupational exposure to aromatic amines, benzene, and ionizing radiation.
- Men are diagnosed **three to four times more frequently than women**, with lifetime risks of 1.1% in men and 0.27% in women.
- In Spain around **24.000 new cases** of bladder cancer are expected in 2026, with an incidence of around 20/105making it the country with the highest incidence worldwide

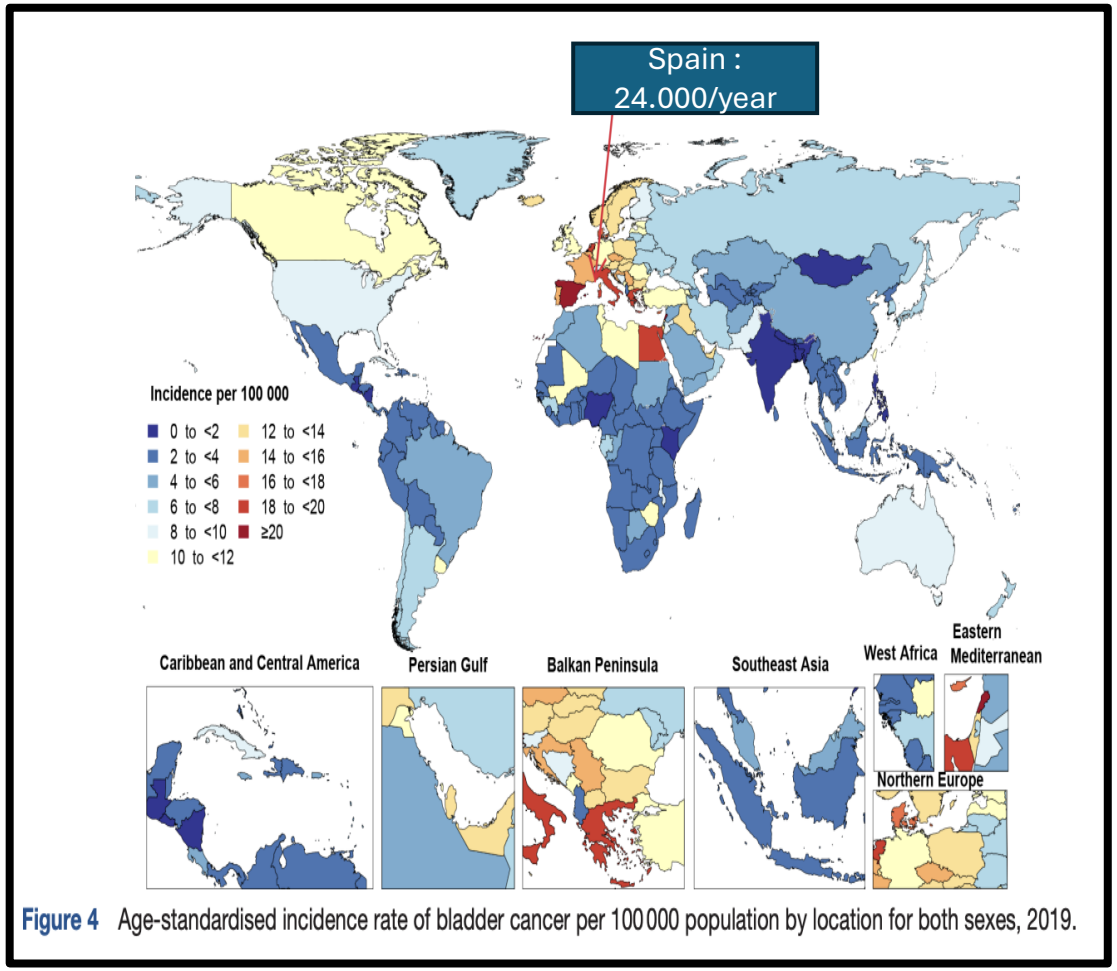


Figure 4 Age-standardised incidence rate of bladder cancer per 100 000 population by location for both sexes, 2019.

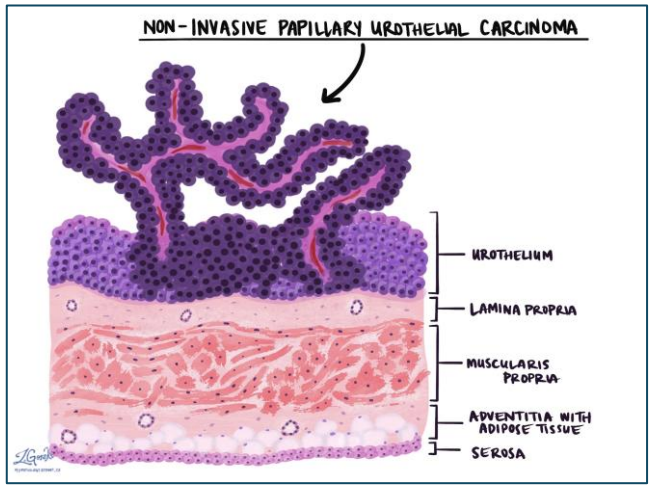
Burger M, Catto JW, Dalbagni G et al Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013 Feb;63(2):234-41.; https://www.iarc.who.int/cancer-type/bladder-cancer/ ; Safiri S, Kolahi AA, Naghavi M; Global Burden of Disease Bladder Cancer Collaborators. Global, regional and national burden of bladder cancer and its attributable risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease study 2019. BMJ Glob Health. 2021 Nov;6(11):e004128. doi: 10.1136/bmjgh-2020-004128.

Introduction

- Bladder cancer is classified by invasion depth into **non-muscle-invasive** (NMIBC) and **muscle-invasive** (MIBC) forms.

- NMIBC, confined to the **urothelium and lamina propria**, represents **nearly 70%** of organ-confined bladder cancer with a generally good prognosis.

- MIBC involves the **muscle layer or beyond**, represent **about 20%** of cases at diagnosis and may progress to advanced disease in about half of the cases.



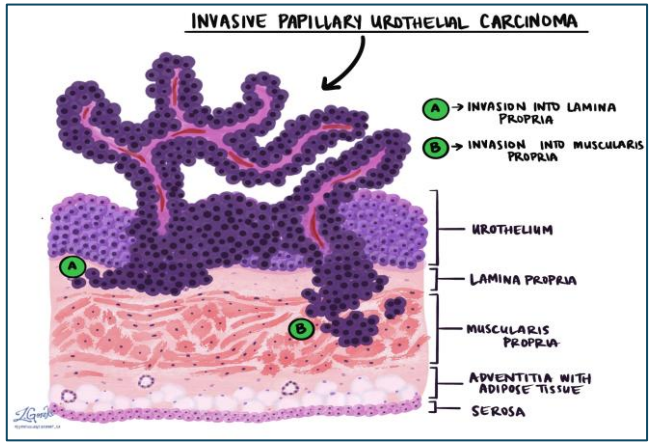
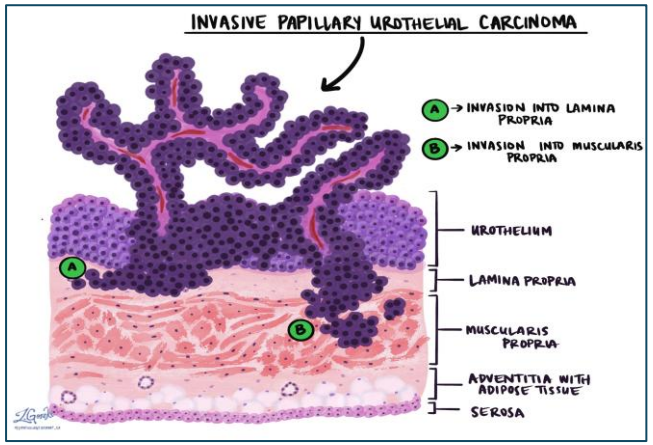


Image from https://www.mypathologyreport.ca/diagnosis-library/high-grade-papillary-urothelial-carcinoma/

Muscle invasive bladder cancer

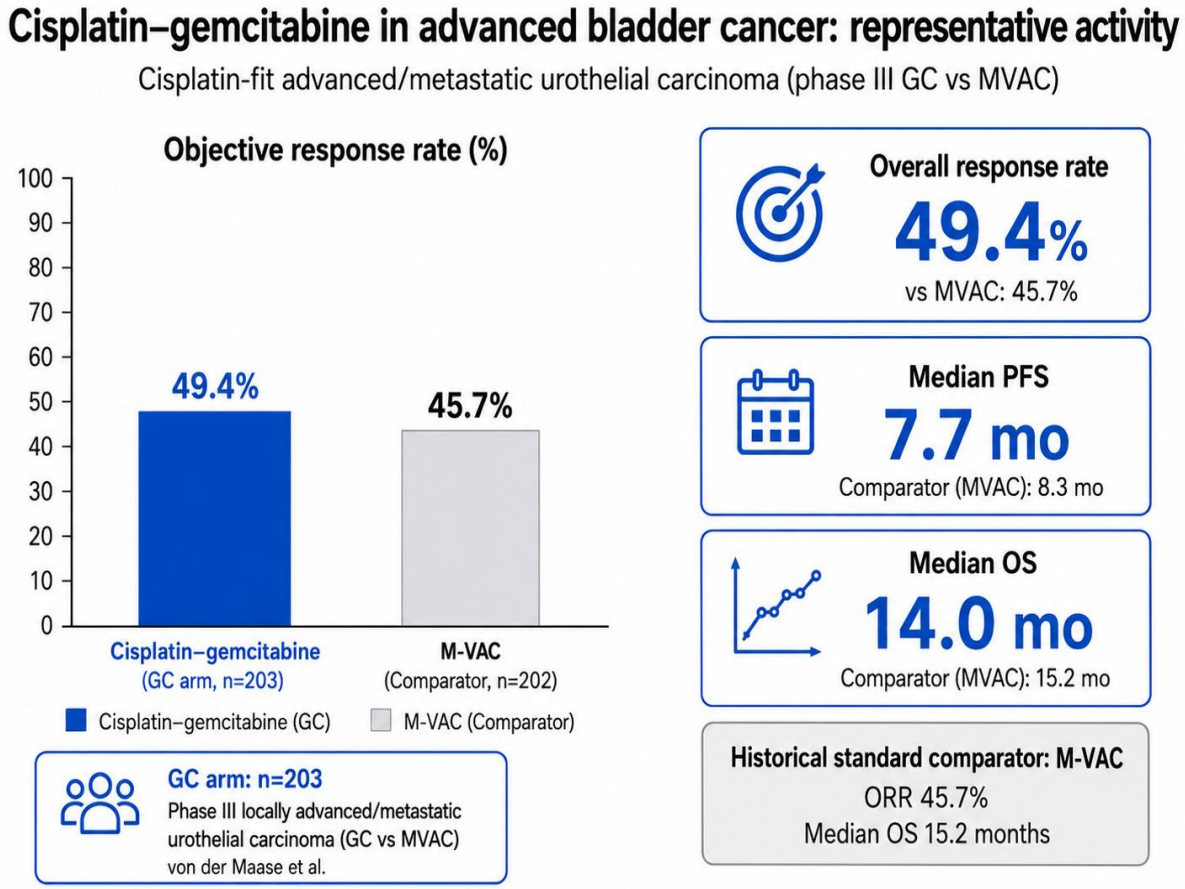
- MIBC management typically involves **perioperative treatment** [platinum-based chemotherapy/ADC plus ICI] followed by **radical cystectomy,** pelvic lymph node dissection, and urinary diversion +/- adjuvant treatments
- Alternatives exist that include **bladder preservation strategies** [i.e. chemoradiation] and partial cystectomy in selected cases.
- Despite optimal treatment, MIBC is aggressive, with about 50% progressing to advanced disease



