ESMO ON AIR

ESMO Webinar:

Advanced Urothelial Cancer

Tom Powles

Chair

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Programme

19 February 2025

2 minutes	**Introduction and Welcome** Tom Powles
15 minutes	**Clinical Case of a patient with localised bladder cancer relapsing with metastatic dissemination: overview of epidemiology and practice patterns** Yüksel Ürün
15 minutes	**State of the art 1st Line therapy options for patients with advanced urothelial cancer** Tom Powles
15 minutes	**2nd and later line therapies: practice- and biology- informed selection of strategy** Viktor Grünwald
15 minutes	**Managing toxicities and optimising tolerability of novel treatment regimens for patients with advanced urothelial cancer** Alison Birtle
10 minutes	**Live discussion, Q&A and Conclusions** All speakers

Thomas Powles
Chair
University of London and Barts Cancer Centre

Yüksel Ürün
Speaker
Ankara University School of Medicine; Department of Medical Oncology

Viktor Grünwald
Speaker
University Hospital Essen Institute for medical GU Oncology

Alison Birtle
Speaker
Lancashire Teaching Hospitals
University of Manchester and The University of Central Lancashire

Learning Objectives

- To improve treatment decisions in the 1st and subsequent lines of therapy of patients with la/mUC due to the rapidly evolving treatment landscape
- To improve the oncologist's knowledge regarding the optimal treatment selection
- To improve the oncologist's knowledge regarding the management of potential adverse events associated with targeted therapeutic modalities

ESMO WEBINARS

Case of a Patient With Localized Bladder Cancer Relapsing with Metastatic Dissemination: Overview of Epidemiology and Practice Patterns

Yüksel Ürün, MD

Professor of Medicine

Ankara University School of Medicine, Dept. Of Medical Oncology

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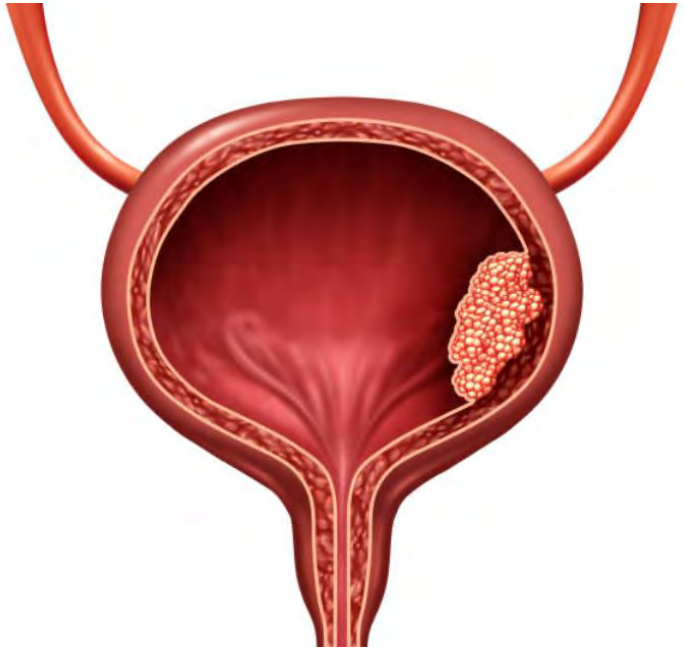
CONFLICT OF INTEREST DISCLOSURE

Advisory boards/Travel, Honoraria or consultation fees:

Abdi-İbrahim, Astellas, AstraZeneca, Bristol Myers-Squibb, Deva, Eczacıbaşı, Gen ilaç, Gilead, GSK, Janssen, Merck, MSD, Novartis, Pfizer, Roche

CASE SUMMARY – 66-YEAR-OLD MALE - Oct 2019

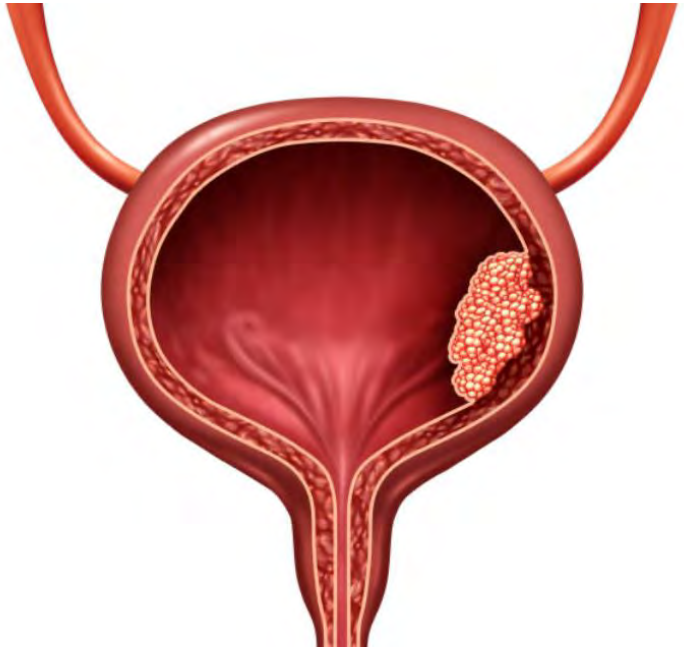


- **Presenting Symptom: Hematuria**
- **Medical History:** Hypertension (on Verapamil/Trandolapril)
- **Smoking History:** 15 pack-years, ex-smoker
- Performance Status (PS): 0
- **Renal Function:** eGFR: 68 mL/min

Imaging Findings

- **Ultrasound (USG):**
  - Left bladder wall thickening
  - Hypoechoic solid mass in the left bladder, suspicious for malignancy
- **CT Scan:**
  - 51 mm solid mass in the left bladder, **extension into perivesical fat**
  - No invasion into adjacent organs
  - No evidence of distant metastasis or lymphadenopathy

CASE SUMMARY – 66-YEAR-OLD MALE - Oct 2019



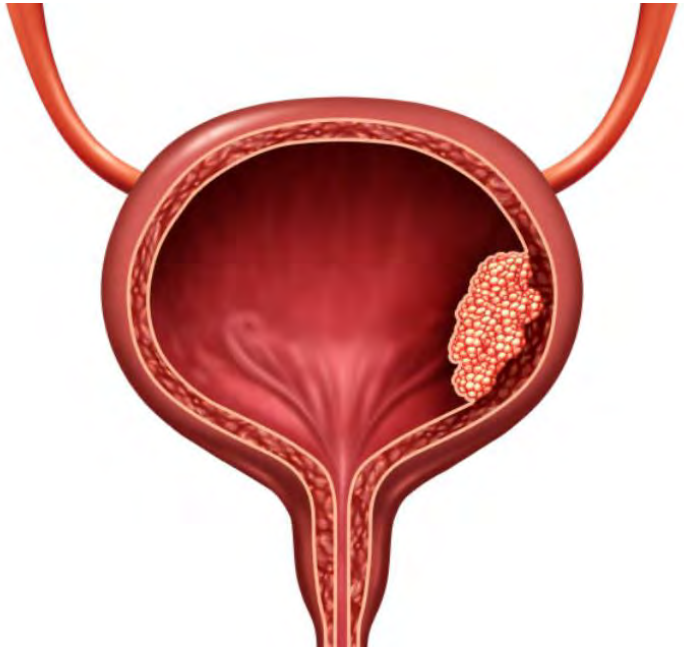
Histopathology (TUR-BT Findings)

- High-grade urothelial carcinoma
- Muscularis propria invasion present

How to manage cT3 diseae?

- Radical Cystectomy + Pelvic Lymph Node Dissection
- Neoadjuvant Chemotherapy (GC/ddMVAC) followed by RS-PLND
- Neoadjuvant Gem-Cis-Durvalumab followed by RS-PLND
- Bladder-Preserving Trimodal Therapy (TMT)

CASE SUMMARY

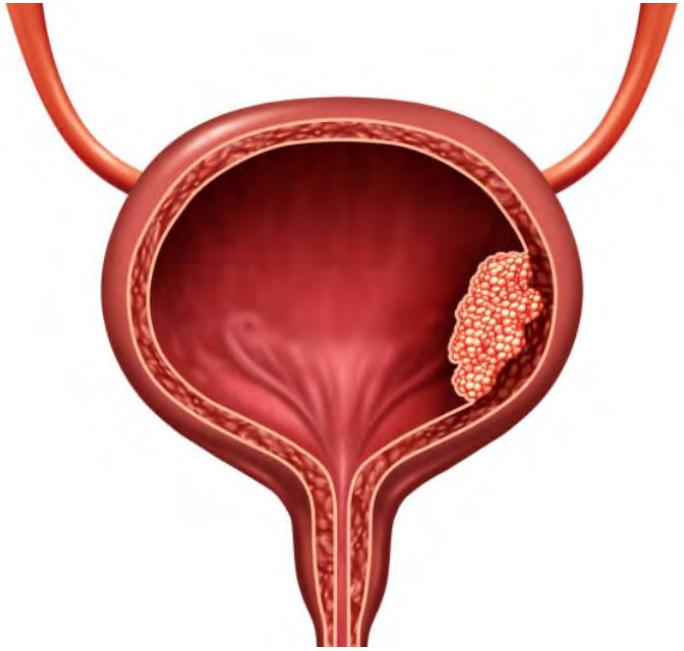


Histopathology (TUR-BT Findings)

- High-grade urothelial carcinoma
- Muscularis propria invasion present
- **cT3**

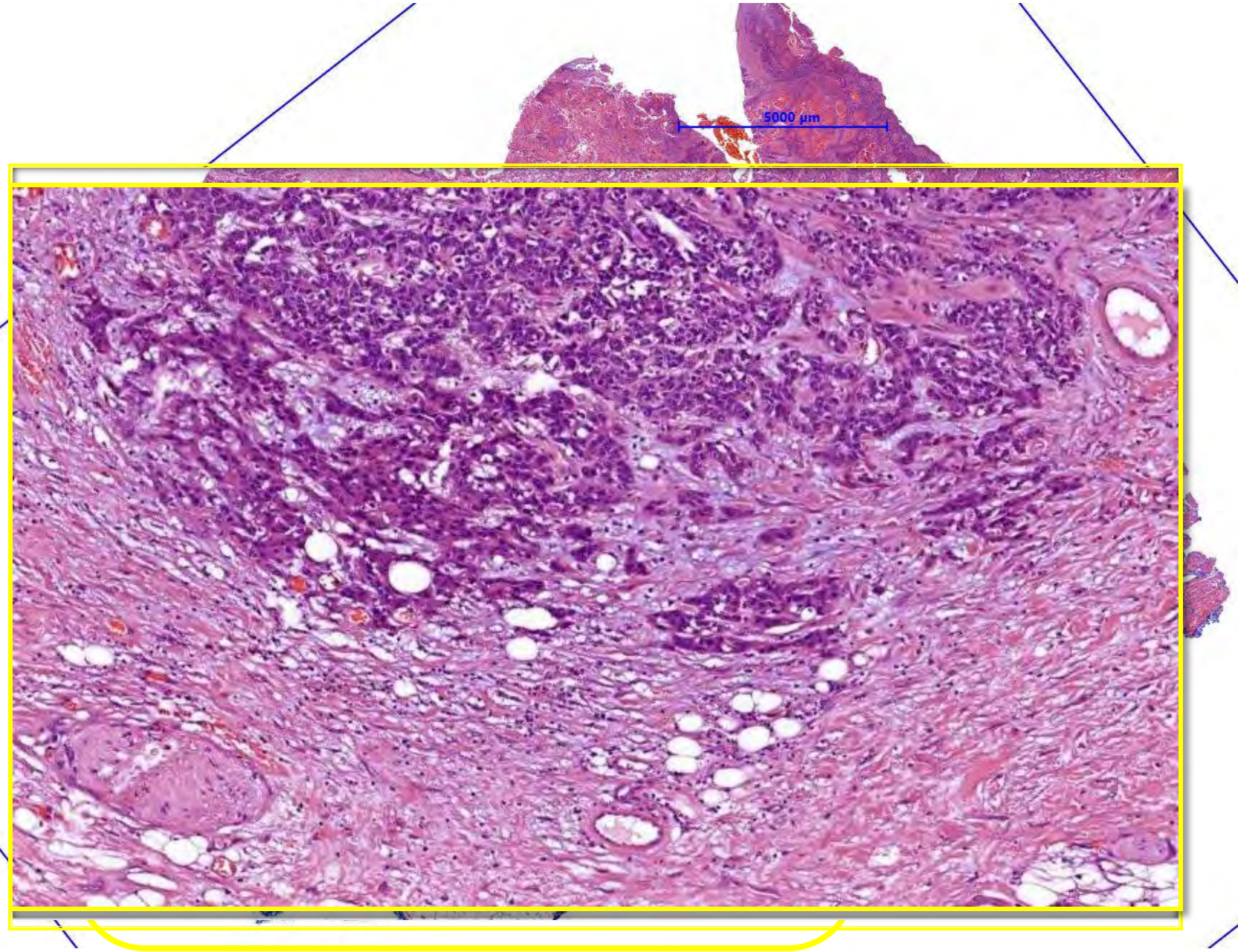
- **Neoadjuvant gem-cis → Radical Cystectomy + Pelvic Lymph Node Dissection**

CASE SUMMARY – JAN 2020



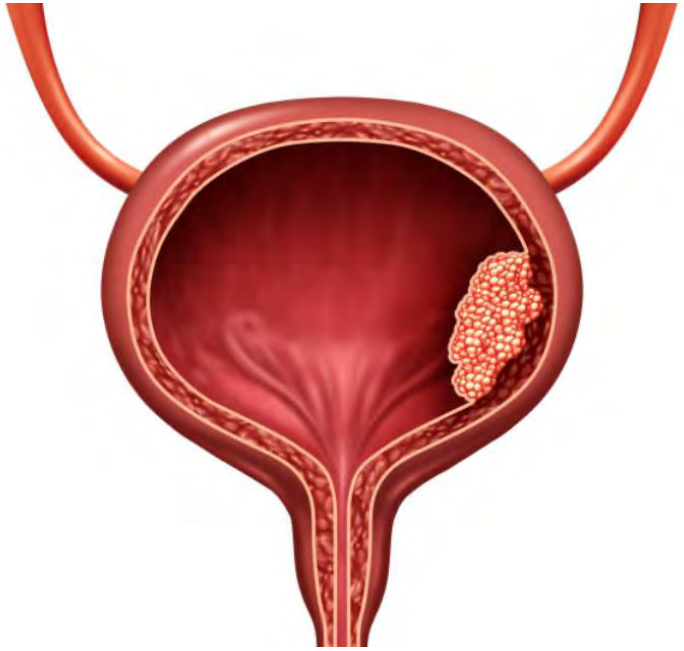
Histopathology (RS Findings)

- High-grade infiltrative urothelial carcinoma with extensive squamous differentiation infiltrates the full thickness of the bladder wall.
- Deep down the bladder wall, perivesical adipose tissue invasion is seen, with tumor cells infiltrating among adipocytes. **(pT3N0)**



Courtesy of Duygu Enneli, MD

CASE SUMMARY – 67-YEAR-OLD MALE



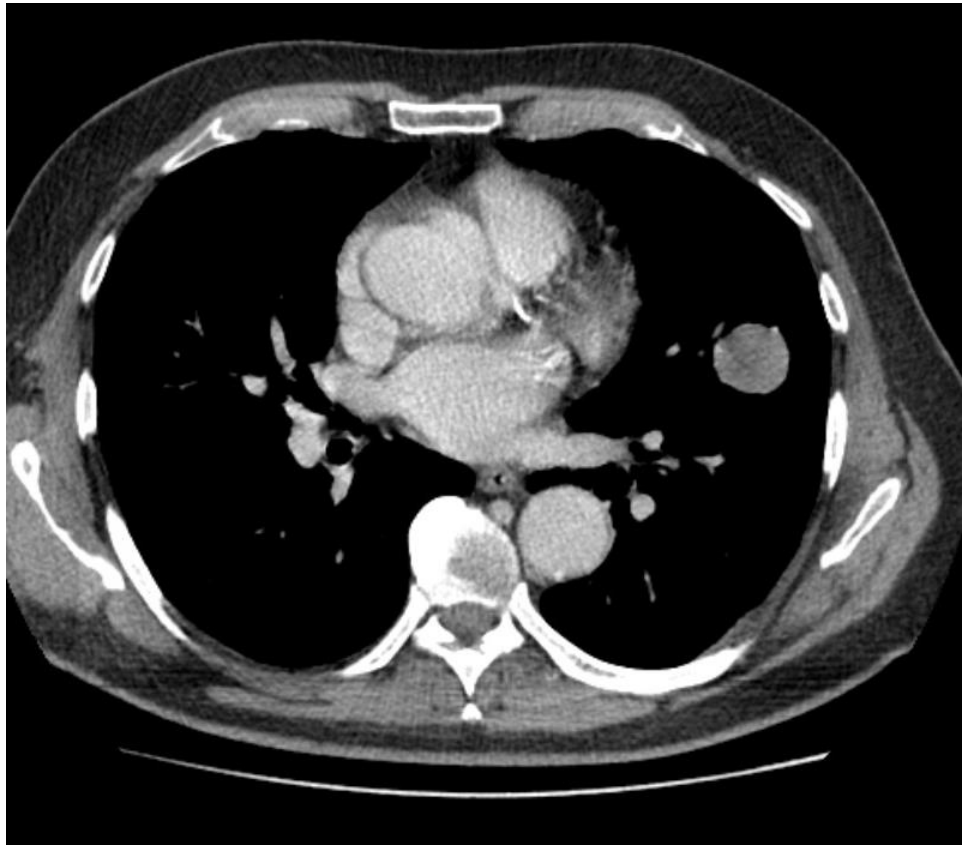
06/2020

- Femoral vein thrombosis detected on CT; treated with anticoagulation (LMWH).