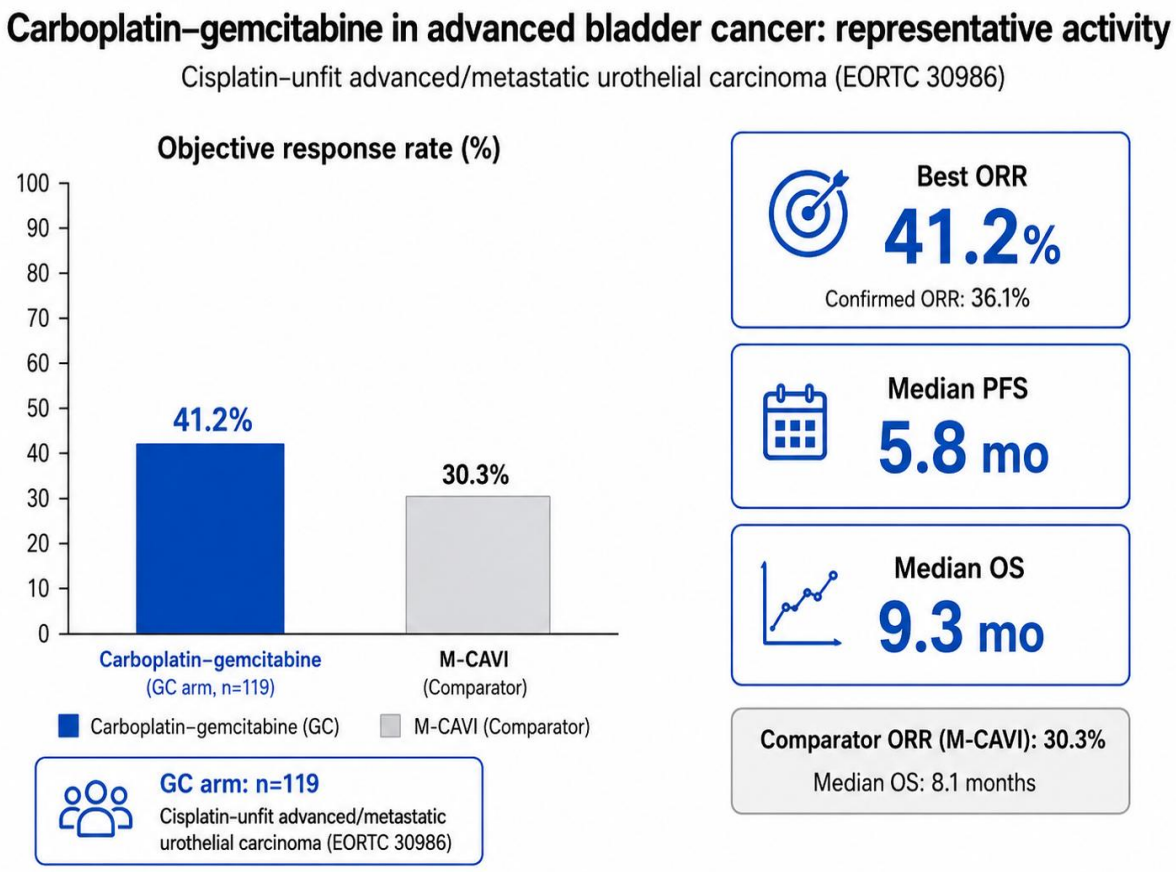
Alfred Witjes, J., et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2023 Guidelines. Eur Urol, 2024. 85: 17.

Our weapons, not so long ago…….

WE USED TO DIVIDE PATIENTS ACCORDING TO ELIGIBILITY TO RECEIVE CISPLATIN



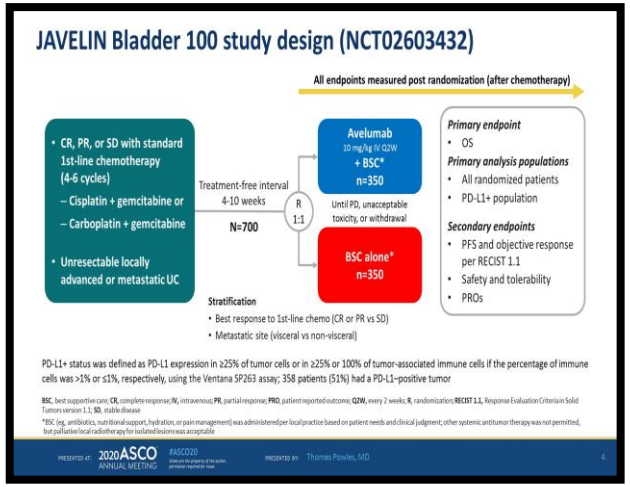
Representative historical efficacy summary based on von der Maase et al., J Clin Oncol 2000 and long-term follow-up J Clin Oncol 2005 in advanced urothelial carcinoma. Values shown for the cisplatin–gemcitabine arm; comparator shown for context.



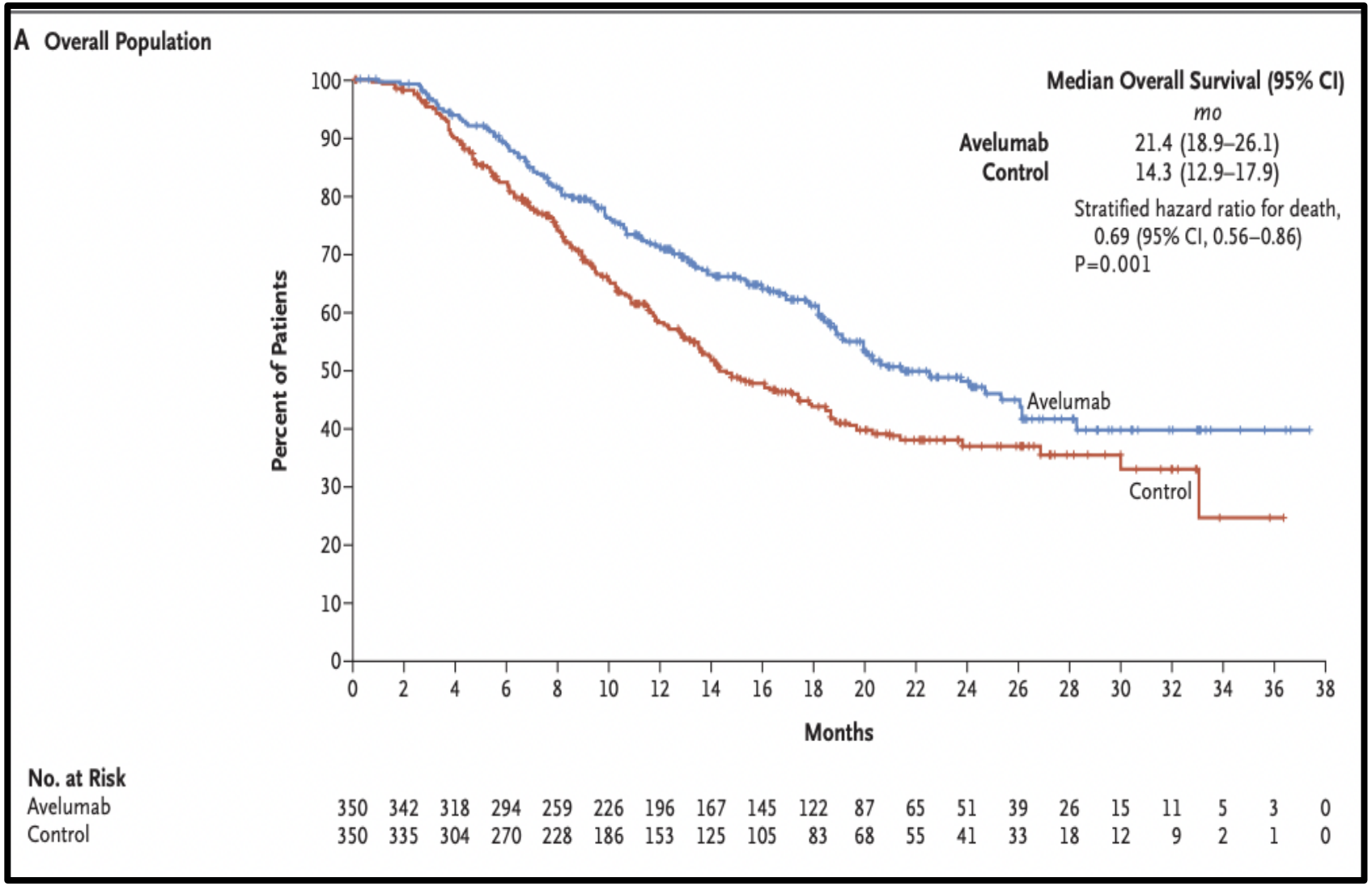
Representative historical efficacy summary based on EORTC 30986 (De Santis et al., J Clin Oncol 2012) in cisplatin–unfit advanced urothelial carcinoma. Values shown for the carboplatin–gemcitabine arm; comparator shown for context.

A historical **median overall survival (OS) of 13-15 months** and <10%of the patients surviving beyond 5 years

CPI as maintenance as a strategy

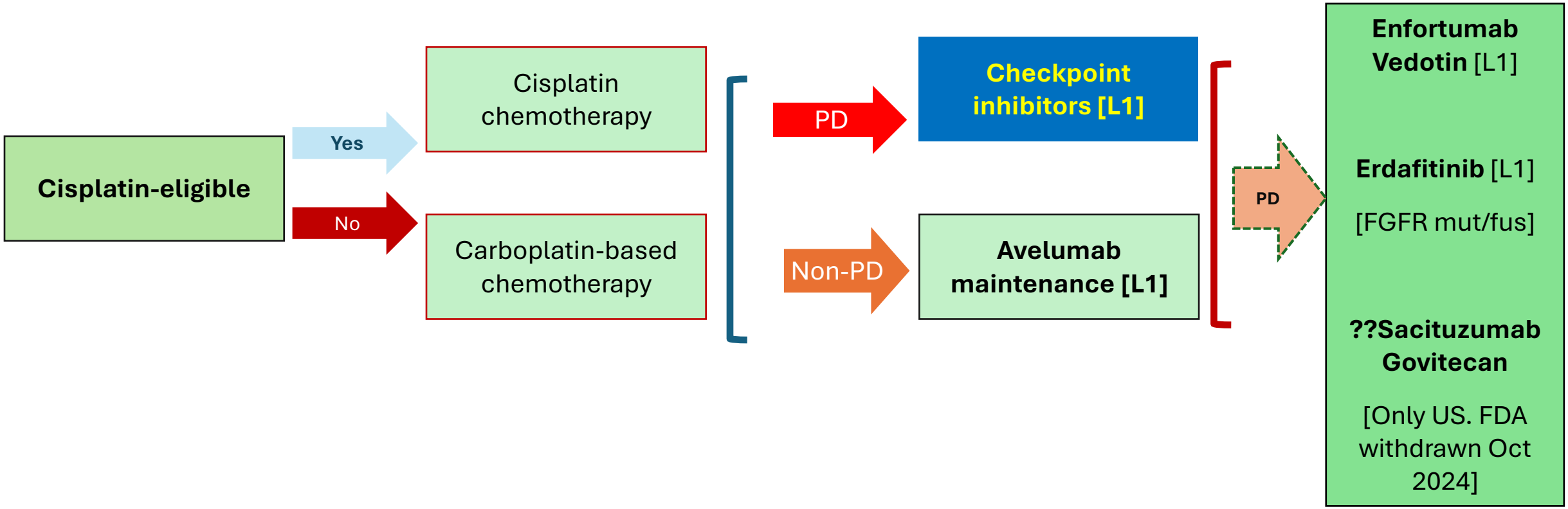


JAVELIN showed that first-line **maintenance avelumab therapy** in patients with advanced urothelial carcinoma with disease that **had not progressed with platinum-based chemotherapy** resulted in significantly longer overall survival than best supportive care alone



Powles T et al. ASCO 2020 Plennary sesión and NEJM 2020

mUC treatment: The picture not so long ago



Where did things start to be cooked?

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY | AUTHOR CHOICE | MAY 12 2016

Enfortumab Vedotin Antibody–Drug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models FREE

Pia M. Challita-Eid ✉; Daulet Satpayev; Peng Yang; Zili An; Karen Morrison; Yuriy Shostak; Arthur Raitano; Rossana Nadell; Wendy Liu; Dawn Ratay Lortie; Linnette Capo; Alla Verlinsky; Monica Leavitt; Faisal Malik; Hector Aviña; Claudia I. Guevara; Nick Dinh; Sher Karki; Banmeet S. Anand; Daniel S. Pereira; Ingrid B.J. Joseph; Fernando Doñate; Kendall Morrison; David R. Stover

Through a suppression subtractive hybridization, it was identified **nectin-4 (PVRL4),** a type I **transmembrane protein** and member of a family of related immunoglobulin-like **adhesion molecules,** as a potential target in epithelial cancers.

They conducted immunohistochemical analysis of 2,394 patient specimens from bladder, breast, lung, pancreatic, ovarian, head/neck, and esophageal tumors and found that **69% of all specimens stained positive for nectin-4.**

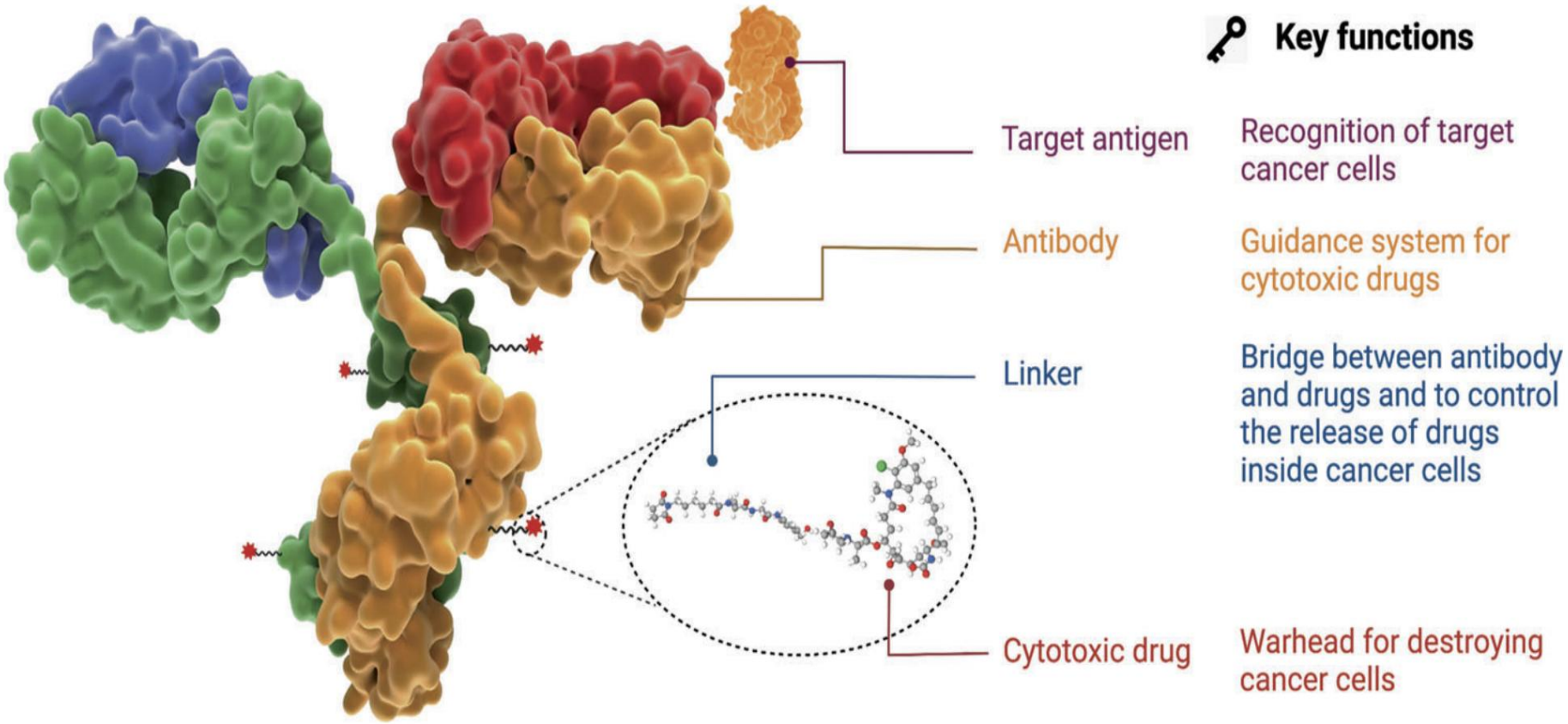
Moderate to strong staining was especially observed in **60% of bladder** and 53% of breast tumor specimens, whereas the expression of nectin-4 in normal tissue was more limited.

They generated a **novel antibody–drug conjugate** (ADC) enfortumab vedotin comprising the human anti-nectin-4 antibody conjugated to the highly potent microtubule-disrupting agent **MMAE**.

The **in vivo efficacy of AGS-22M6E** generally **correlated well with the expression level of nectin-4 in xenografts** and cell lines.

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 May 15;76(10):3003-13.

A “new” class of drugs: Antibody Drug Conjugate

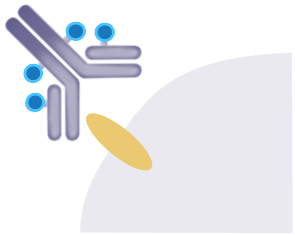


ADC consists of a tumor targeting **mABS** conjugated to a **CYTOTOXIC PAYLOAD** through a sophisticatedly designed **CHEMICAL LINKER,** enabling the ability of precise targeting and potent effectiveness simultaneously.

Sievers, E. L. & Senter, P. D. Antibody-drug conjugates in cancer therapy. Annu. Rev. Med. 64, 15–29 (2013).