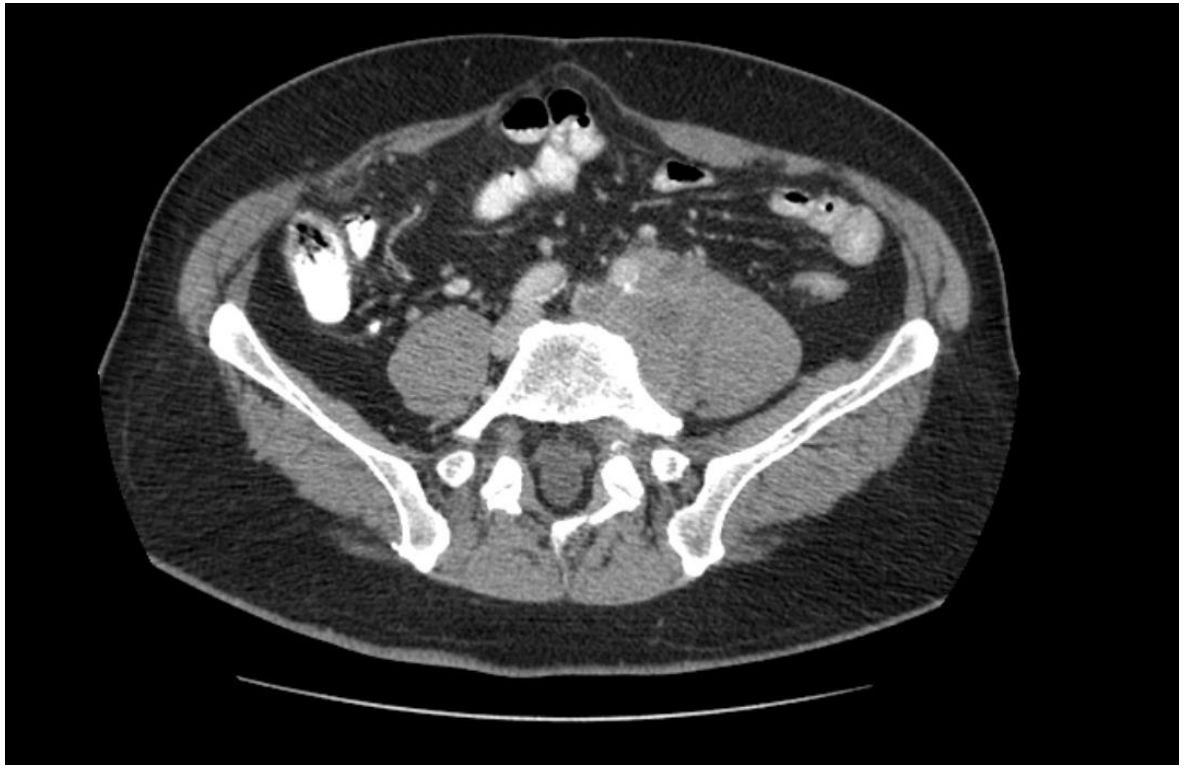
Aug/2020 - Nov/2023

- Regular follow-ups with CT
- No signs of recurrence (NED).

CASE SUMMARY – 71-YEAR-OLD MALE - July 2024

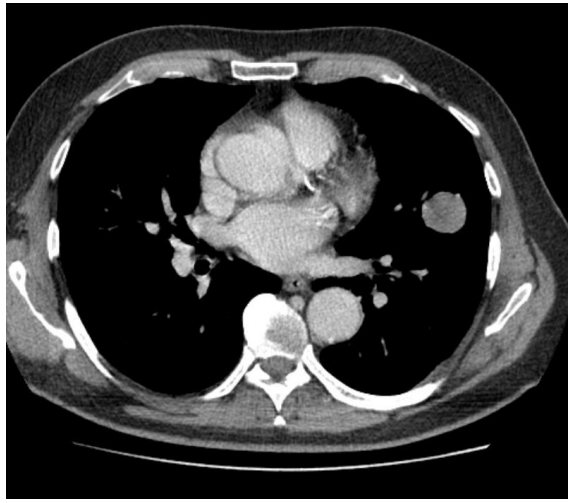


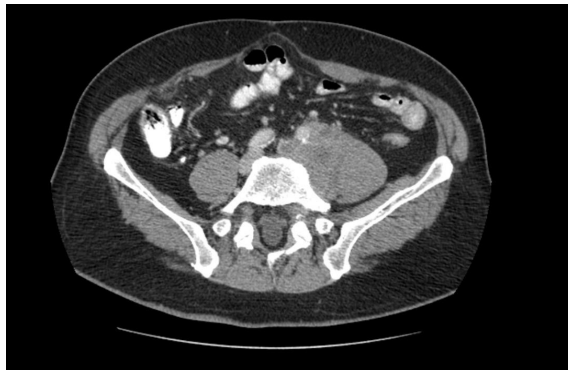
CT of the chest shows a ~2 cm solid, nodular lesion



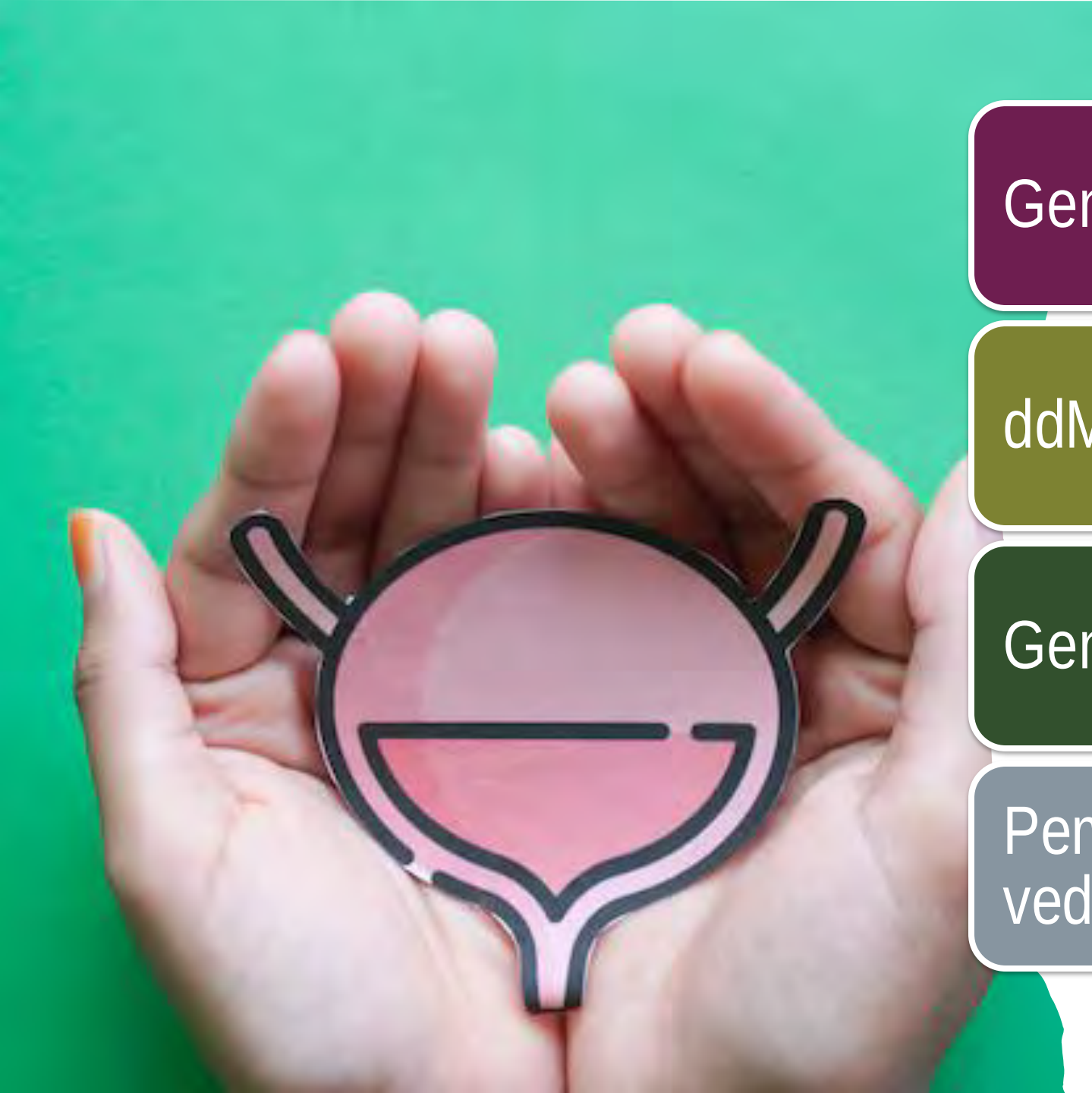
Large retroperitoneal nodular lesion near the left common iliac vessels

CASE SUMMARY – 71-YEAR-OLD MALE - July 2024





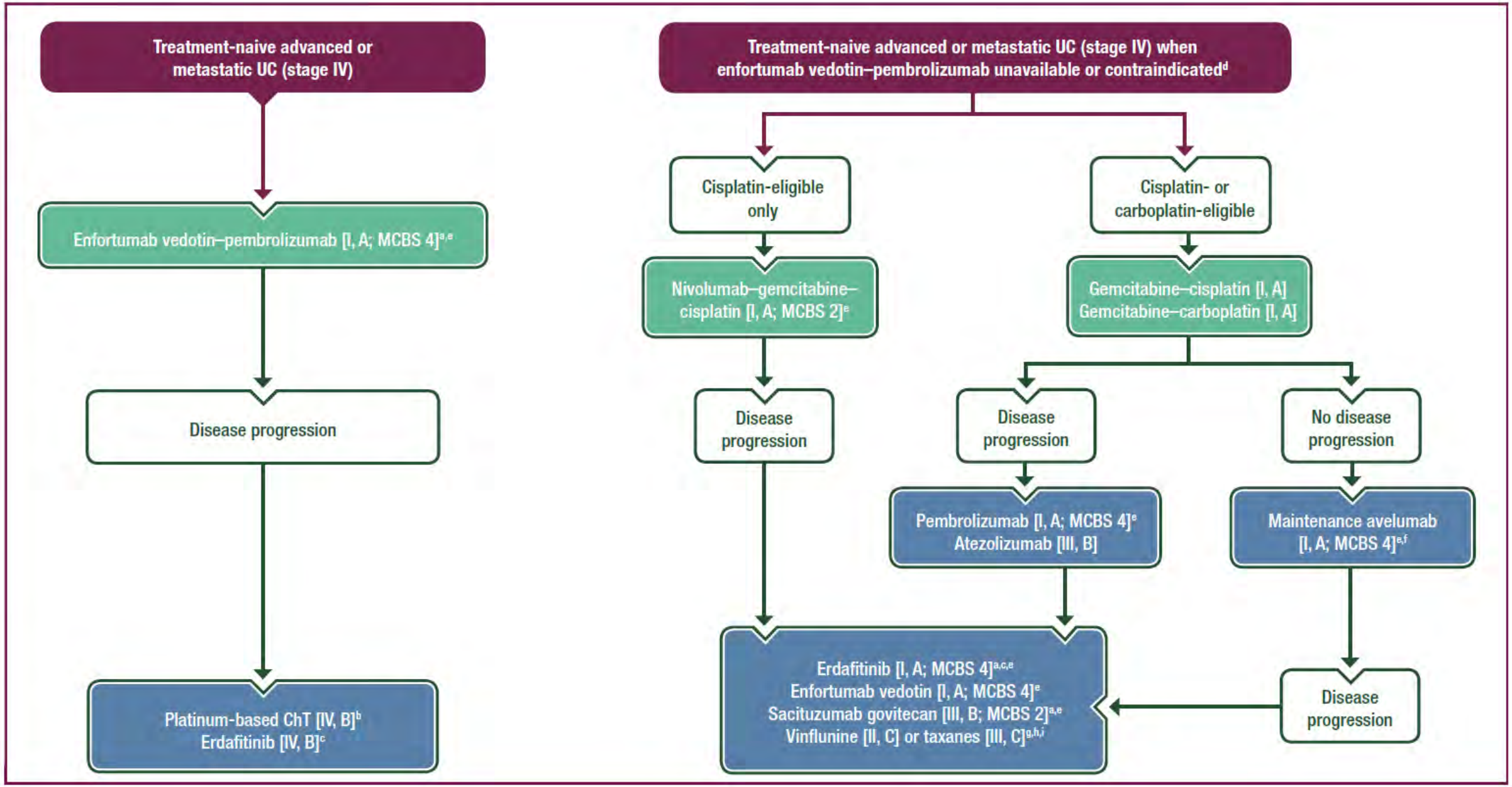
- **Medical History:** Hypertension (on Verapamil/Trandolapril)
- **Smoking History:** 15 pack-years, ex-smoker
- Performance Status (PS): 1
- **Renal Function:** eGFR: 55 mL/min
- **CT:** metastases in lungs, liver, lymph nodes, bones, and iliopsoas muscle invasion.



- Gem-Cis→Avelumab
- ddMVAC→ Avelumab
- Gem-Cis -nivolumab
- Pembrolizumab-Enfortumab vedotin

Optimal Treatment Selection and Sequencing

- PDL1?
- DDR-NER-ERCC1/2
- Nectin-4
- FGFR
- MSI
- HER2
- Clonal TMB/ APOBEC signature



Powles T. , et al. Annals of Oncology 2024

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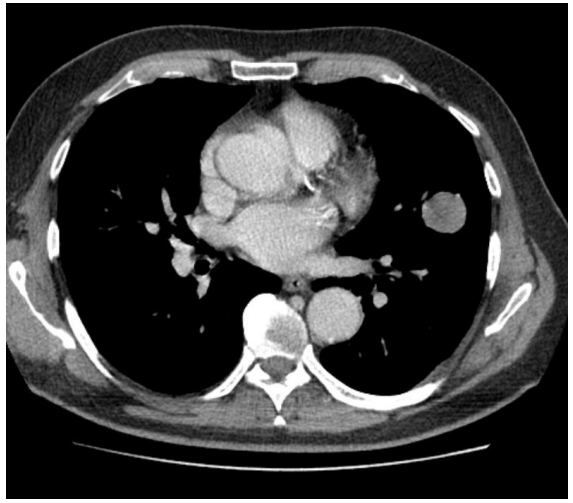

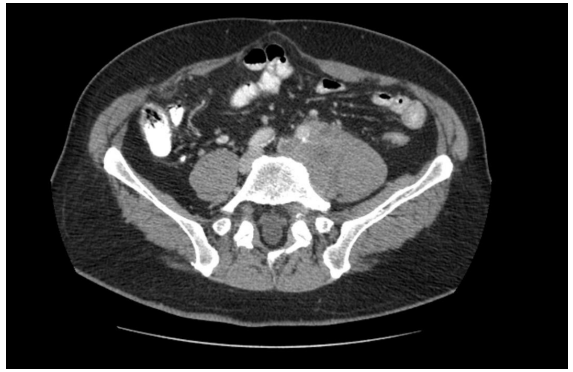

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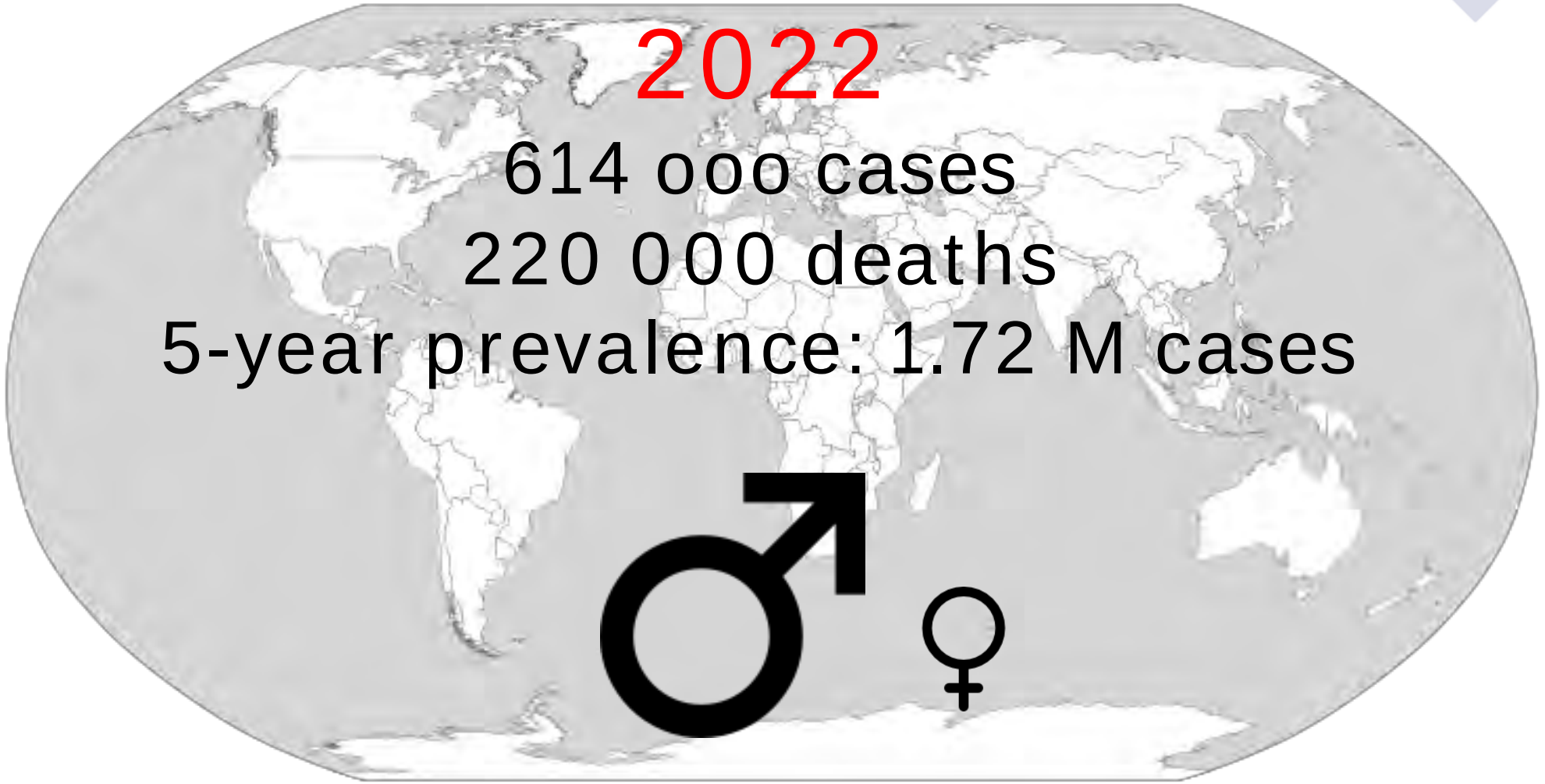
- Performance Status (PS): 1
- **Renal Function:** eGFR: 55 mL/min
- **CT:** metastases in lungs, liver, lymph nodes, bones, and iliopsoas muscle invasion.