Mechanism of action

1

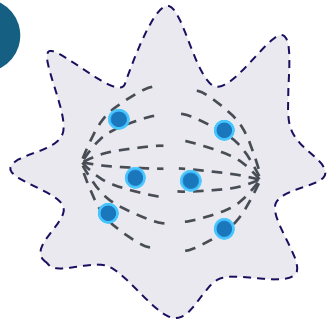


EV **binds to Nectin-4** on the surface of UC cells

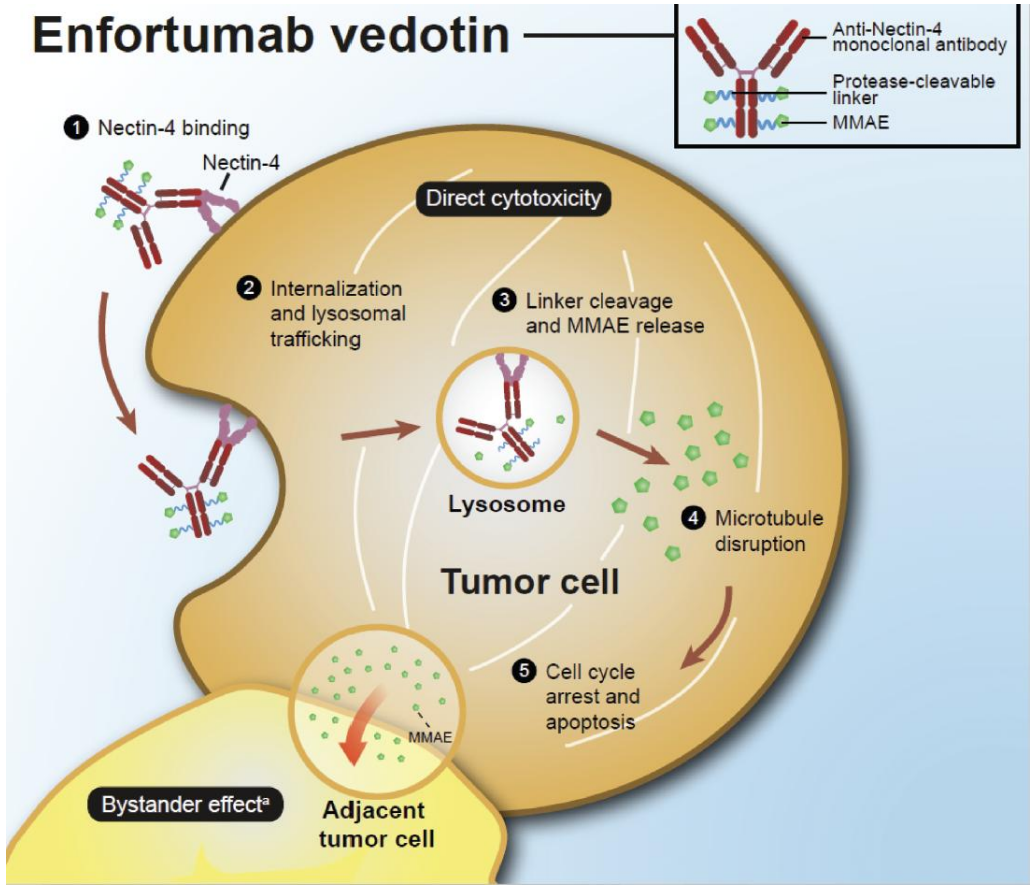
2

EV is **internalised** and the linker is cleaved, releasing MMAE

3

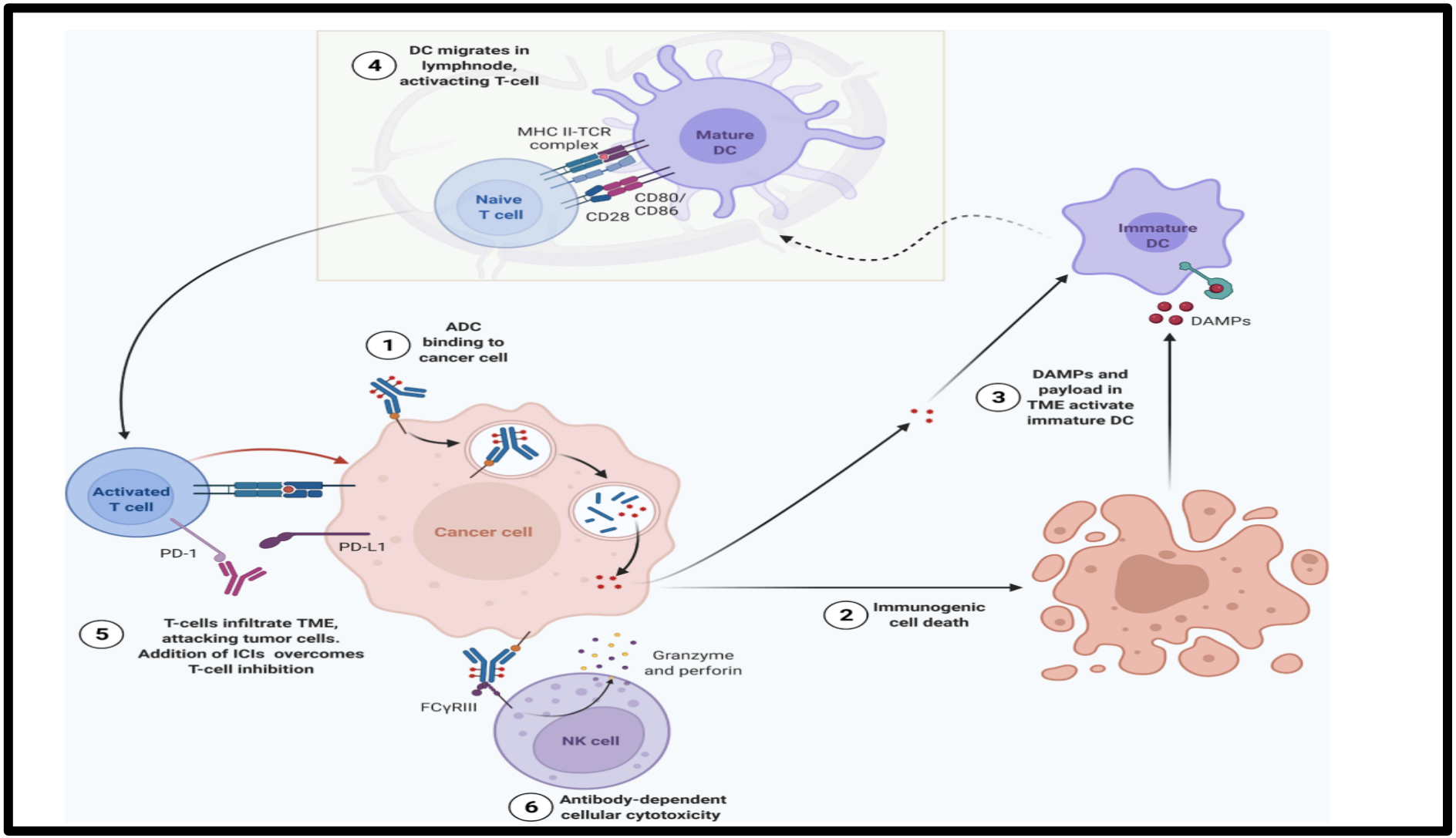


MMAE disrupts microtubules and causes cell apoptosis



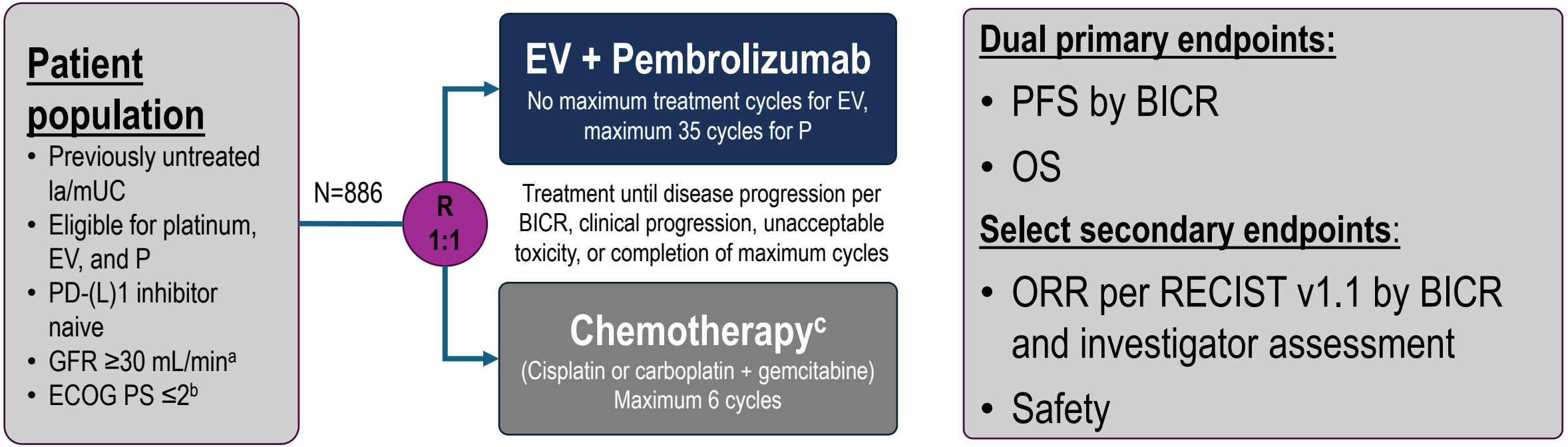
- Image of EV structure adapted from Alt M et al. 2020.[3]
- ADC, antibody–drug conjugate; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; UC, urothelial carcinoma.
- 1. Moussa M et al. *Drug Des Dev Ther* 2021;15:453–462; 2. Jain RK et al. *Cancer Manag Res* 2020;12:8379–8386; 3. Alt M et al. *Ther Adv Urol* 2020;12:1756287220980192.

Could Immunotherapy be a good partner of EV?



DAMPs: Damage-associated molecular patterns

EV-302/KEYNOTE-A39 (NCT04223856)



Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors

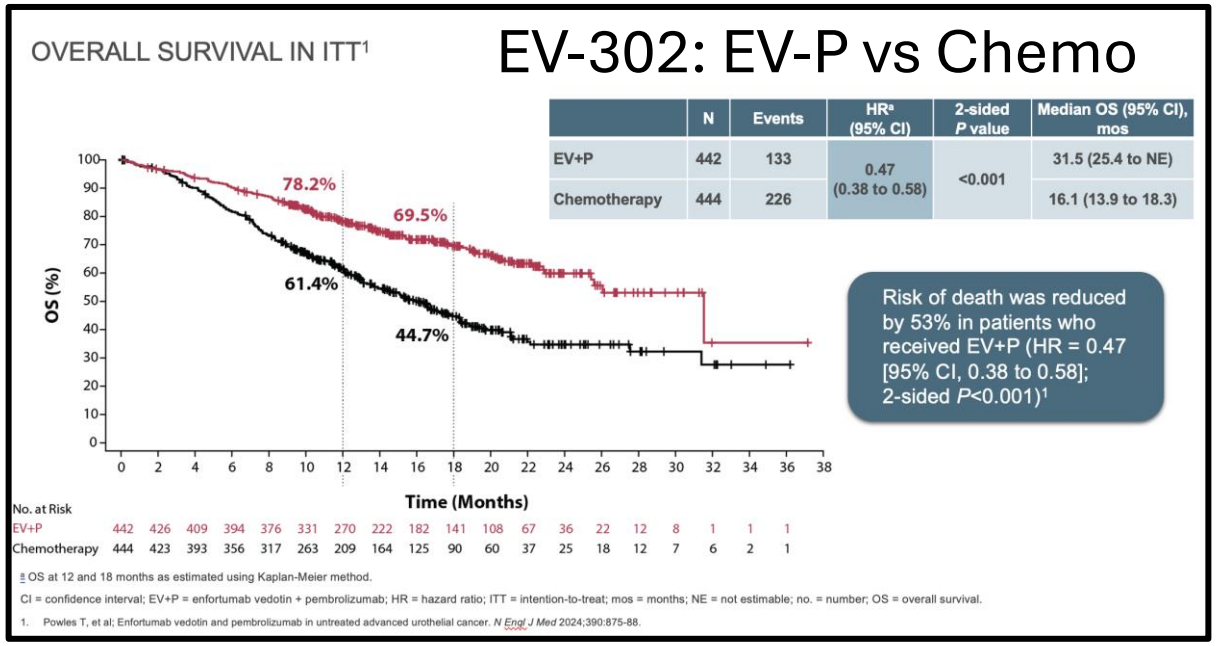
[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine

[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure

[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy

Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

mUC treatment: Upside down



The PD-1 inhibitor **pembrolizumab** combined with the antibody drug conjugate **enfortumab vedotin** (EV) received accelerated Food and Drug Administration (FDA) approval for cisplatin-ineligible la/mUC patients and **full approval for first-line la/mUC regardless of platinum eligibility**, recommended by ESMO since March 2024 based upon data shared in **ESMO 2023** by Thomas Powles (**Study EV 302-KN-A39**) that showed a substantial benefit for this combo.

Powles T, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, Iyer G, Vulsteke C, Park SH, Shin SJ, Castellano D, Fornarini G, Li JR, Gümüş M, Mar N, Loriot Y, Fléchon A, Duran I, Drakaki A, Narayanan S, Yu X, Gorla S, Homet Moreno B, van der Heijden MS; EV-302 Trial Investigators. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med. 2024 Mar 7;390(10):875-888.

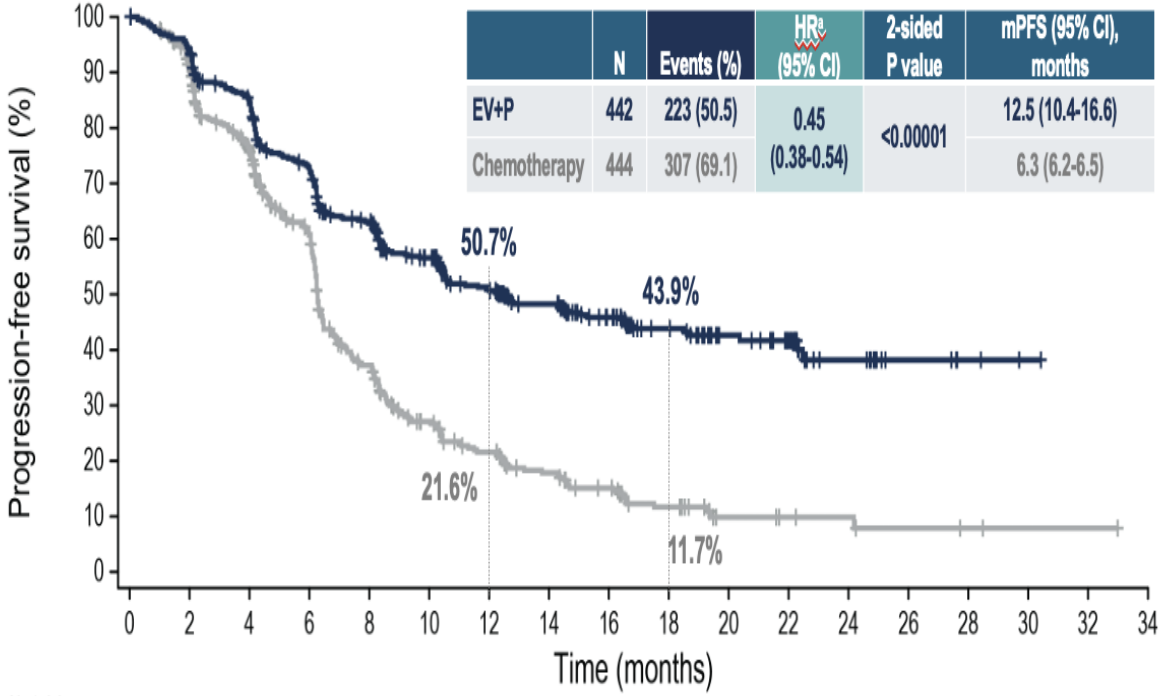
The data matured well

Progression-Free Survival per BICR

ESMO 2023

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

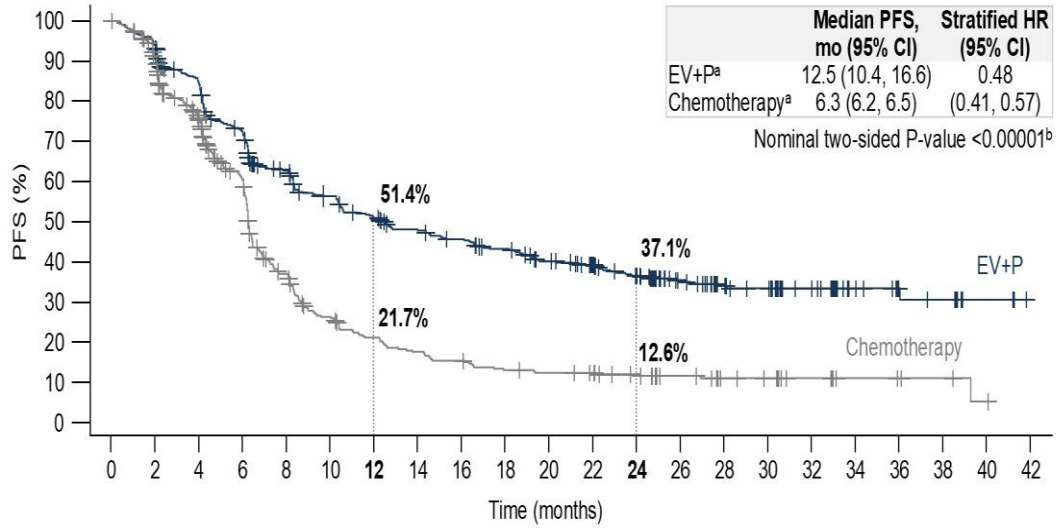
PFS by BICR in the Overall Population

ASCO GU 2025

PFS benefit with EV+P was maintained with 1 additional year of follow-up

	Median PFS, mo (95% CI)	Stratified HR (95% CI)
EV+P[a]	12.5 (10.4, 16.6)	0.48
Chemotherapy[a]	6.3 (6.2, 6.5)	(0.41, 0.57)

Nominal two-sided P-value <0.00001[b]



No. at risk

EV+P	442	409	361	304	254	223	200	182	172	159	143	128	109	82	62	57	42	22	14	10	4
Chemotherapy	444	379	296	213	125	86	68	57	50	42	39	37	31	23	16	14	9	5	4	3	1

Data cutoff: August 8, 2024.

EV, enfortumab vedotin; P, pembrolizumab; PFS, progression-free survival.

[a]Events/N were 262/442 for EV+P and 317/444 for chemotherapy. [b]P-value is nominal and descriptive.

ASCO Genitourinary Cancers Symposium #GU25

PRESENTED BY: Thomas B. Powles, MD

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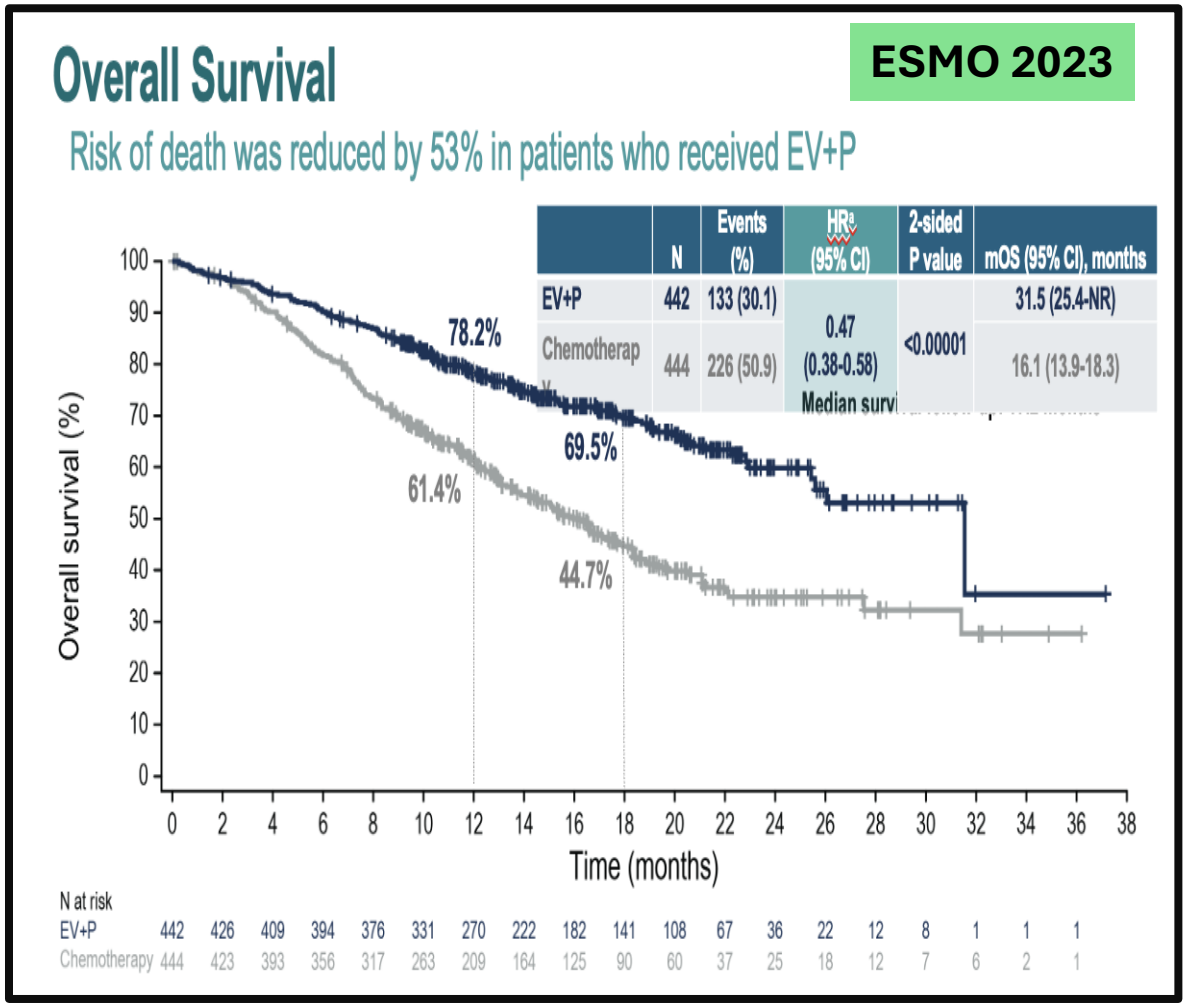
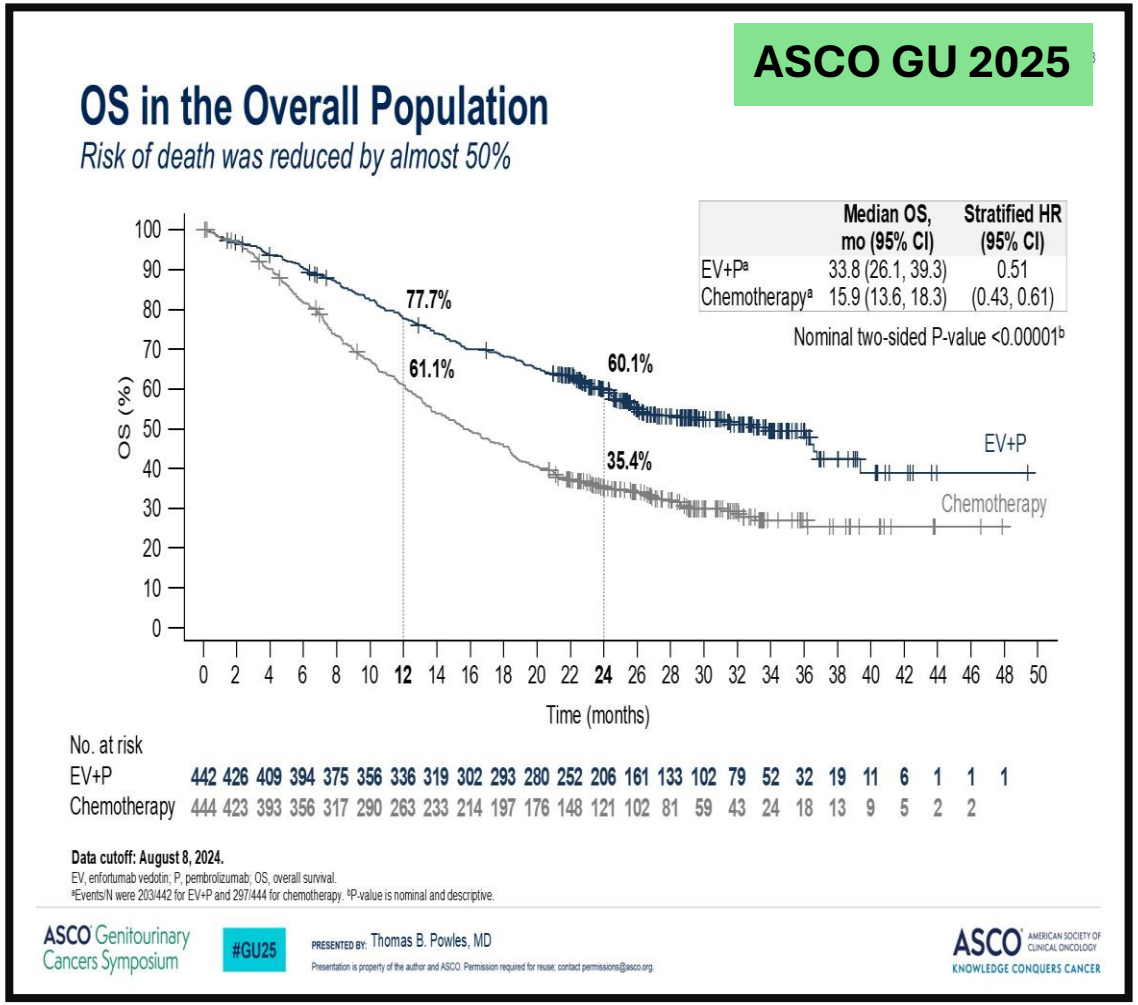
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Update PFS unchanged and HR slightly increased: 0.45--→ HR 0.48

Powles T et al. ESMO 2023. Powles T et al. NEJM 2024; Powles T et al. ASCO GU 2025