- **07/2024**: **Enfortumab Vedotin (EV) + Pembrolizumab** initiated
- **09/2024**: CT shows **partial response (PR)**—lesions in lungs, liver, lymph nodes, and pelvis reduced or resolved.
- **12/2024**: Further CT confirms **PR**
- **01/2025**: New **widespread lung infiltrates!**
- **Progression vs Toxicity?**


2022
614 ooo cases
220 000 deaths
5-year prevalence: 1.72 M cases
♂
♀

ETIOLOGY

- Age
- Sex
- Tobacco smoking* – The biggest risk factor (2-5x increased risk). 50% of cases!
- Occupational exposures* – Chemicals in dye, rubber, printing industries.
- Arsenic in drinking water
- Chronic infection
  - TBC, longterm catheter, Schistosomiasis*
- Other factors – Diabetes, obesity, chronic infections, and certain medications*.

**moderate-to-large increase in risk*

van Hoogstraten LMC., *Nature Reviews Clinical Oncology* 2023

Emerging Risk Factors

- **Dietary Factors**:
  - **Western diet (processed foods, high red meat)** increases risk.
  - **Mediterranean diet** and **high fiber intake** lower risk.
  - **High coffee intake* (>500 mL/day)** may increase risk.
  - **Tea and yogurt consumption** may reduce risk.
- **Microbiome**:
  - Loss of **Lactobacillus** linked to bladder cancer.
  - **Dysbiosis** in the gut and urinary microbiome may contribute.
- **Gene-environment interactions**:
  - NAT-2, GSTM1, and GSTT1 polymorphisms affect carcinogen metabolism.

Jubber I., et al, 2023 EUROPEAN UROLOGY

Table 1 – BC risk factor summary according to IARC monographs

Smoking 1. Tobacco smoking[a]	Occupational agents 1. Benzidine (dye manufacturing)[a] 2. 4-Aminobiphenyl (dye and rubber manufacturing)[a] 3. Ortho-toluidine (dye and rubber manufacturing)[a] 4. 2-Naphthylamine (dye and rubber manufacturing)[a] 5. 4-Chloro-ortho-toluidine[b] (dye manufacturing) 6. 2-Mercaptobenzothiazole[b] (rubber manufacturing) 7. Tetrachloroethylene[b] (dry cleaning, automotive, and metalwork industries) 8. Soot[b] 9. Coal tar pitch[b]
Occupations 1. Aluminium production[a] 2. Rubber manufacturing industry[a] 3. Dye industry (magenta, auramine)[a] 4. Painter[a] 5. Firefighter[a] 6. Dry cleaning[b] 7. Hairdressers or barbers[b] 8. Printing processes[b] 9. Textile manufacturing[b]	
Environmental factors 1. Arsenic and inorganic arsenic compounds[a] 2. X and gamma radiation[a] 3. Outdoor air pollution[b] 4. Diesel exhaust[b]	Diseases and medications or drugs 1. Chlornaphazine[a] 2. Schistosomiasis[a] 3. Cyclophosphamide[a] 4. Opium consumption[a] 5. Pioglitazone[b]

Jubber I., et al, 2023
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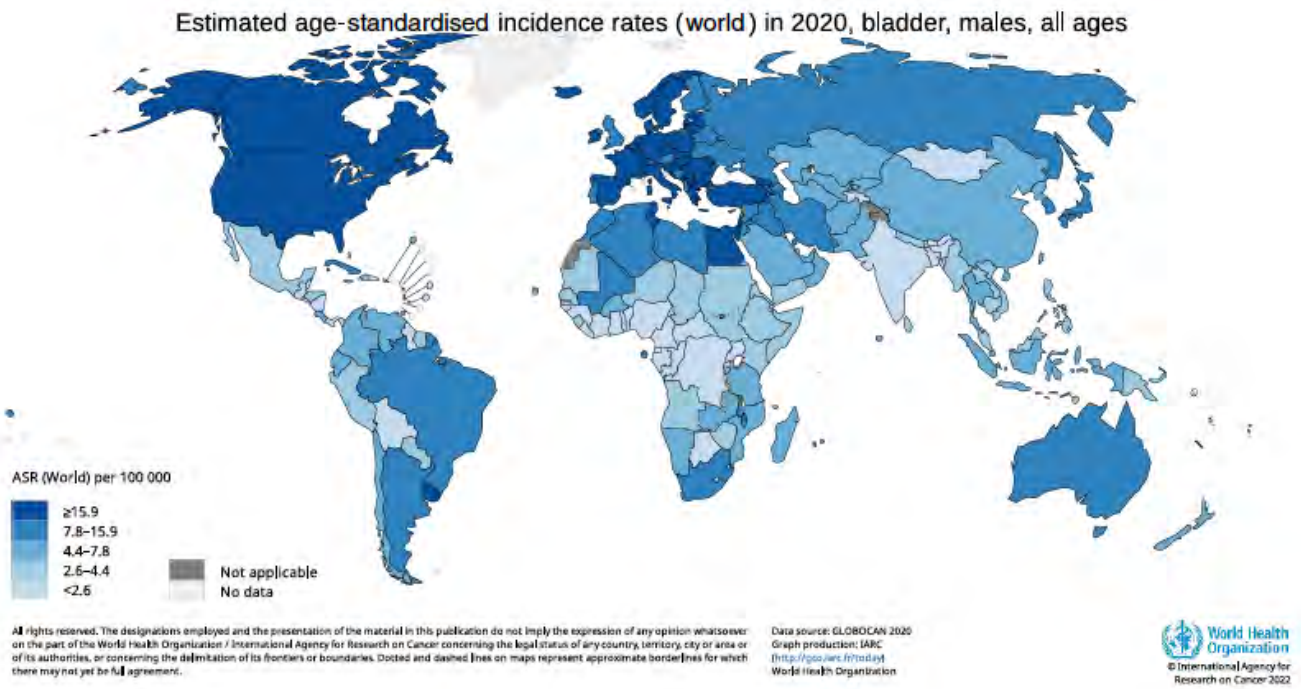
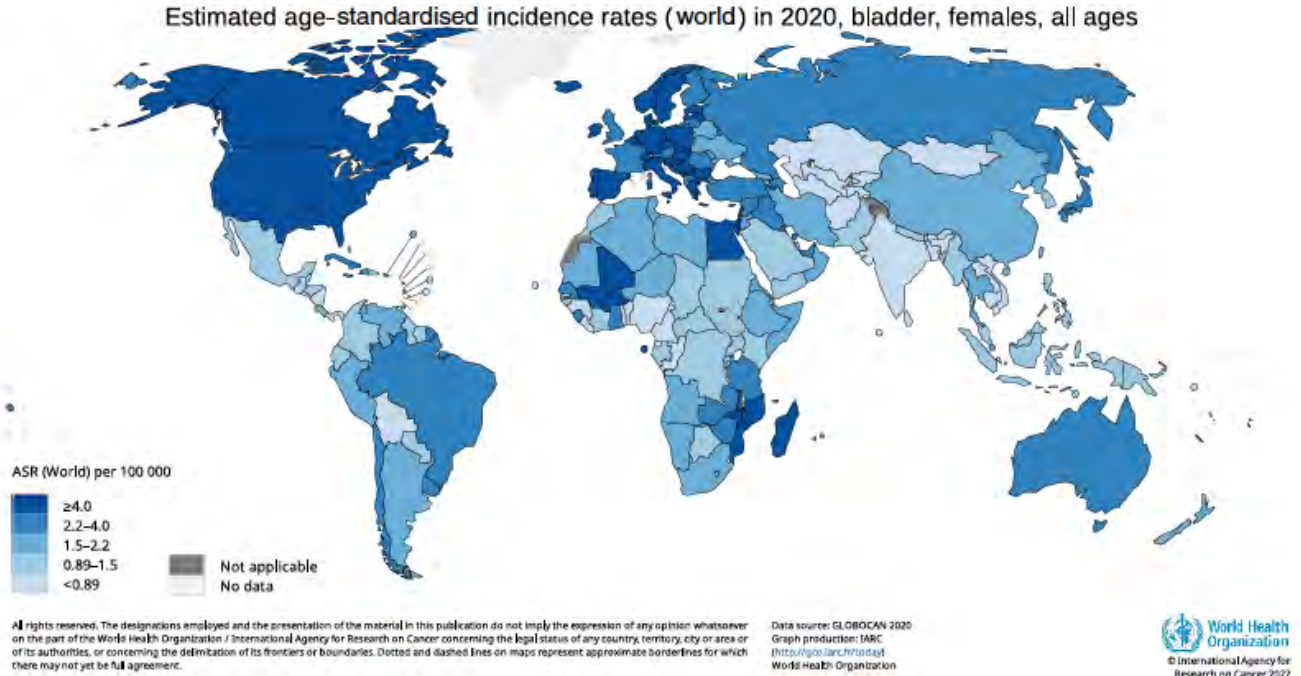
Highest incidence

- Europe,
- North America,
- North Africa,
- West Asia.





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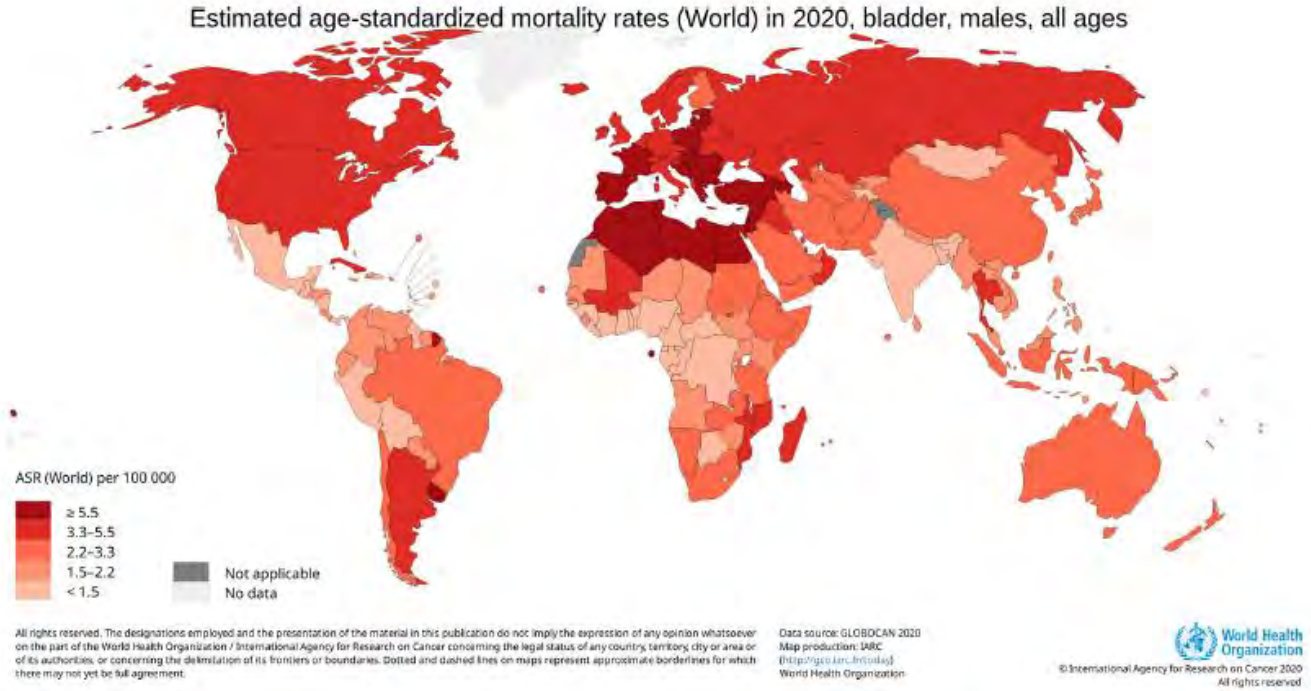

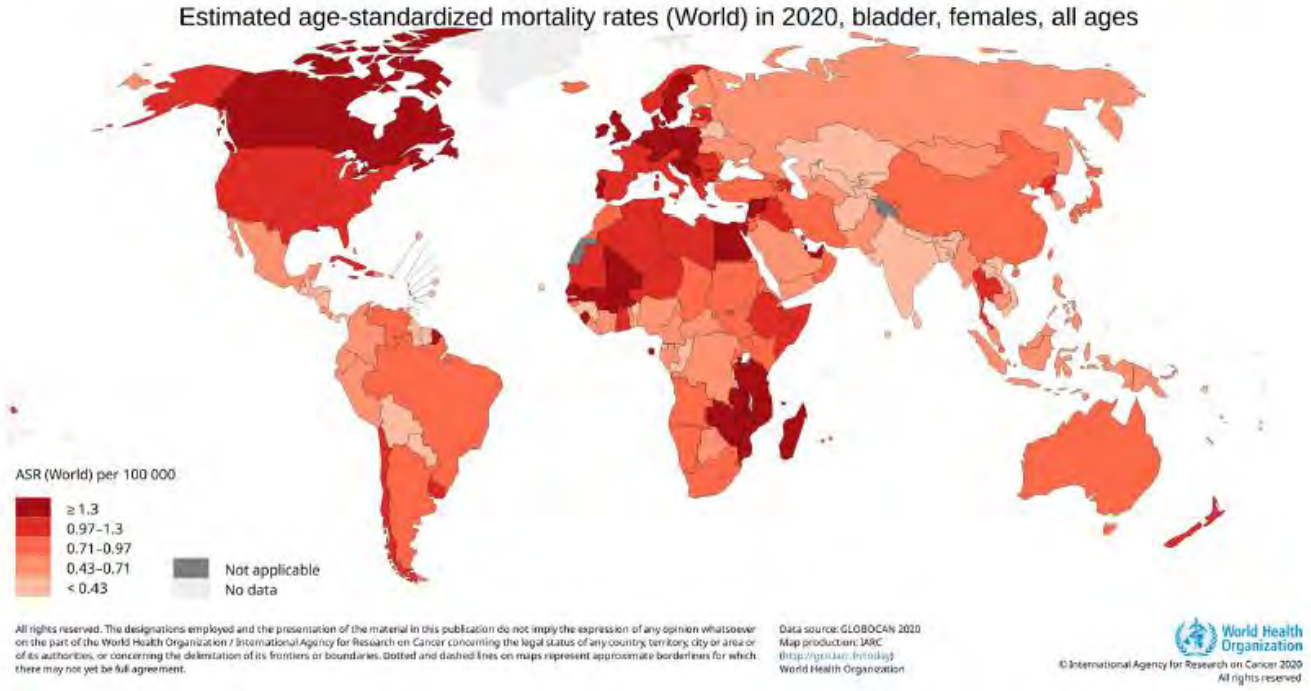

Jubber I., et al, 2023
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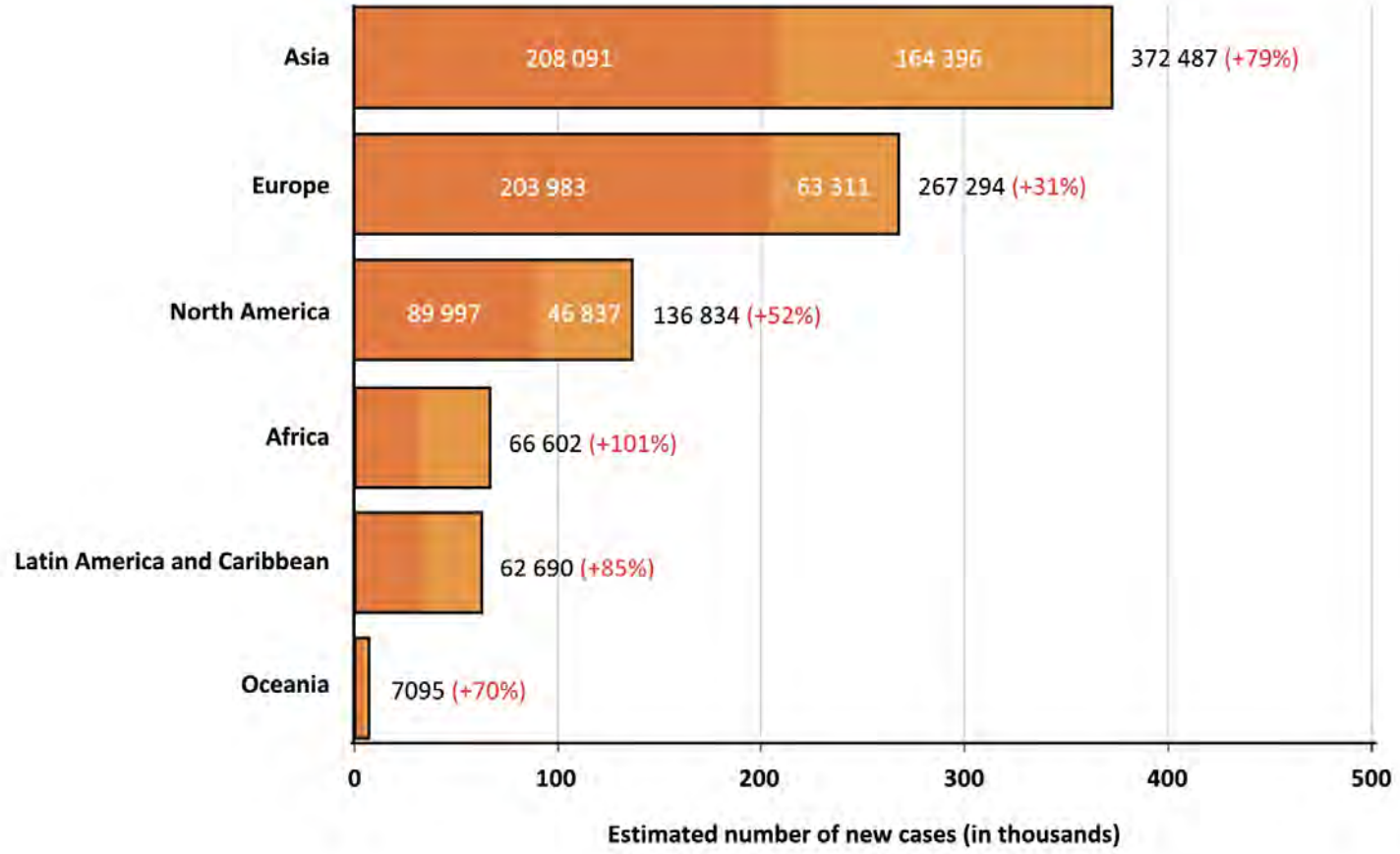
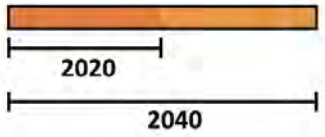


Totals	
2020	573 278
2040	913 002



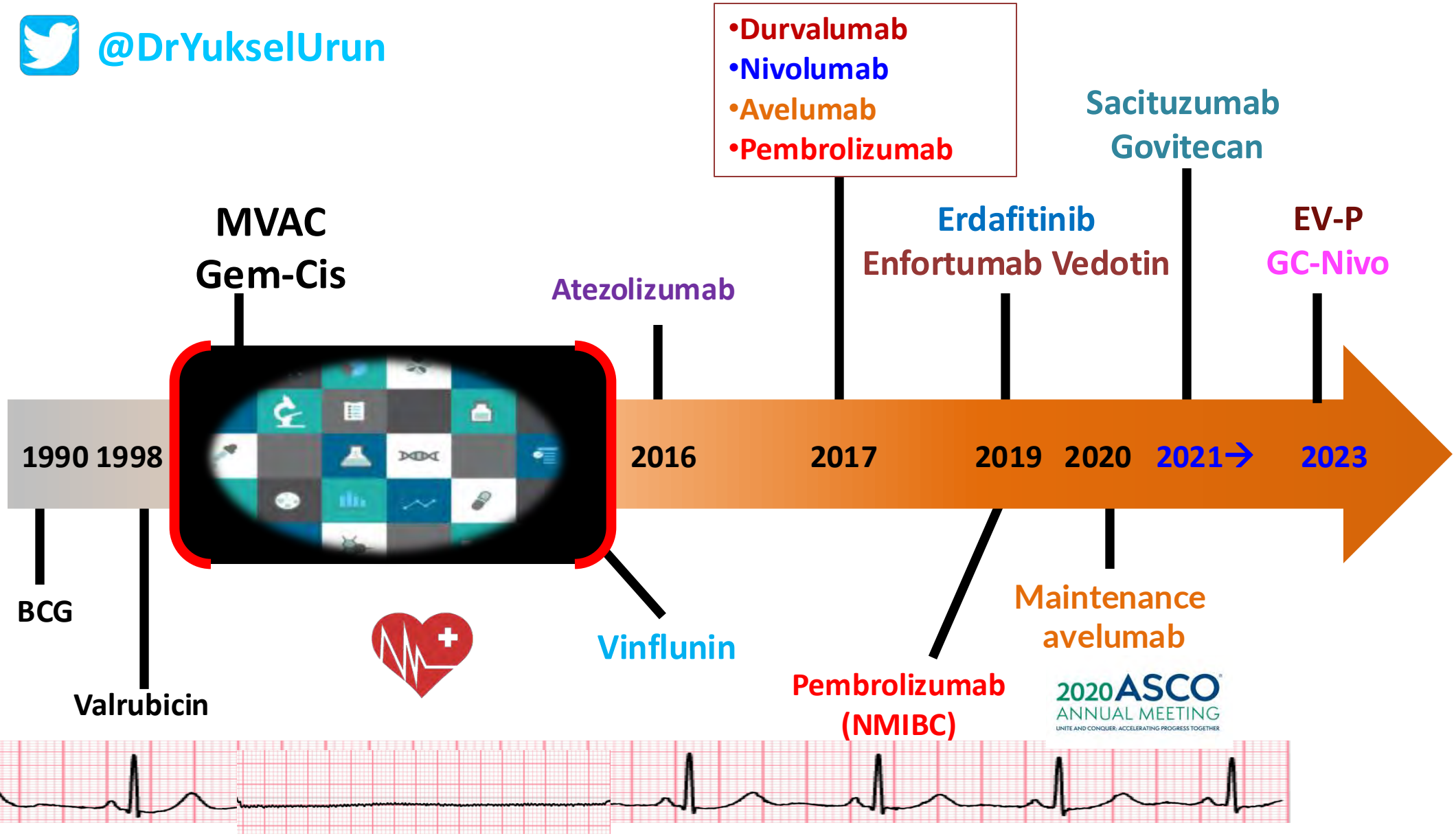
Jubber I., et al, 2023
EUROPEAN UROLOGY

Preventive Strategies

- Smoking cessation/avoid passive smoking.
- Occupational safety
- Dietary changes
- Avoidance of radiation exposure – Where possible, minimize pelvic RT.
- Reducing air pollution and environmental carcinogens.

Jubber I., et al, 2023 EUROPEAN UROLOGY

@DrYukselUrun



Urothelial Cancer Treatments Landscape

Take-Home Messages:

Bladder Cancer Management & Future Directions

Early Diagnosis is Crucial

- Smoking remains the most significant modifiable risk factor.

Personalized Treatment is the Future

- Neoadjuvant chemotherapy ± immunotherapy improves survival in MIBC.

Expanding Treatment Options

- Access to novel therapies is critical for better patient outcomes.

Optimal Sequencing Remains Unclear

- More data is needed to define the best treatment order.

Biomarkers (PD-L1, Nectin-4) Not Yet Standard for Therapy Selection

- Their role in guiding treatment decisions is still evolving.

Thank you!

@dryukselurun

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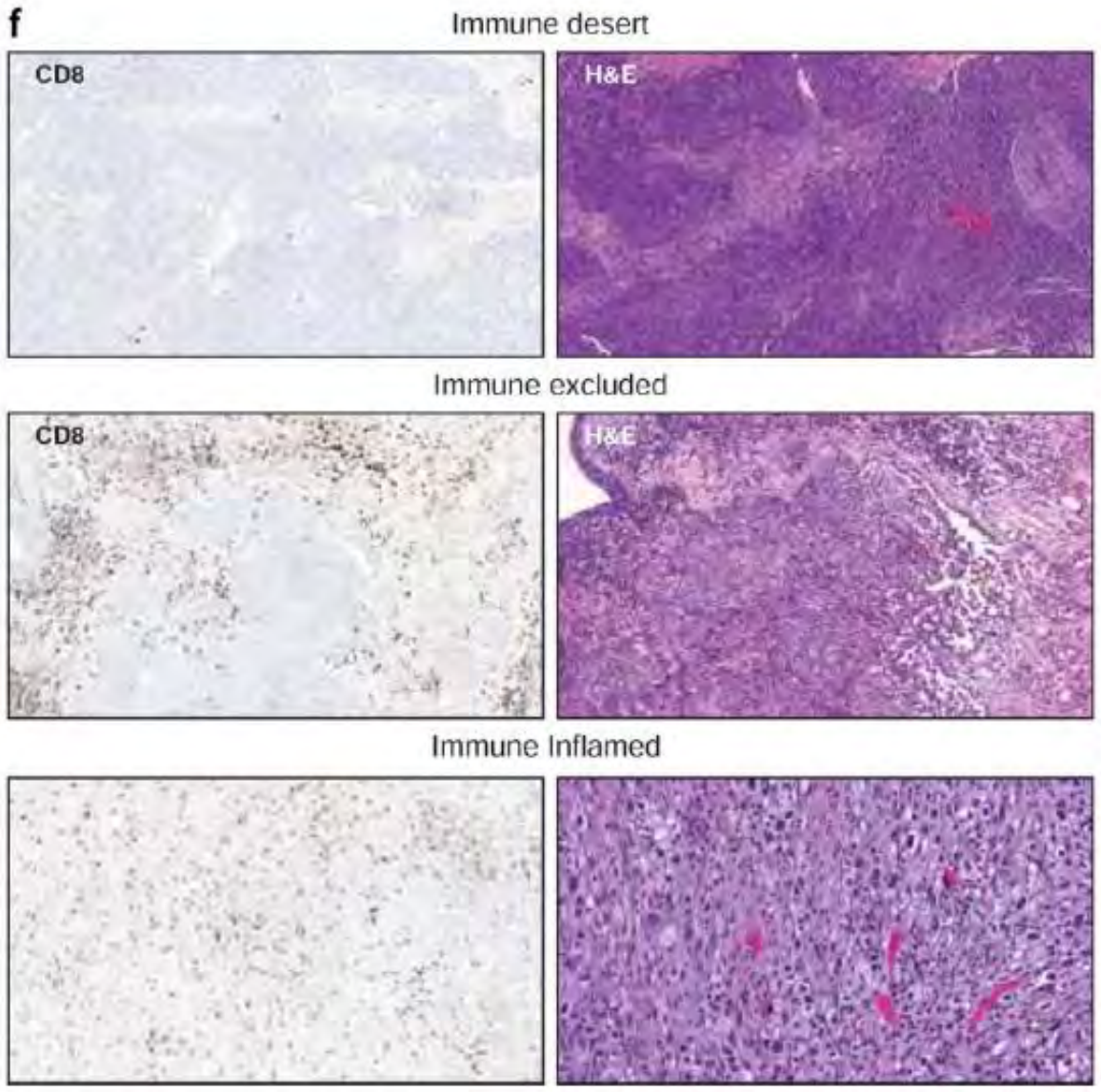
Outlining the current 1st line landscape.

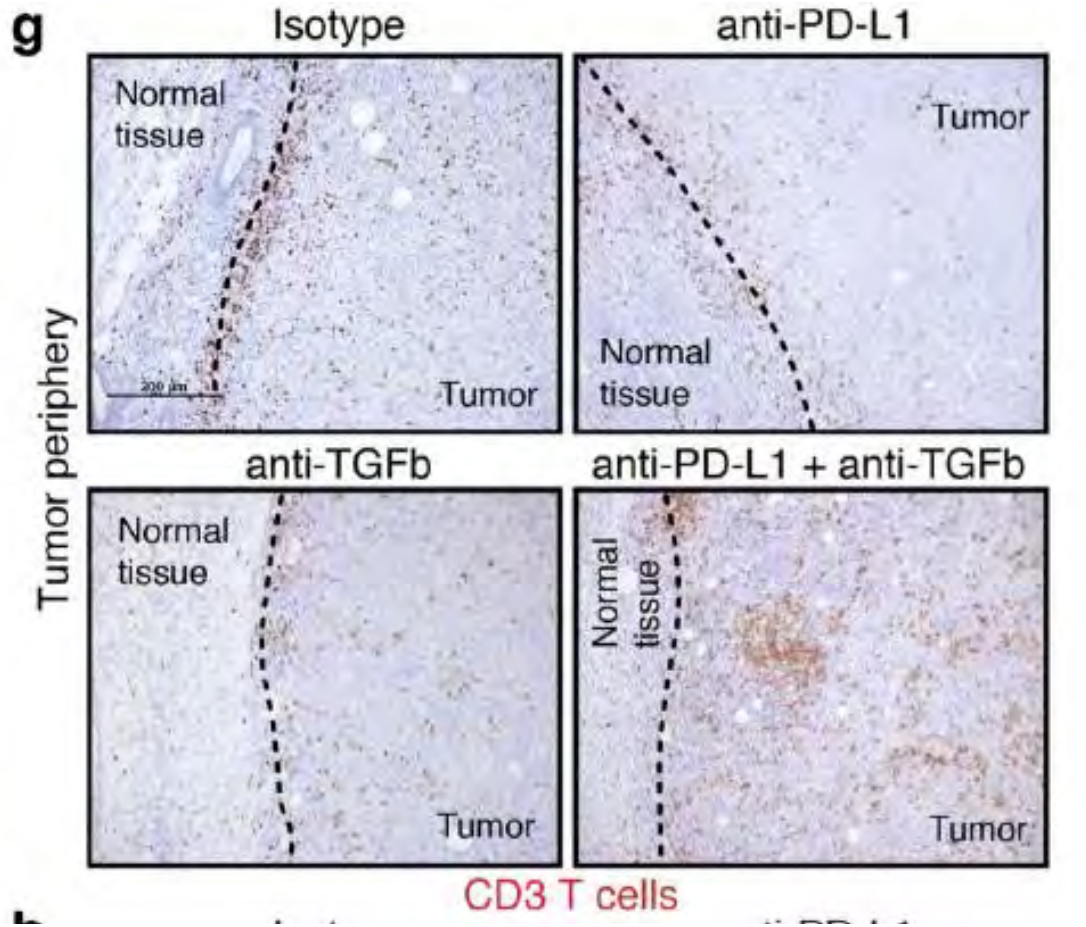
Thomas Powles

Director of Barts Cancer Center.
Professor of Urology Cancer, Barts Cancer Institute.