The data matured well





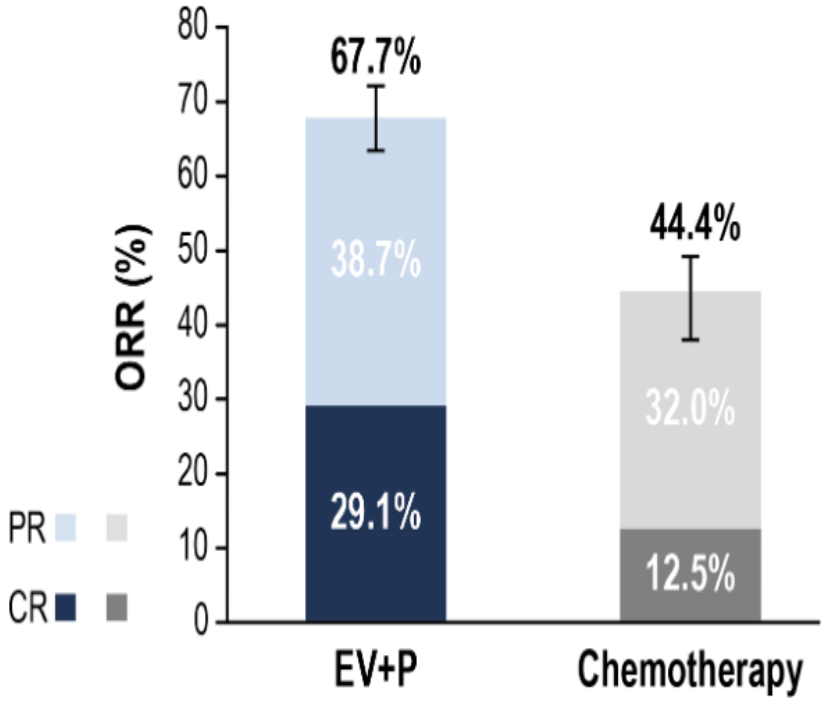
Update OS approaches 3 years (almost 34 months): HR almost unchanged [HR 0.47--→ HR 0.51]

Powles T et al. ESMO 2023. Powles T et al. NEJM 2024; Powles T et al. ASCO GU 2025

The main outcomes

Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



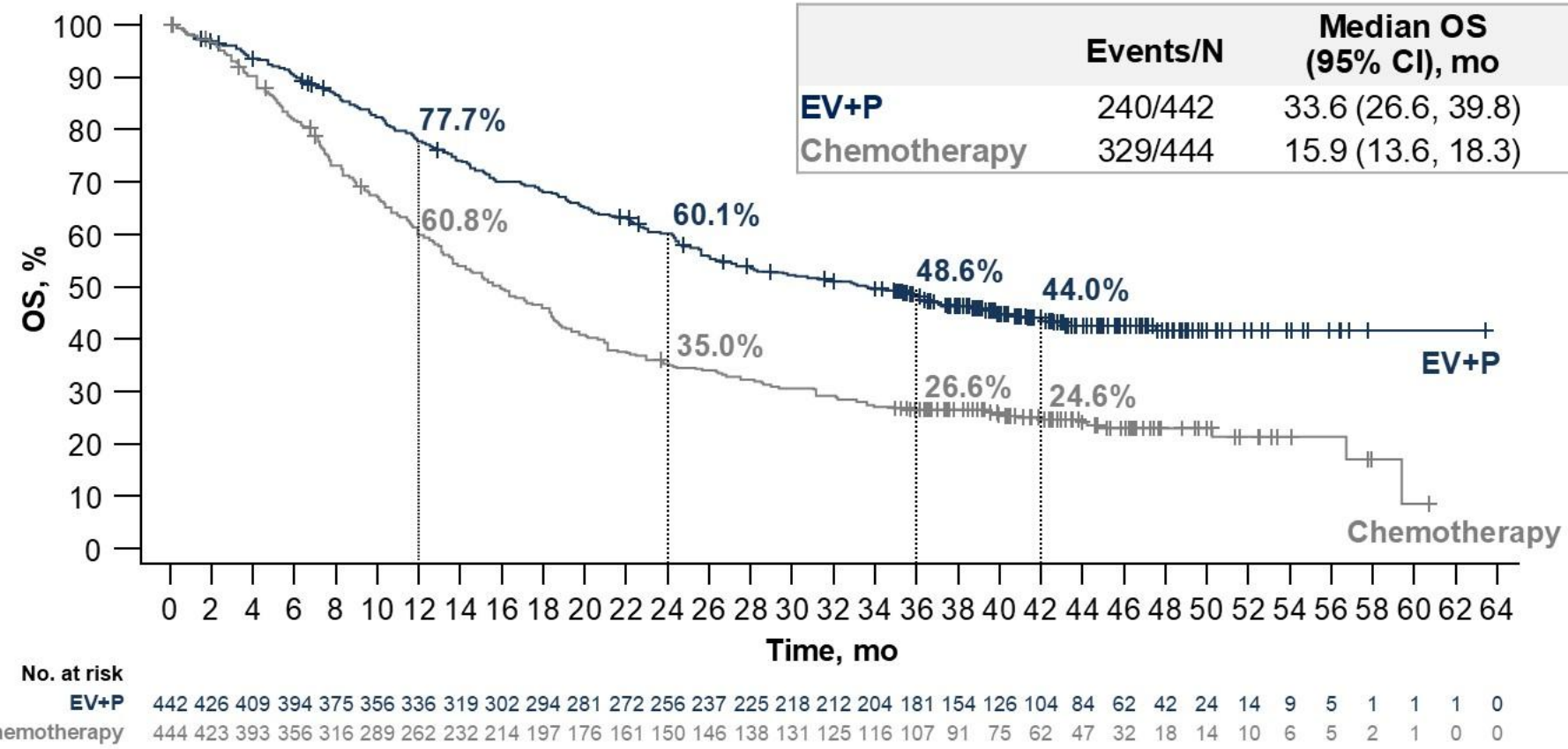
	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)
Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

- ❑ Most patient benefit from EV-P
- ❑ SD+ ORR= 86%
- ❑ 1 in 3 patients achieve a CR
- ❑ The magnitude of the difference is remarkable

Are we curing some patients?

At 3.5 years, an estimated 44.0% of patients in the EV+P arm were alive vs 24.6% in the chemotherapy arm[a]

	Events/N	Median OS (95% CI), mo	Stratified HR (95% CI)
EV+P	240/442	33.6 (26.6, 39.8)	0.53 (0.45, 0.63)
Chemotherapy	329/444	15.9 (13.6, 18.3)	

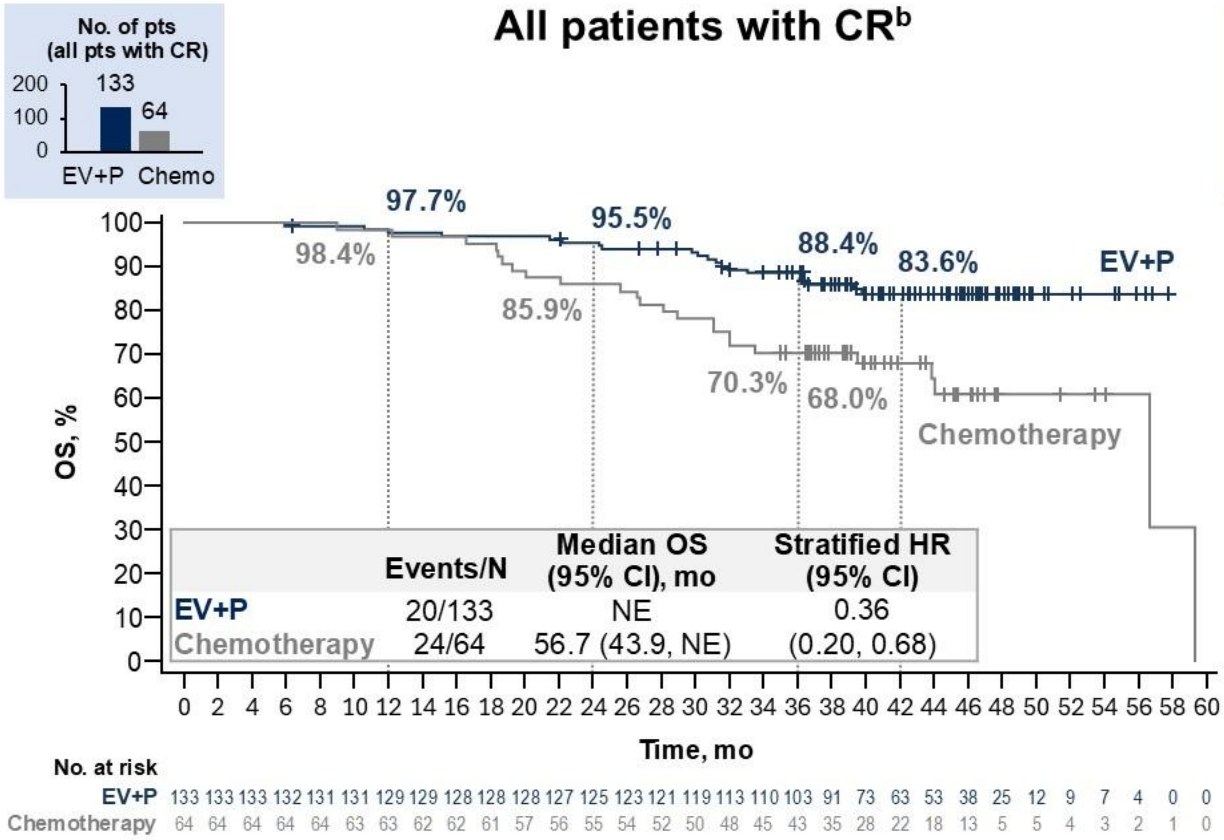


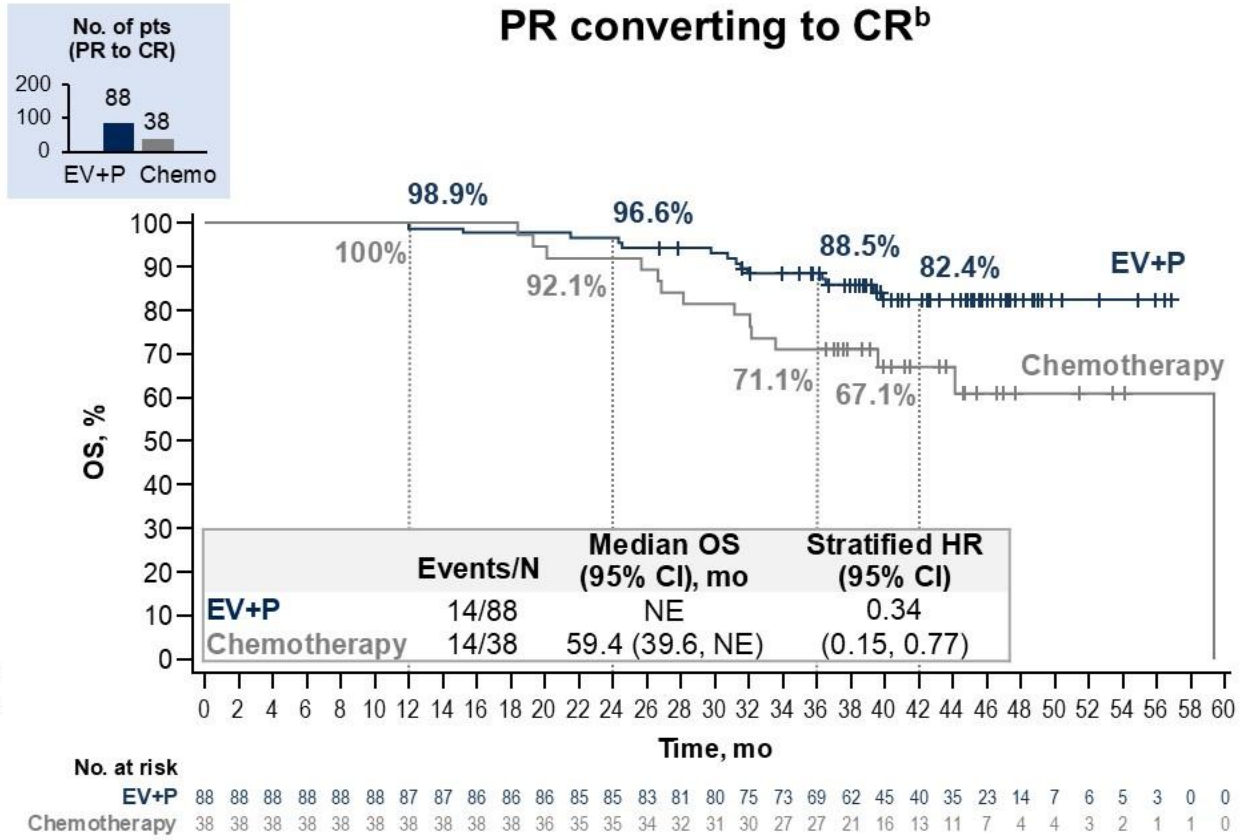
Data cutoff: October 6, 2025. Median follow-up, 42.8 mo.
EV, enfortumab vedotin; ITT, intention to treat; OS, overall survival; P, pembrolizumab.
[a]Based on Kaplan-Meier estimates.