Excluded immune phenotype in bladder cancer





Mariathasan S et al Nature 2018

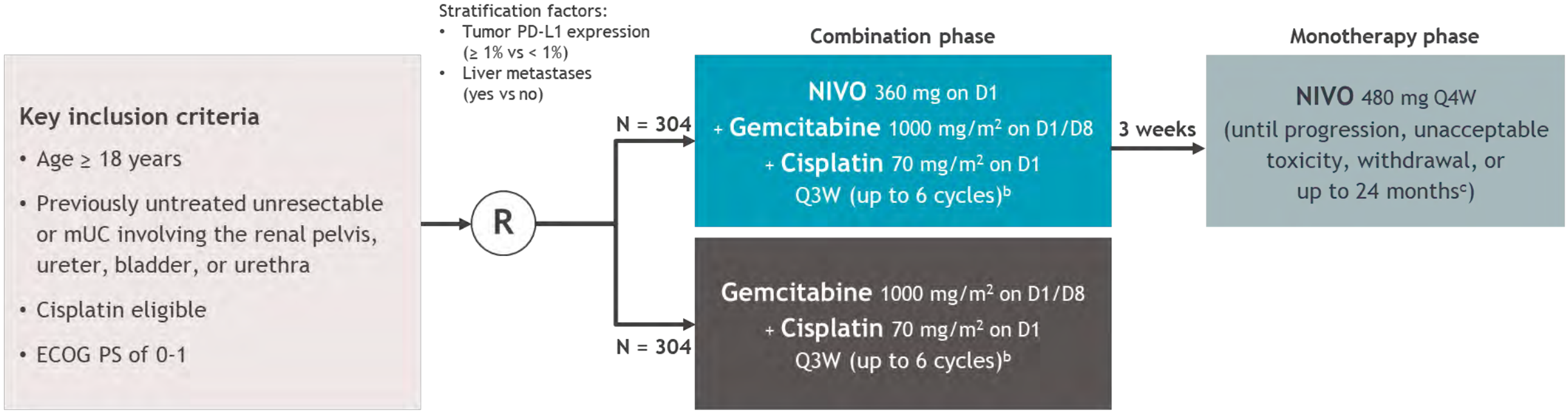
Beating first line chemotherapy in bladder cancer seemed beyond us, despite terrible outcomes with chemotherapy.

	Study arm	endpoint	OS HR	OS outcome
DANUBE	Durvalumab	biomarker	0.89	-ve
	Durvalumab/tremilimumab	ITT	0.85	-ve
IMVIGOR 130	atezolizumab	Biomarker	0.68	-ve
	Atezolizumab/chemotherapy	ITT	0.83	NA
KEYNOTE 361	pembrolizumab	Biomarker	1.01	-ve
	Pembrolizumab/chemotherapy	ITT	0.86	-ve

Study design

- NIVO+GC versus GC in cisplatin-eligible patients[a]

GEM/CIS/NIVO



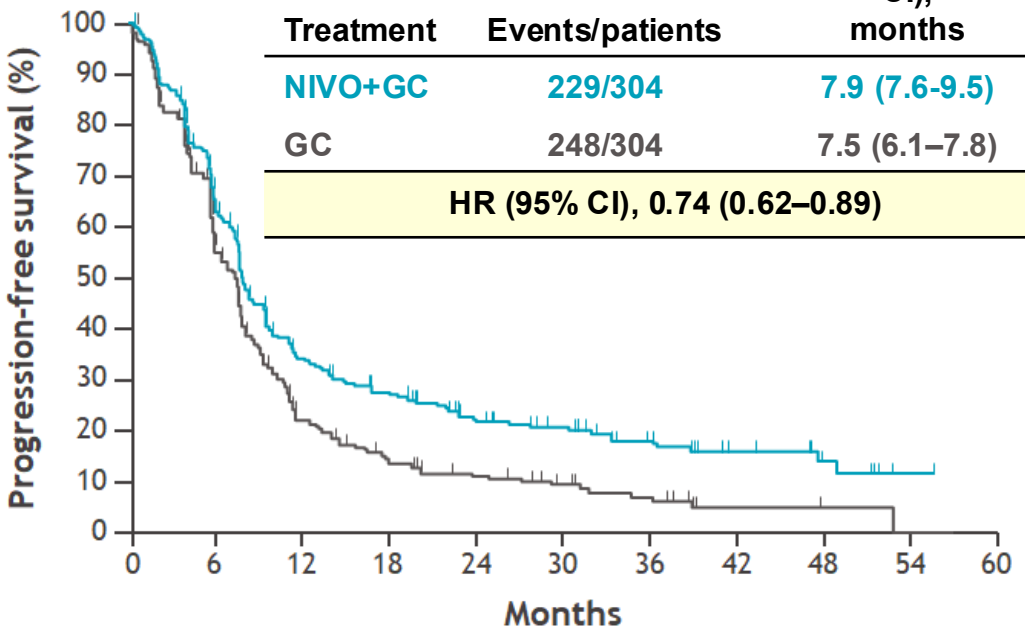
Median (range) study follow-up:
33.6 (7.4-62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS per BICR by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

Current analysis includes: baseline characteristics, ORR, OS, and PFS in all randomized LN-only patients

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO+GC combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA).

The PFS curves for chemo + IO suggest benefit is in the maintenance phase.



Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	229/304	7.9 (7.6-9.5)
GC	248/304	7.5 (6.1–7.8)
HR (95% CI), 0.74 (0.62–0.89)		

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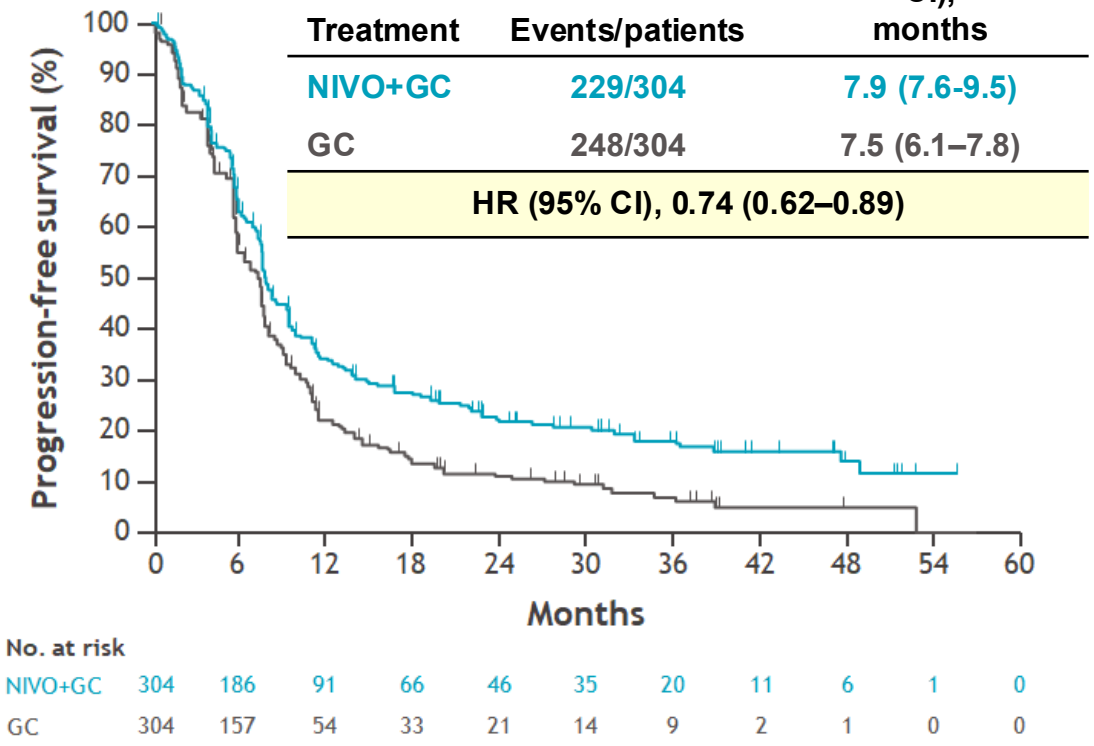

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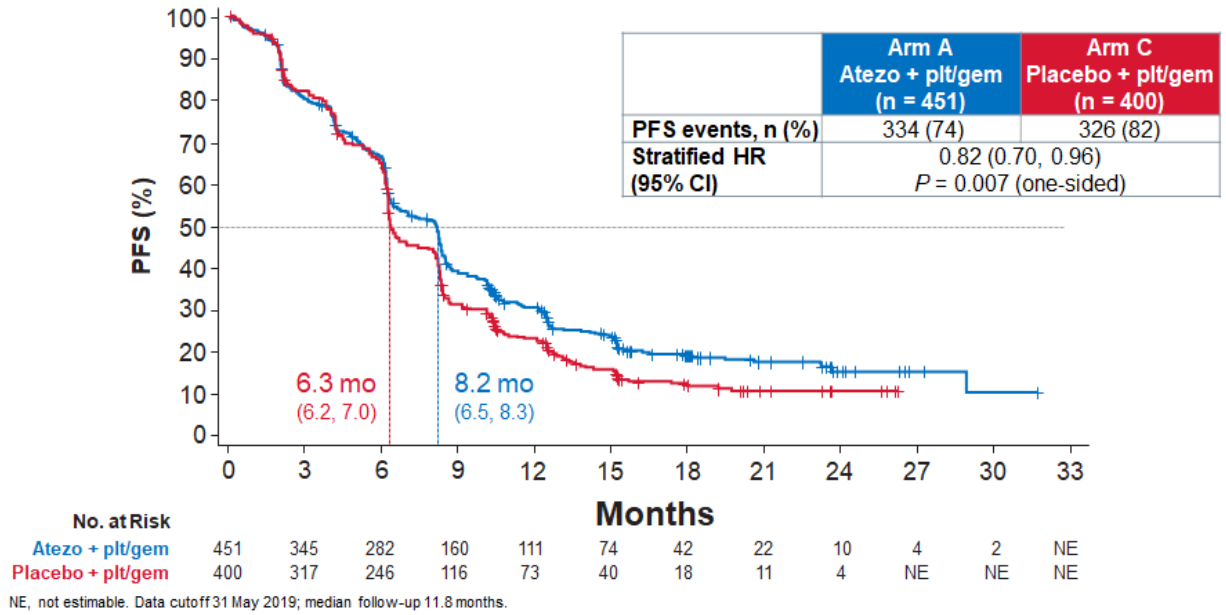
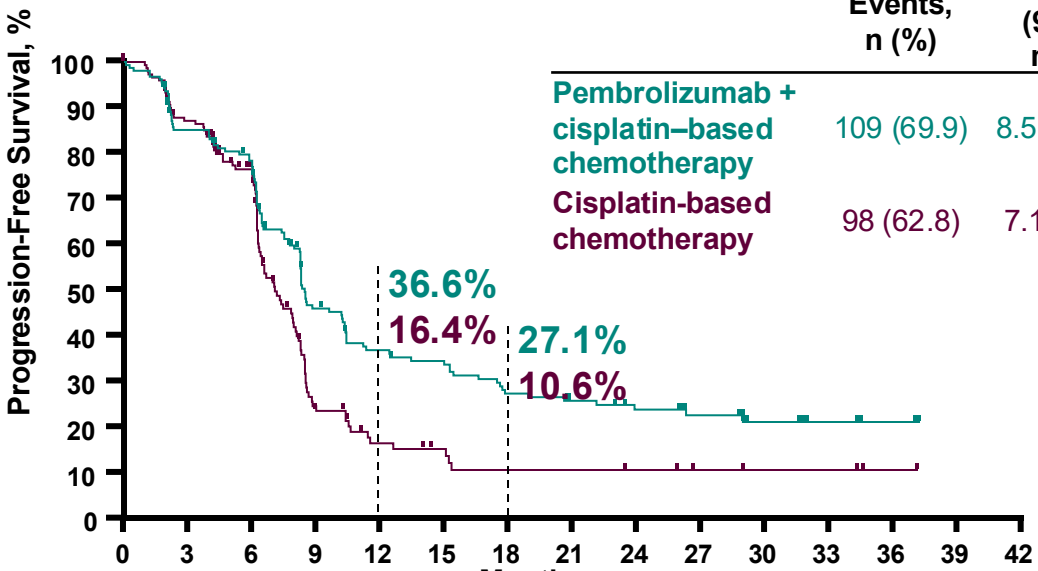


	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

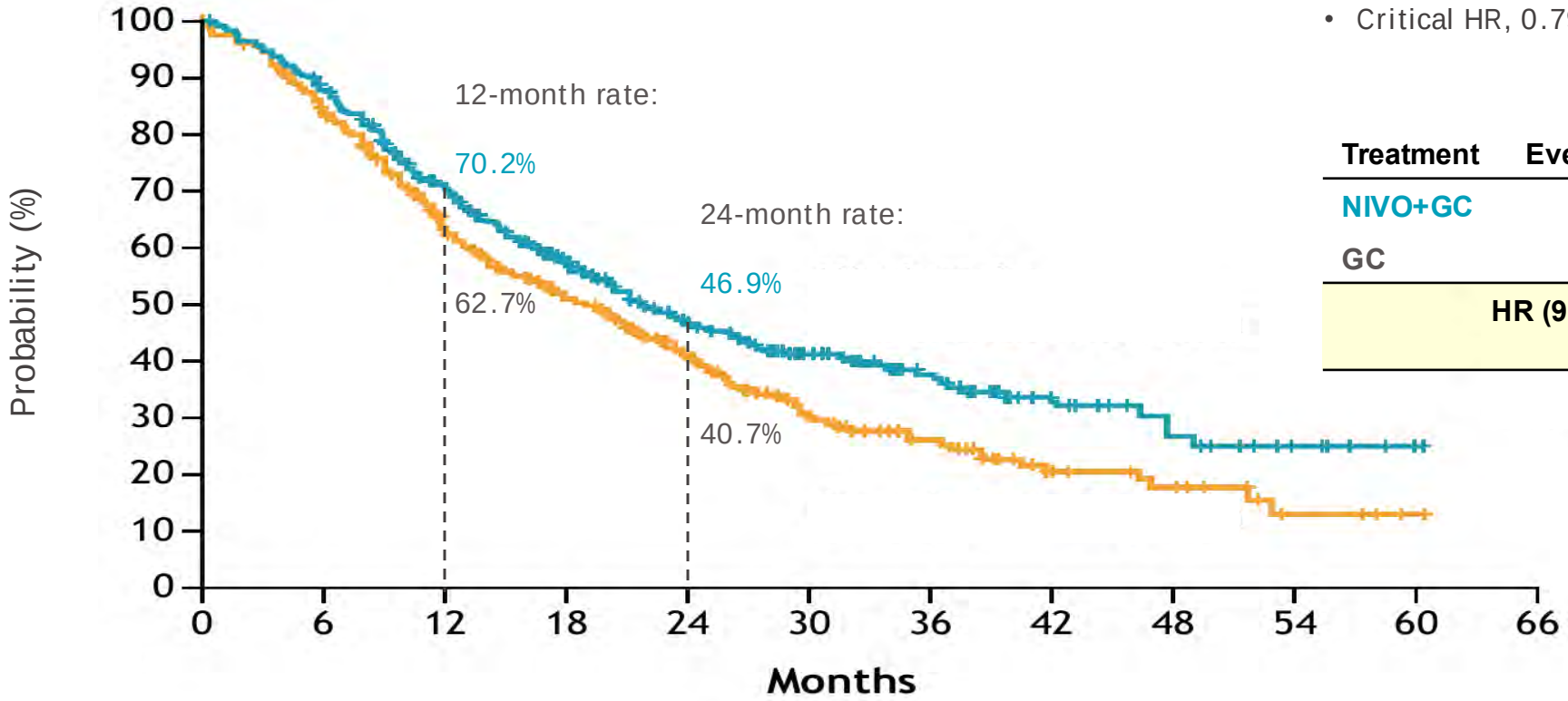
NE, not estimable. Data cutoff 31 May 2019; median follow-up 11.8 months.



	Events, n (%)	PFS, median (95% CI), months	HR (95% CI)
Pembrolizumab + cisplatin–based chemotherapy	109 (69.9)	8.5 (8.2-10.3)	0.67 (0.51-0.89)
Cisplatin-based chemotherapy	98 (62.8)	7.1 (6.3-8.0)	

OS (primary endpoint)

OS final analysis statistical boundaries:
- *P* value boundary, 0.0311
- Critical HR, 0.7980



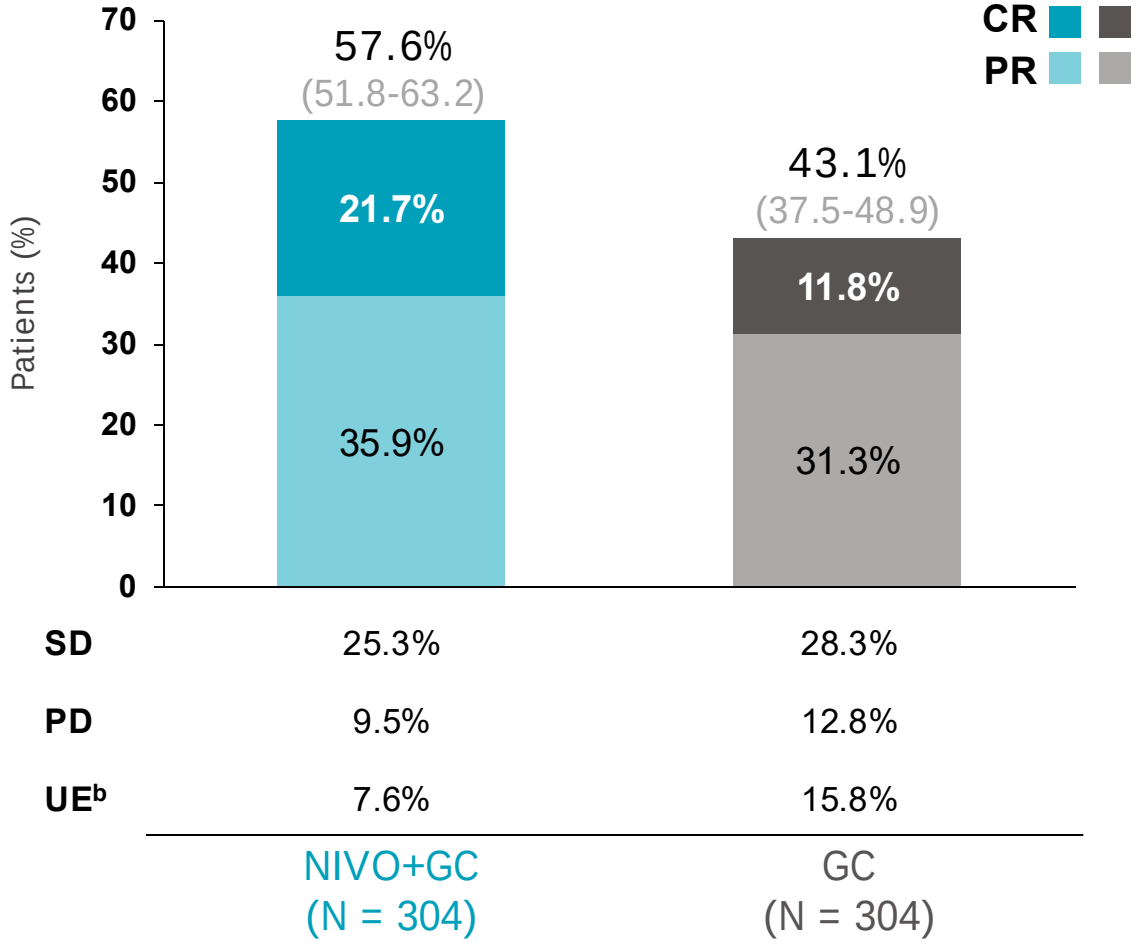
Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7–22.4)
HR (95% CI), 0.78 (0.63–0.96) *P* = 0.0171		

No. at risk

NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as the time from date of randomization to date of death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with no follow-up, OS was censored at the date of randomization.

Objective response outcomes



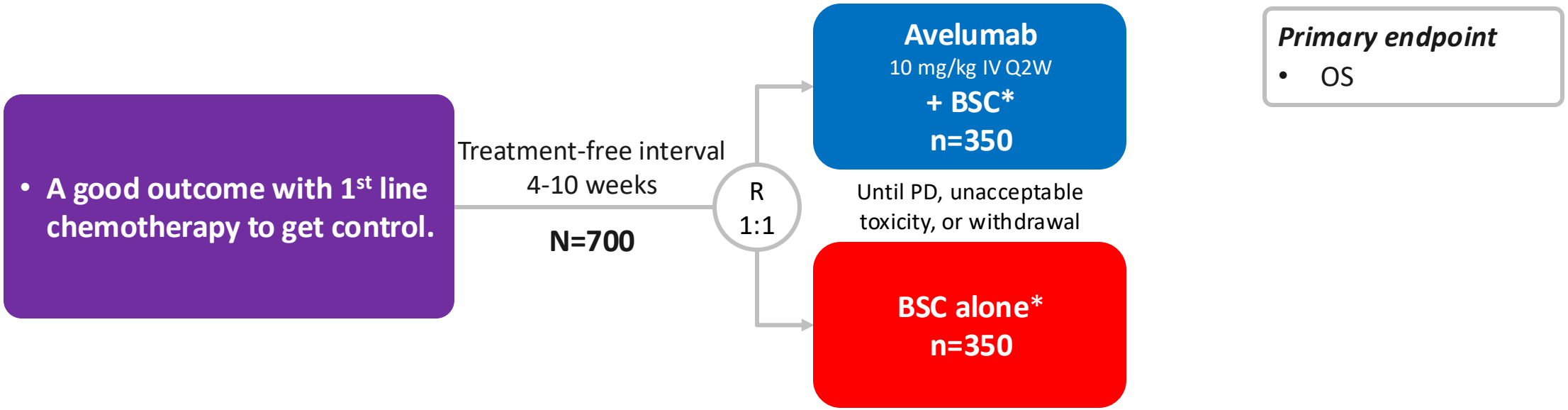
Time to and duration of responses

Any objective response[c]	NIVO+GC (n = 175)	GC (n = 131)
Median TTR (Q1-Q3), months	2.1 (2.0–2.3)	2.1 (2.0–2.2)
Median DoR (95% CI), months	9.5 (7.6–15.1)	7.3 (5.7–8.9)
Complete response[d]	**NIVO+GC (n= 66)**	**GC (n = 36)**
Median TTCR (Q1-Q3), months	2.1 (1.9-2.2)	2.1 (1.9-2.2)
Median DoCR (95% CI), months	37.1 (18.1-NE)	13.2 (7.3-18.4)

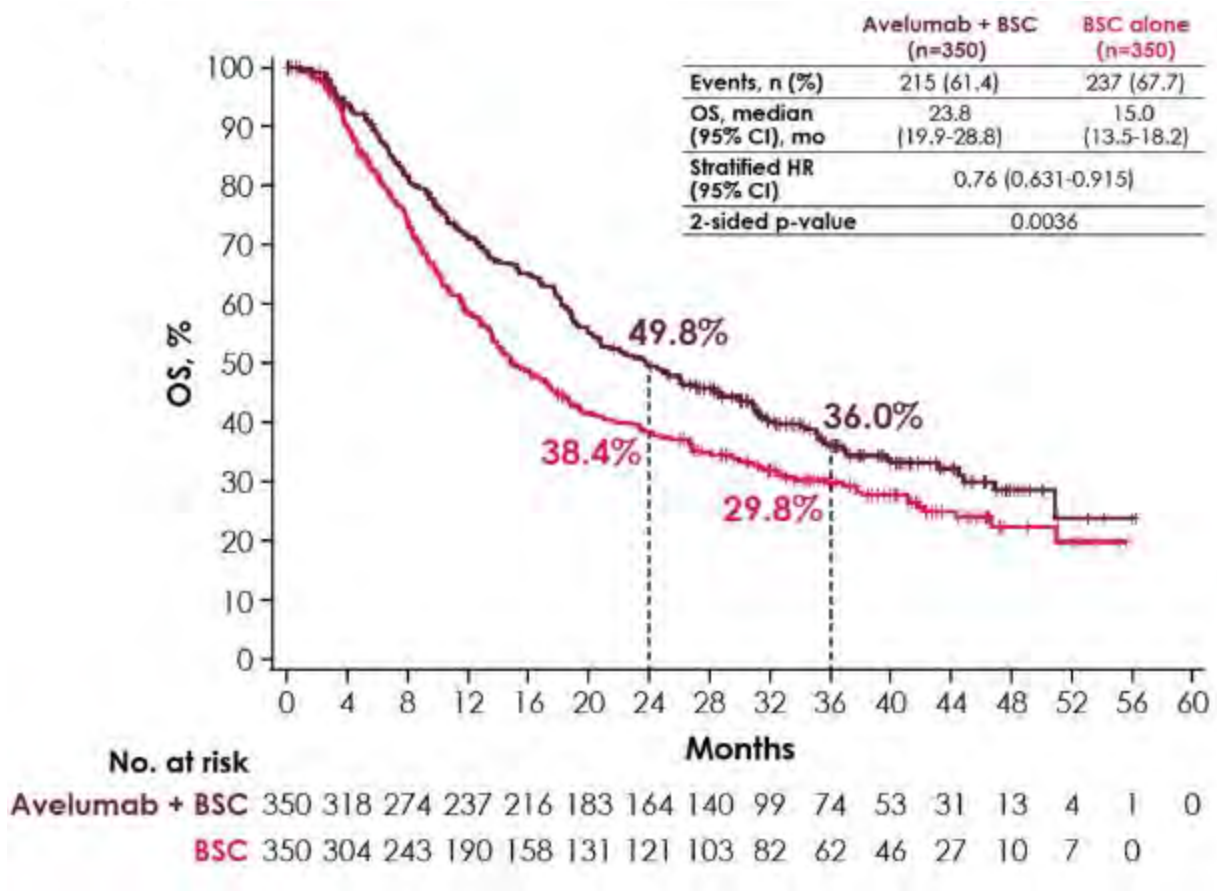
ORR (95% CI) and BOR per BICR[a]

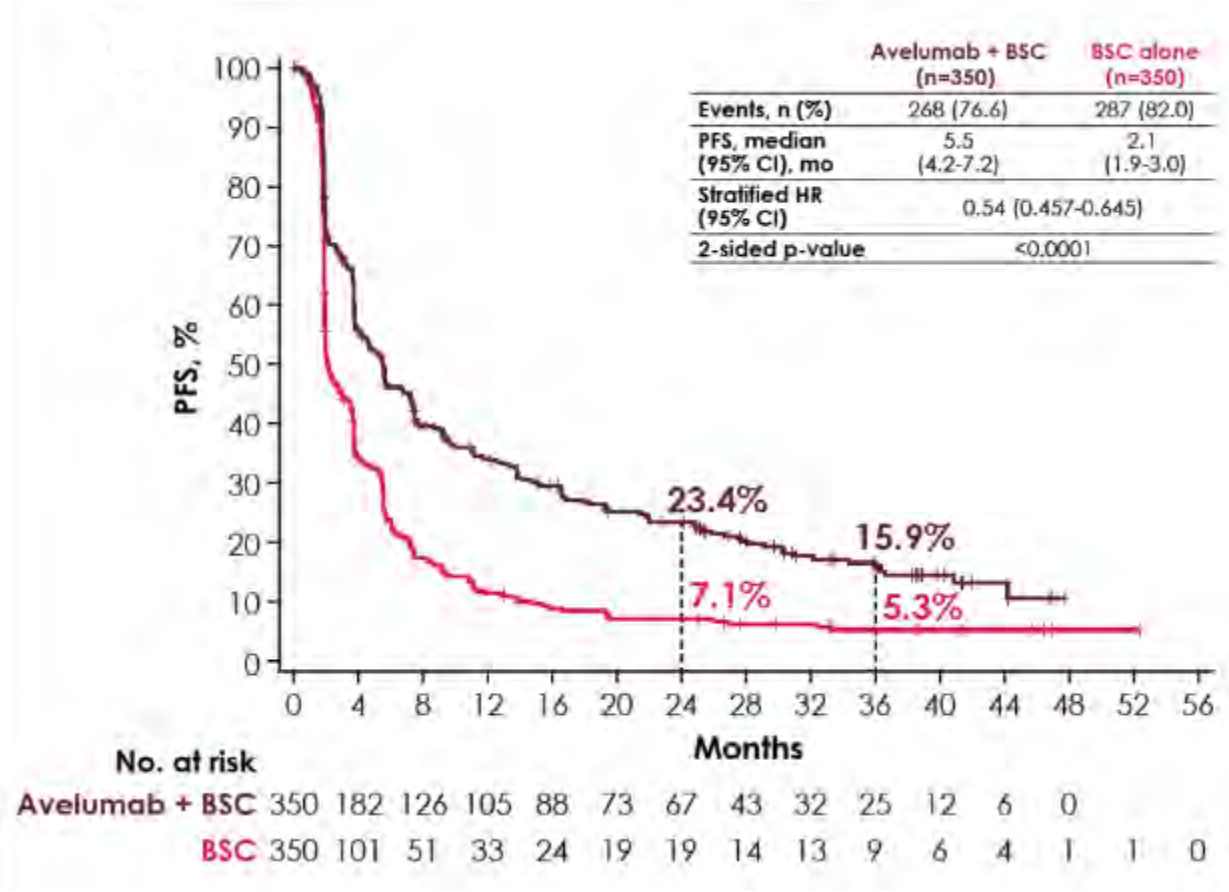
[a]In all randomized patients. [b]The most common reasons for UE response included death before first tumor assessment, withdrawal of consent, treatment stopped due to toxicity, patient never treated, and receipt of subsequent anticancer therapy before first tumor assessment. [c]Based on patients with an objective response per BICR (PR or CR as BOR). [d]Based on patients with a CR per BICR.
BOR, best overall response; CR, complete response; DoCR, duration of complete response; DoR, duration of objective response; NE, not estimable; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease; TTCR, time to complete response; TTR, time to objective response; UE, unevaluable.

Sequencing immune therapy after chemotherapy in bladder cancer



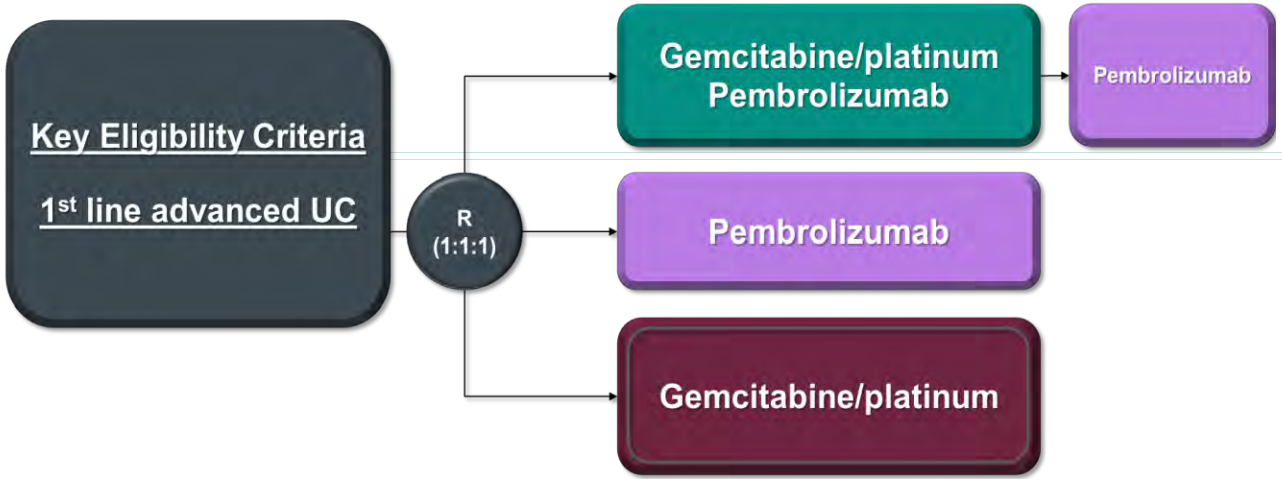
Sequenced immune therapy was associated with a 25% reduction in death, but only half the patients made it.



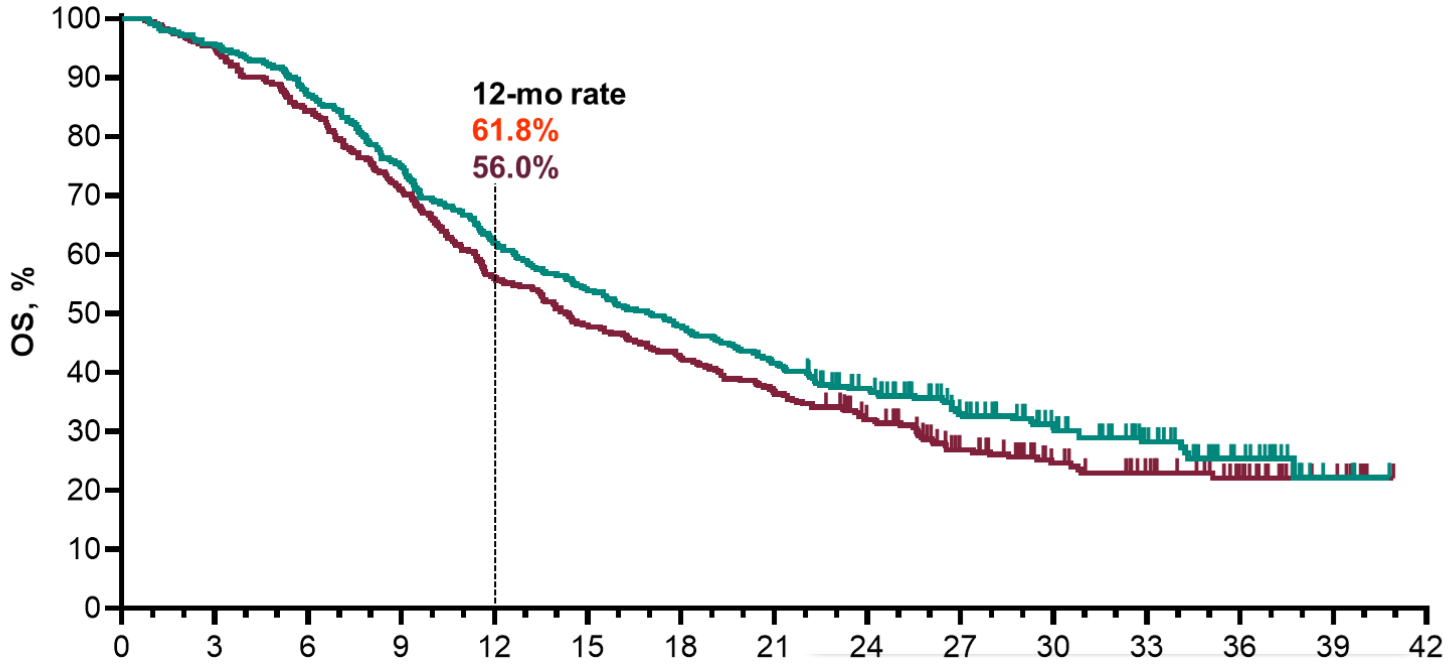


Thomas Powles, MD

KEYNOTE-361: 1st line metastatic bladder cancer.