Update OS 3.5 Years HR evolution: HR 0.47--→ HR 0.51]---→ HR 0.53

Are we curing some patients?

Among patients who achieved CR, those whose response deepened from PR to CR had similar 3.5-year survival to the overall CR group (82.4% vs 83.6%)[a]





Data cutoff: October 6, 2025 (BICR data cutoff August 8, 2024).

BICR, blinded independent central review; Chemo, chemotherapy; CR, complete response; EV, enfortumab vedotin; HR, hazard ratio; NE, not estimable; OS, overall survival; P, pembrolizumab; PR, partial response.

[a]Based on Kaplan-Meier estimates. [b]In the response-evaluable set by BICR.

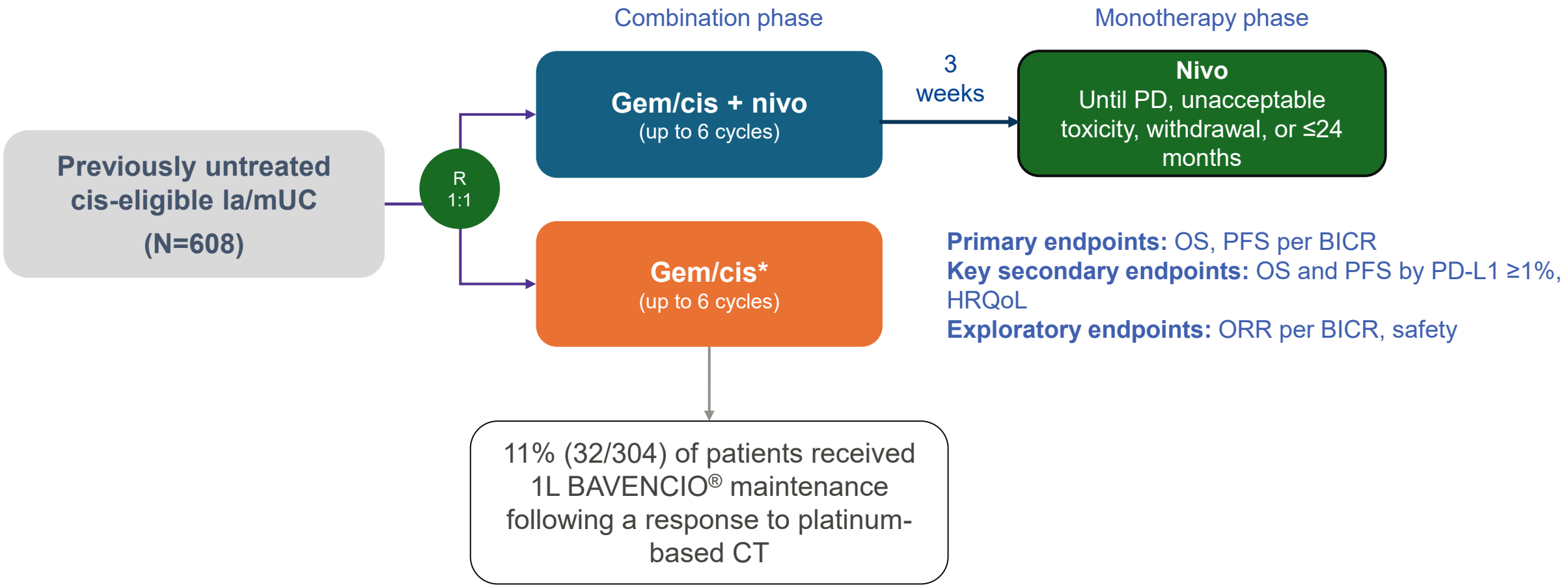
1. Powles T, et al. Ann Oncol 2025;36:1212-19. 2. Gupta S, et al. ASCO 2025. Abstract 4502 (Oral).

PARADIGM SHIFT

A change from one way of thinking to another.

CheckMate 901 substudy: nivo + gem/cis vs gem/cis in la/mUC

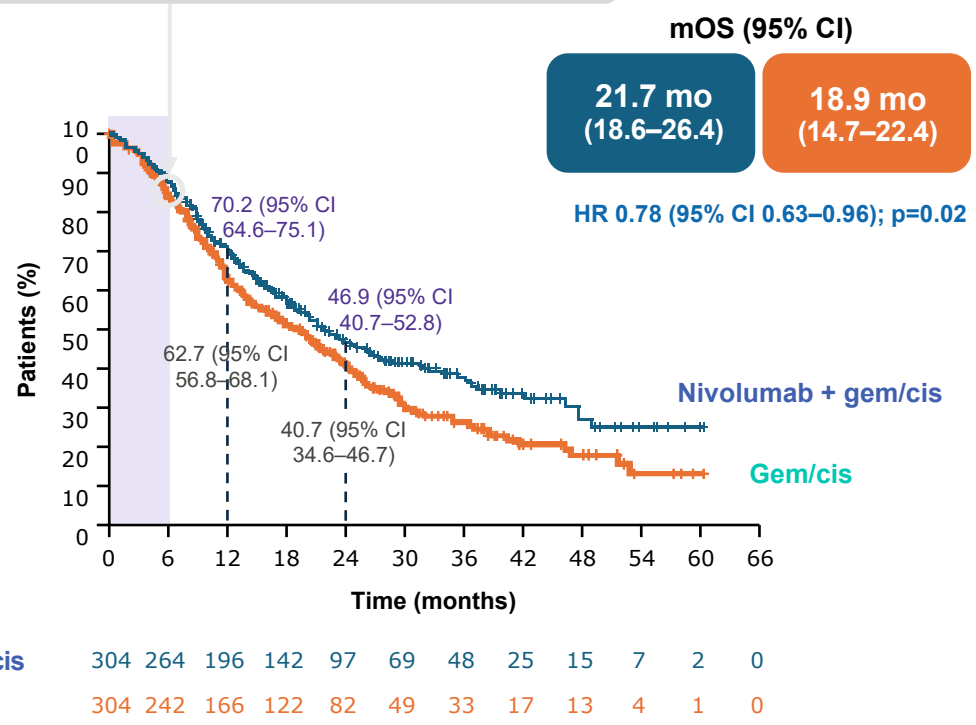
Phase III, international, open-label, randomized trial to evaluate the efficacy and safety of nivo plus gem/cis vs gem/cis for previously untreated unresectable UC or mUC



1. Van der Heijden MS, et al. ESMO 2023 (Abstract No. LBA7 – presentation); 2. Van der Heijden MS, et al. N Engl J Med 2023;389:1778–1789.

CheckMate 901 Substudy: OS, PFS, and TRAE outcomes – overall population

OS benefit was seen after 6 months[1]



OS

mOS (95% CI)

Nivolumab + gem/cis	Gem/cis
21.7 mo (18.6–26.4)	18.9 mo (14.7–22.4)

HR 0.78 (95% CI 0.63–0.96); p=0.02

PFS by BICR

mPFS (95% CI)

Nivolumab + gem/cis	Gem/cis
7.9 mo (7.6–9.5)	7.6 mo (6.1–7.8)

HR 0.72 (95% CI 0.59–0.88); p=0.001

Most common (≥30%) TRAEs

AE	Nivolumab + gem/cis (n=304)		Gem/cis alone (n=288)	
	Any grade n (%)	Grade ≥3* n (%)	Any grade n (%)	Grade ≥3* n (%)
Anemia	174 (57.2)	67 (22.0)	137 (47.6)	51 (17.7)
Nausea	142 (46.7)	1 (0.3)	138 (47.9)	3 (1.0)
Neutropenia	93 (30.6)	57 (18.8)	86 (29.9)	44 (15.3)

*One grade 5 event occurred in each group (sepsis in the nivolumab plus gemcitabine–cisplatin group and acute kidney injury in the gemcitabine–cisplatin group).

Nivolumab + gem/cis was associated with improved OS (+2.8 months) and PFS (+0.3 months) vs gem/cis

1. Van der Heijden MS, et al. N Engl J Med 2023;389:1778–1789.

STANDARD OF CARE IN ADVANCED DISEASE

Management of advanced disease

Treatment-naive advanced or metastatic UC (stage IV)

Treatment-naive advanced or metastatic UC (stage IV) when enfortumab vedotin–pembrolizumab unavailable or contraindicated[d]

Biomarker	Method	Use	LoE, GoR
FGFR3 gene alteration[9]	DNA alterations to FGFR3 can either be detected by PCR (FGFR RT-PCR Kit), by whole exome sequencing or gene panels	FGFR-targeted therapy (erdafitinib) is recommended in patients with FGFR gene alteration in the platinum refractory setting [FGFR3 mutations, or FGFR3 fusions (FGFR RT-PCR Kit)]	I, A
HER2 expression in metastatic setting[10]	IHC to identify HER2 expression on tumor cells.	To select patients for trastuzumab deruxtecan in metastatic setting	III, B

Genomic testing [polymerase chain reaction (PCR) or next-generation sequencing (NGS)-based] should be used for detection of *FGFR2/3* mutations and fusions