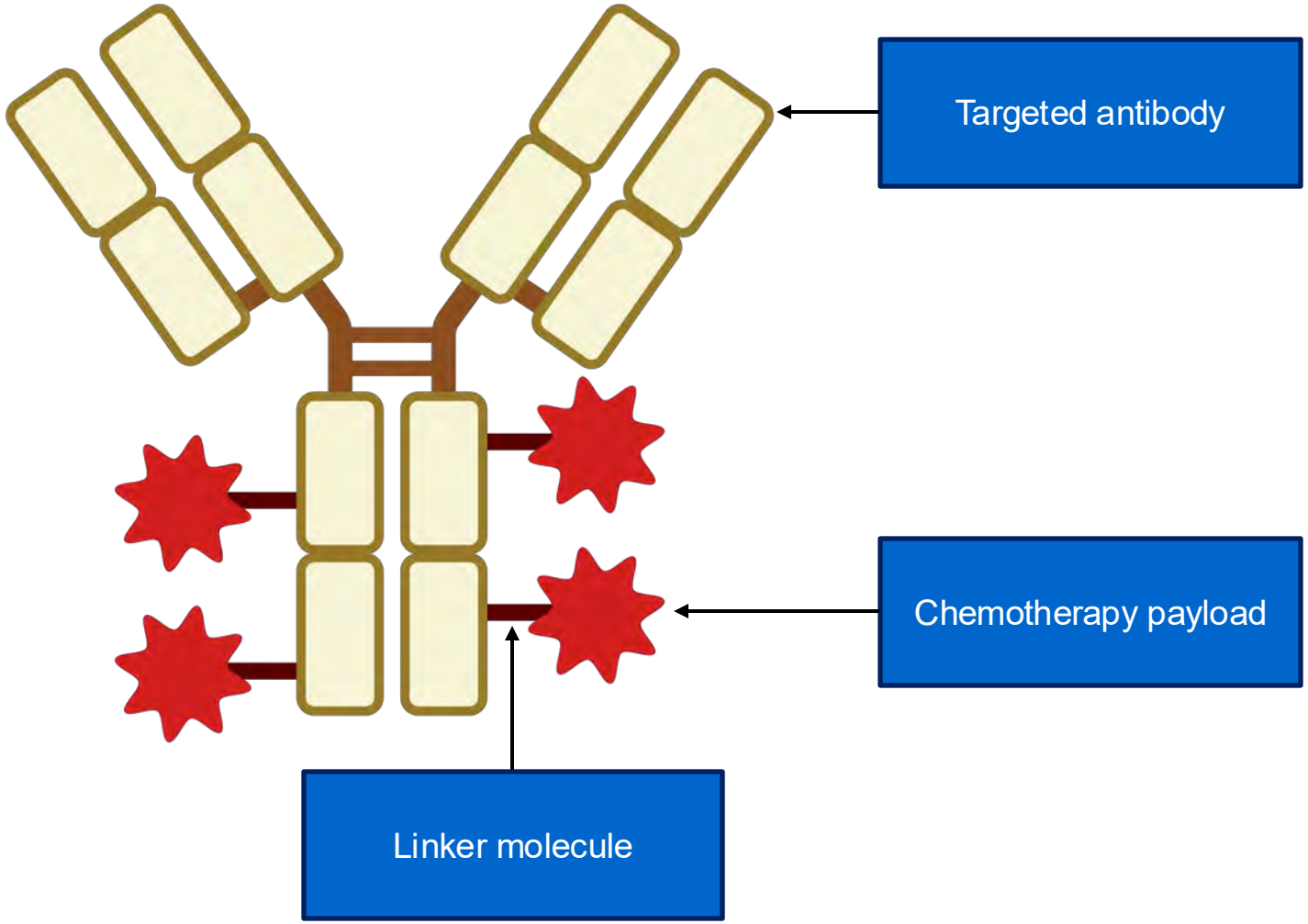
Overall Survival of chemo vs chemo+pembro



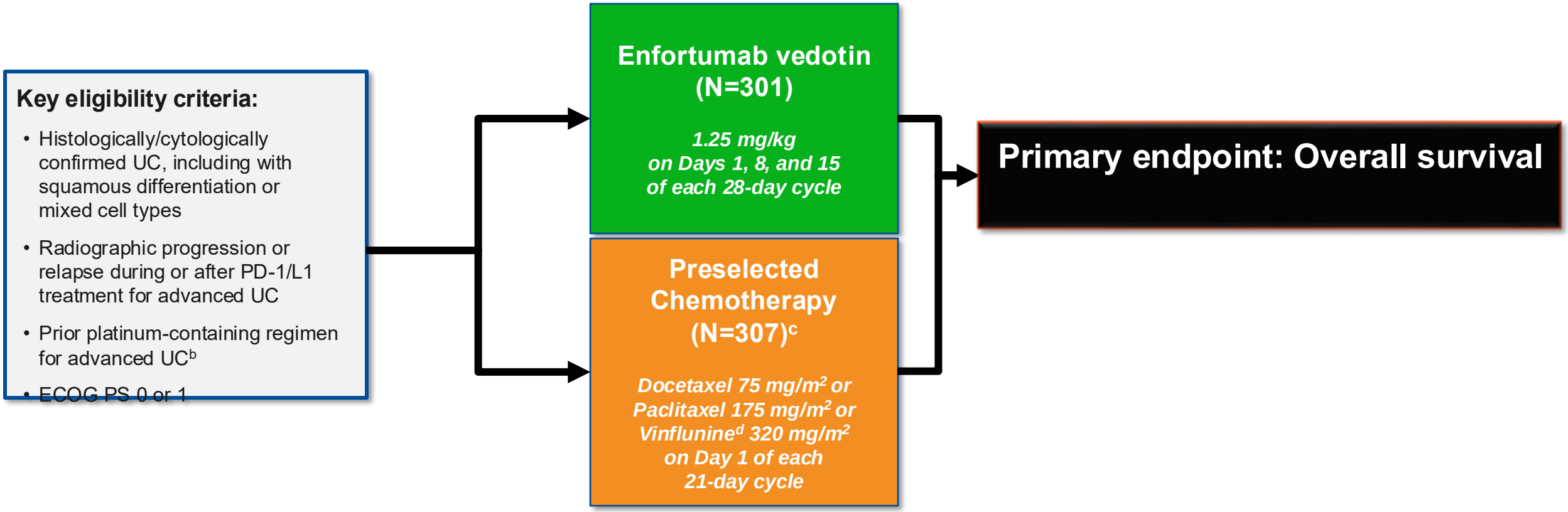
Median OS 17 months

For chemo+pembro followed by maintenance pembrolizumab for all that get there!

The Anatomy of an Antibody-Drug Conjugate: a new dawn



Antibody drug conjugate vs standard chemotherapy in bladder cancer



Overall Survival

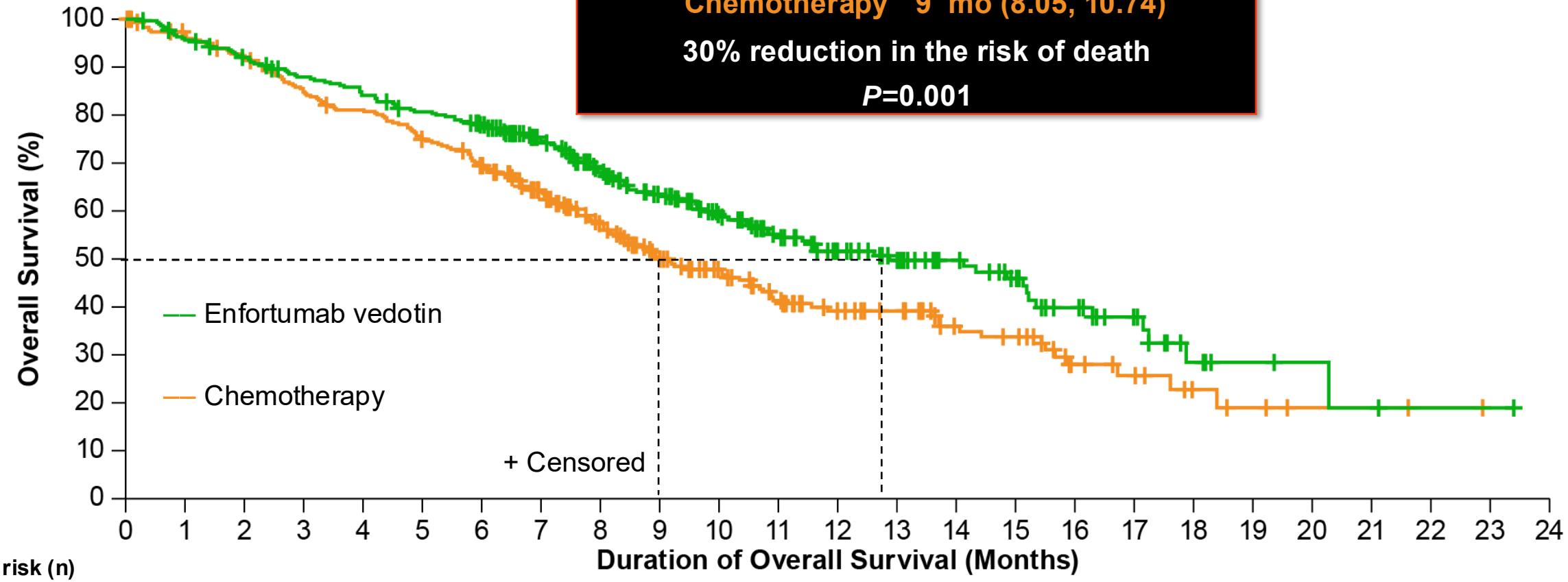
Median OS

Enfortumab vedotin 13 mo (10.58, 15.21)

Chemotherapy 9 mo (8.05, 10.74)

30% reduction in the risk of death

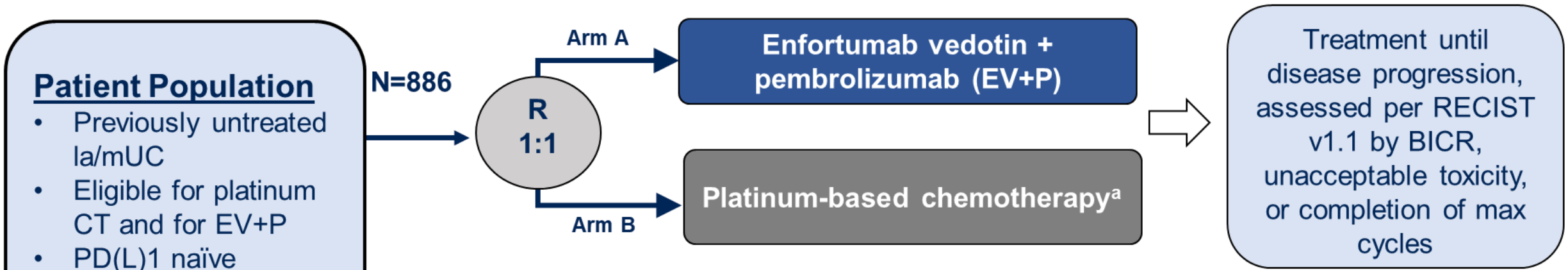
***P*=0.001**



Patients at risk (n)

Enfortumab vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapy	307	288	274	250	238	219	198	163	131	101		84	66	51	44	32	29	16	11	6	4	2	2	1	0	0

EV-302 Study Design



- No maximum treatment cycles for EV+P, maximum 35 cycles of pembrolizumab in Arm A
- Maximum 6 cycles of gemcitabine and platinum CT in Arm B

Efficacy and Safety Endpoints:
- Dual primary endpoints (PFS by BICR and OS)
- Prespecified secondary endpoints: ORR by BICR, PFS and ORR per investigator, DOR, DCR, Safety

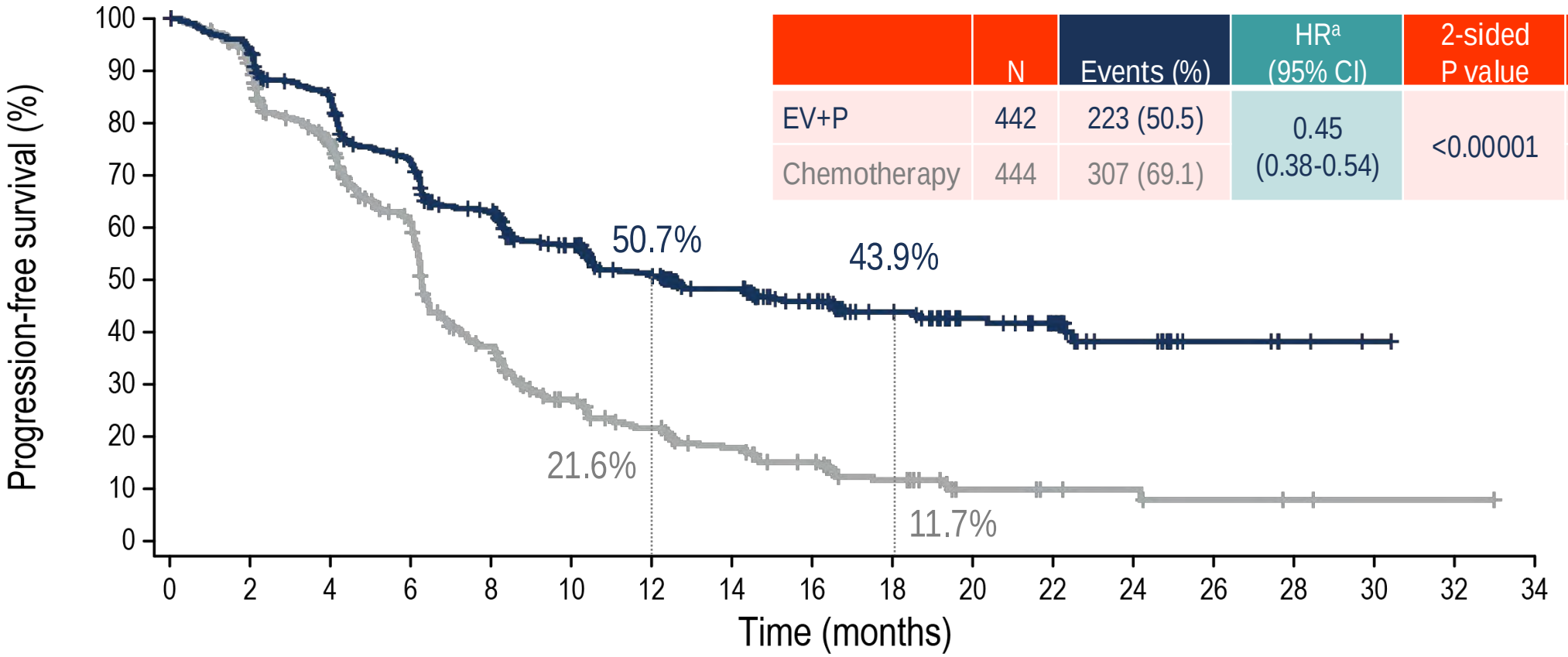
PRO Endpoints:
- Key secondary endpoints: Time to pain progression (TTPP), Change from baseline in BPI-SF worst pain at week 26
- Other pre-specified secondary endpoints: PROs (descriptive with no adjustment for multiplicity)

[a]Maintenance therapy could be used following completion and/or discontinuation of platinum chemotherapy.
BICR, Blinded Independent Central Review; BPI-SF, Brief Pain Inventory-Short Form; CT, chemotherapy; DCR, disease control rate; DOR, duration of response; EV+P, enfortumab vedotin plus pembrolizumab; la/mUC, locally advanced or metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumours.