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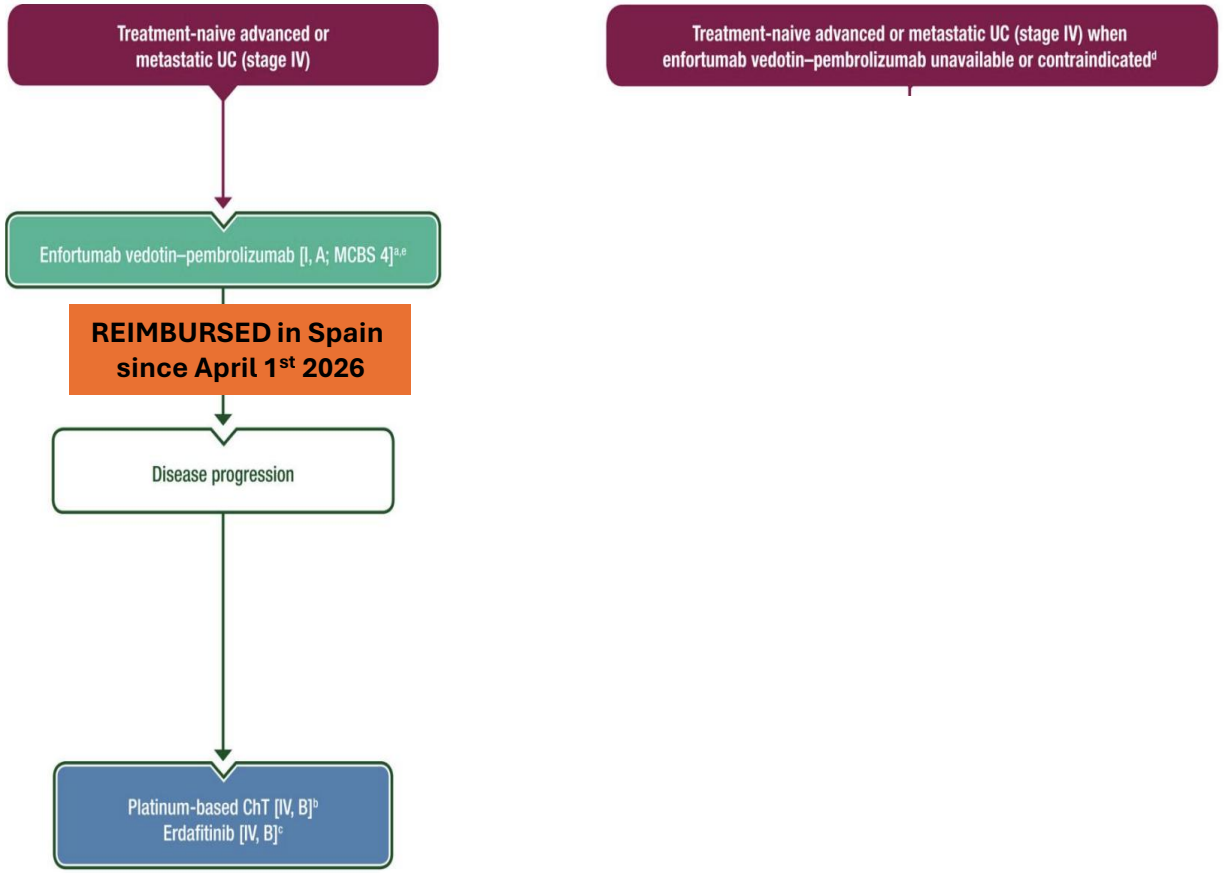
STANDARD OF CARE IN ADVANCED DISEASE

Management of advanced disease



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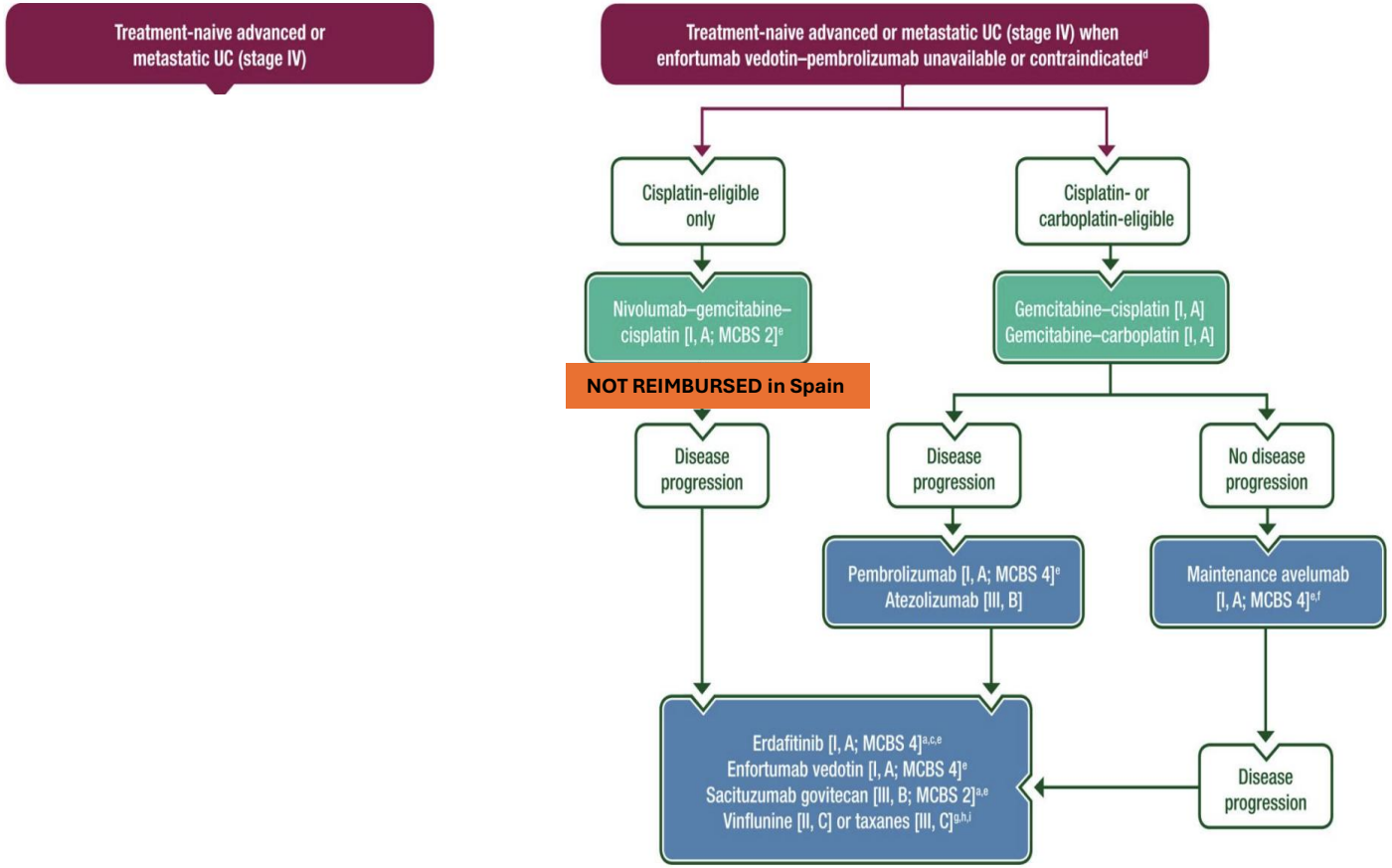

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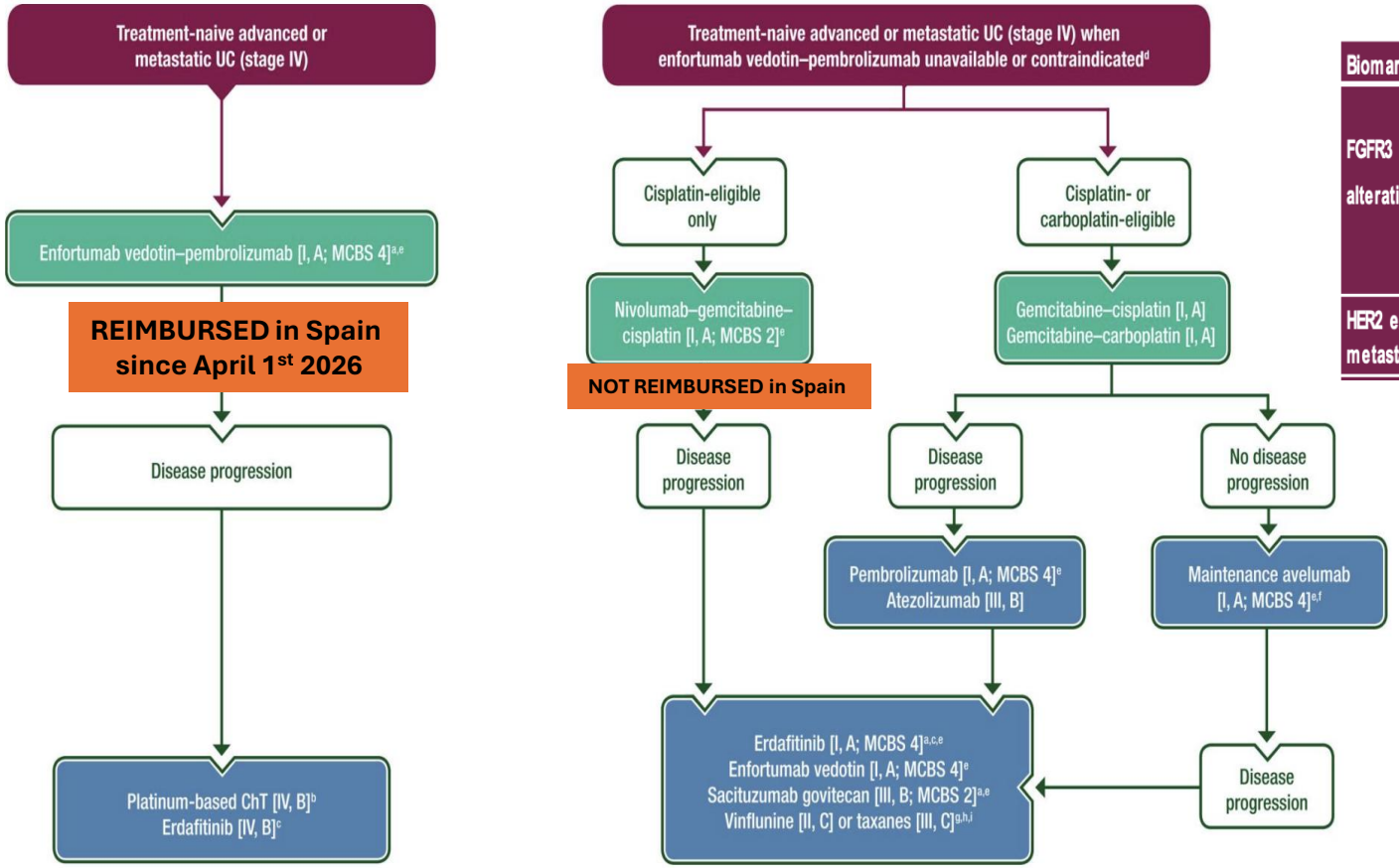

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Ignacio Duran MD, PhD

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CHALLENGES/ UNANSWERED QUESTIONS

- Dosing and role/need of dose adjustments
- Identification/ Management of special toxicities
- Duration of treatment / role of consolidative approaches
- Subsequent therapies upon progression
- Effect of EV-P incorporation to the perioperative setting

TAKE HOME MESSAGE

- The combination of the ADC targeting Nectin-4 **Enfortumab Vedotin plus Pembrolizumab** has become the SOC in mUC based on the efficacy data of EV-302/KEYNOTE A39

- A **PARADIGM SHIFT** has happened around not only the management but the expectations in this patient population

- Perhaps in 2026 we have **DIFFERENT AIMS** than historically but also new challenges to confront [toxicity management, # cycles, subsequent treatments]

FELIZ VERANO

Ignacio Duran MD, PhD