Progression-Free Survival per BICR

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

Data cutoff: 08 Aug 2023

PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

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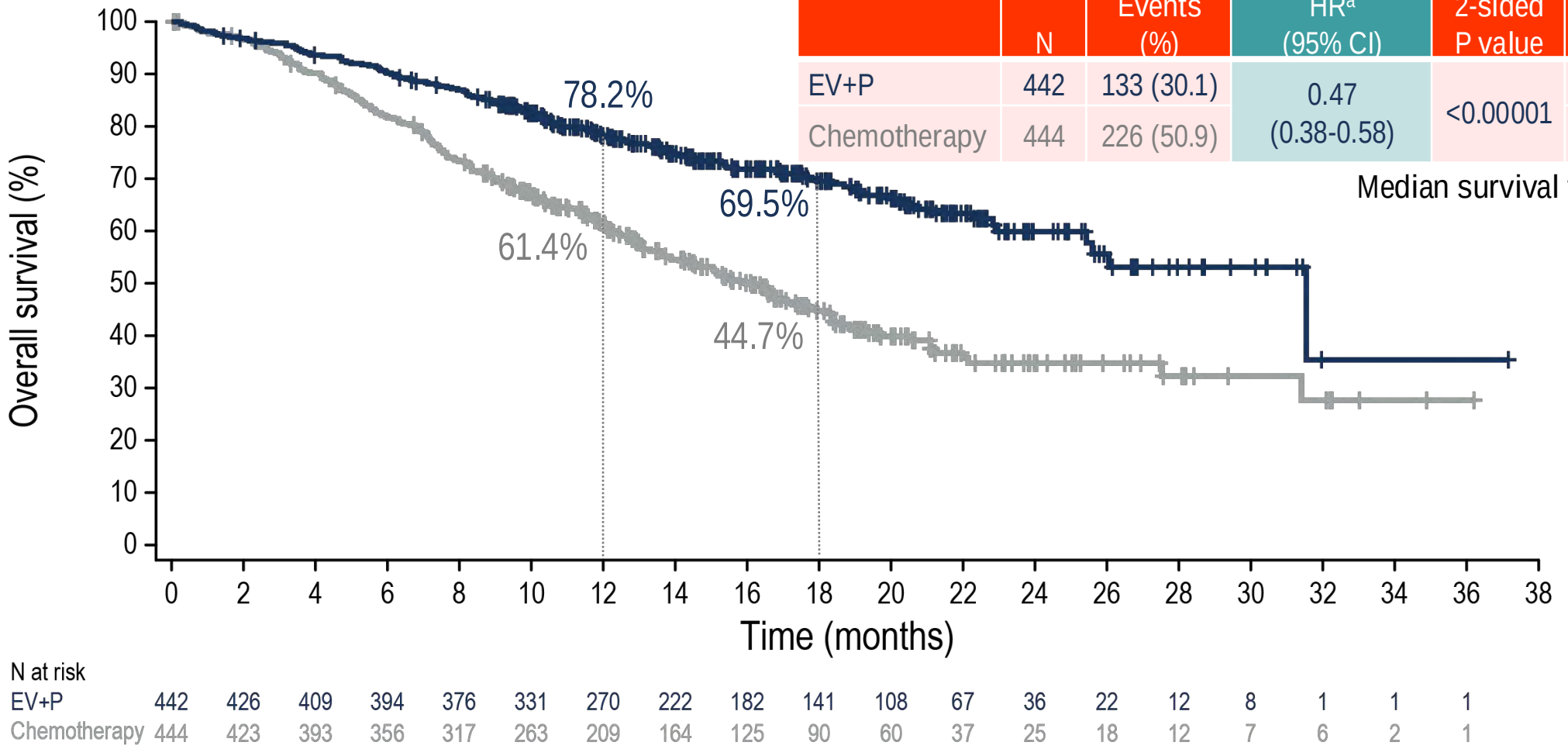
Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



N at risk

EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Data cutoff: 08 Aug 2023

OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

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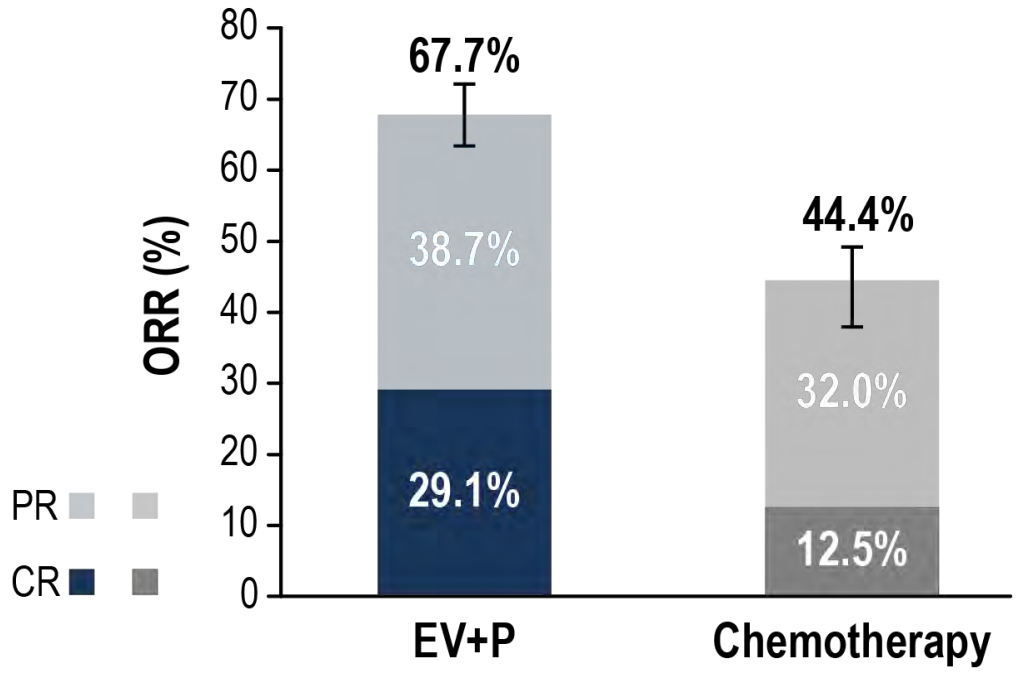
Confirmed Overall Response per BICR

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)

CR, complete response; DOR, duration of response; PR, partial response
[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response
[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline

Data cutoff: 08 Aug 2023

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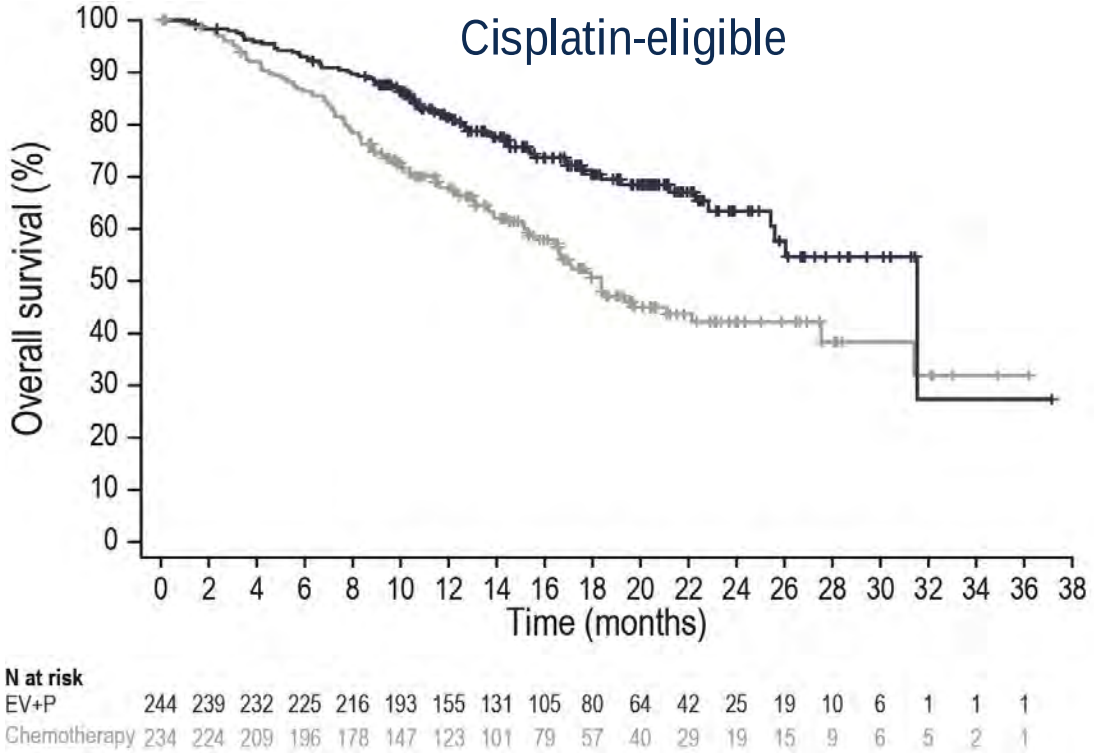
OS Subgroup Analysis: Cisplatin Eligibility

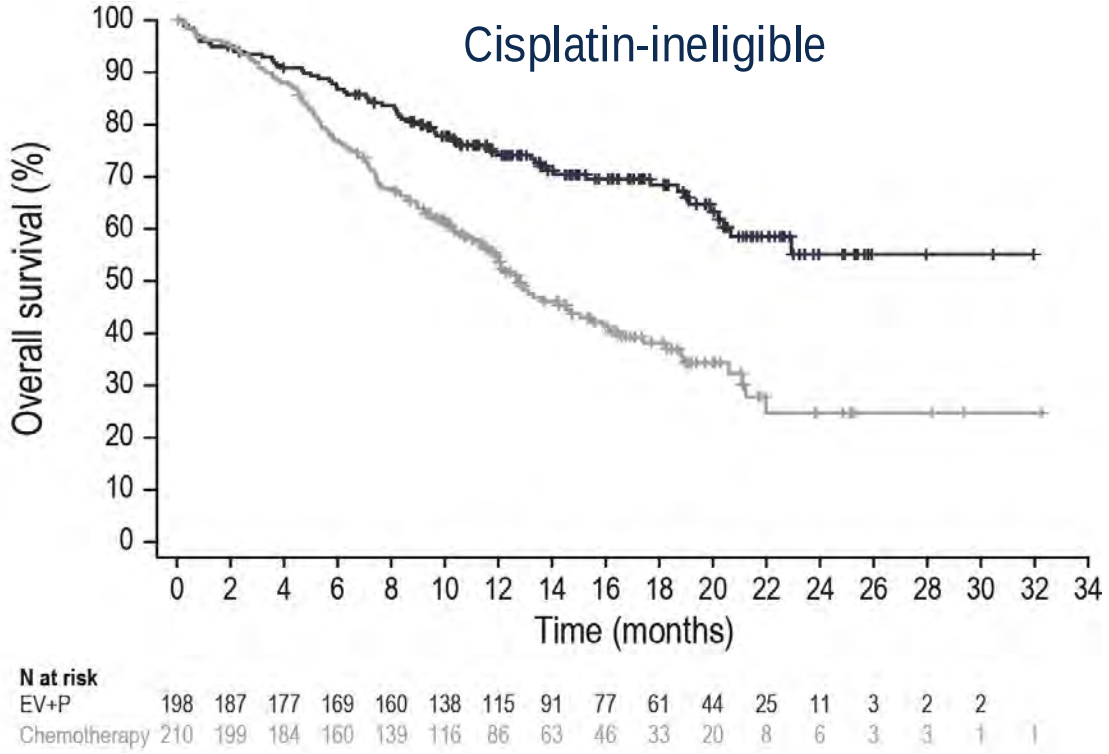
OS benefit was consistent with overall population regardless of cisplatin eligibility

Cisplatin-eligible



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	69	0.53 (0.39-0.72)	31.5 (25.4-NR)
Chemotherapy	106		18.4 (16.4-27.5)

Cisplatin-ineligible

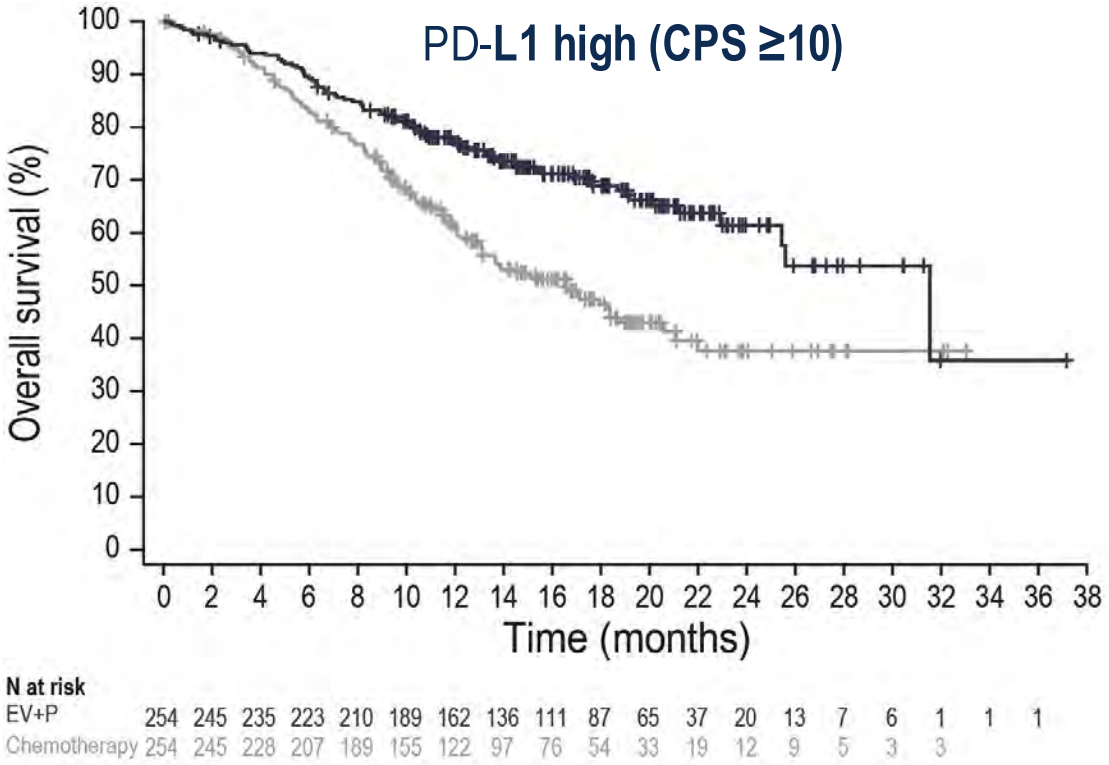


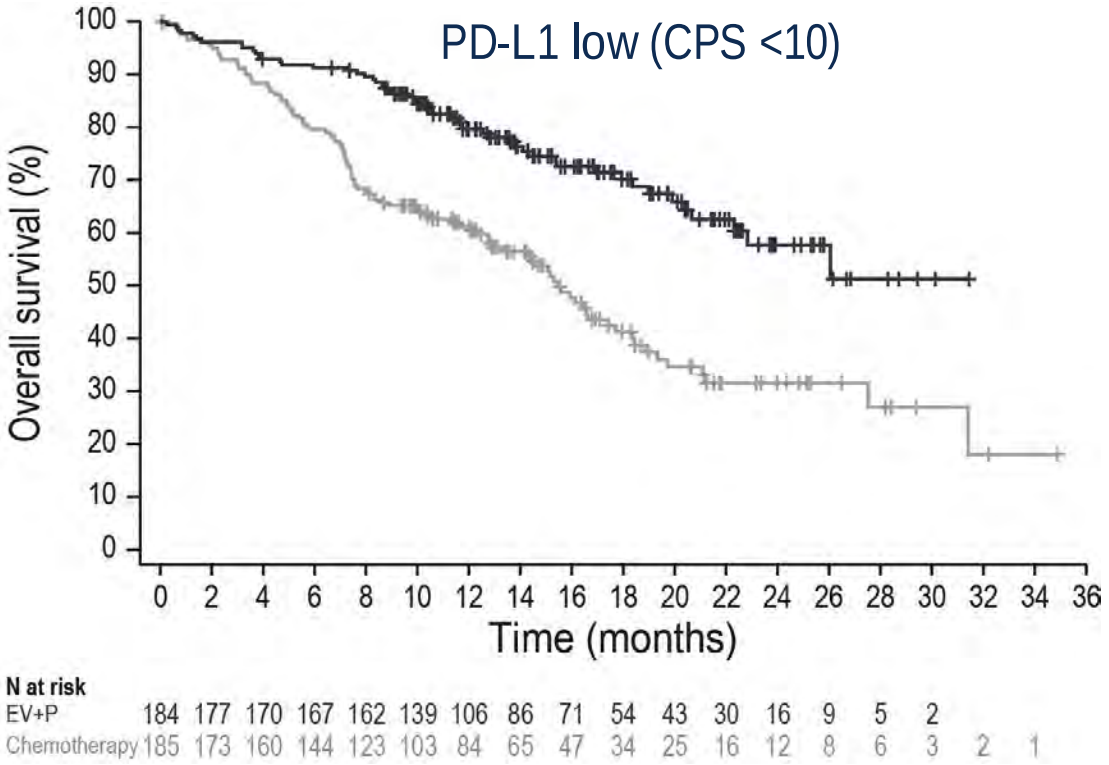
	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43 (0.31-0.59)	NR (20.7-NR)
Chemotherapy	120		12.7 (11.4-15.5)

Data cutoff: 08 Aug 2023

OS Subgroup Analysis: PD-L1 Expression

OS benefit was consistent with overall population regardless of PD-L1 expression status





	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	79	0.49 (0.37-0.66)	31.5 (25.4-NR)
Chemotherapy	125		16.6 (13.1-20.6)

	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	53	0.44 (0.31-0.61)	NR (22.3-NR)
Chemotherapy	99		15.5 (12.9-17.7)

Data cutoff: 08 Aug 2023

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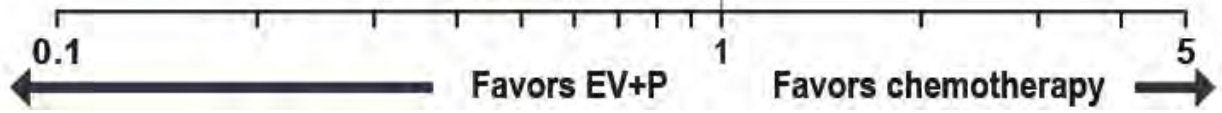
Subgroup Analysis of OS

OS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)



Data cutoff: 08 Aug 2023

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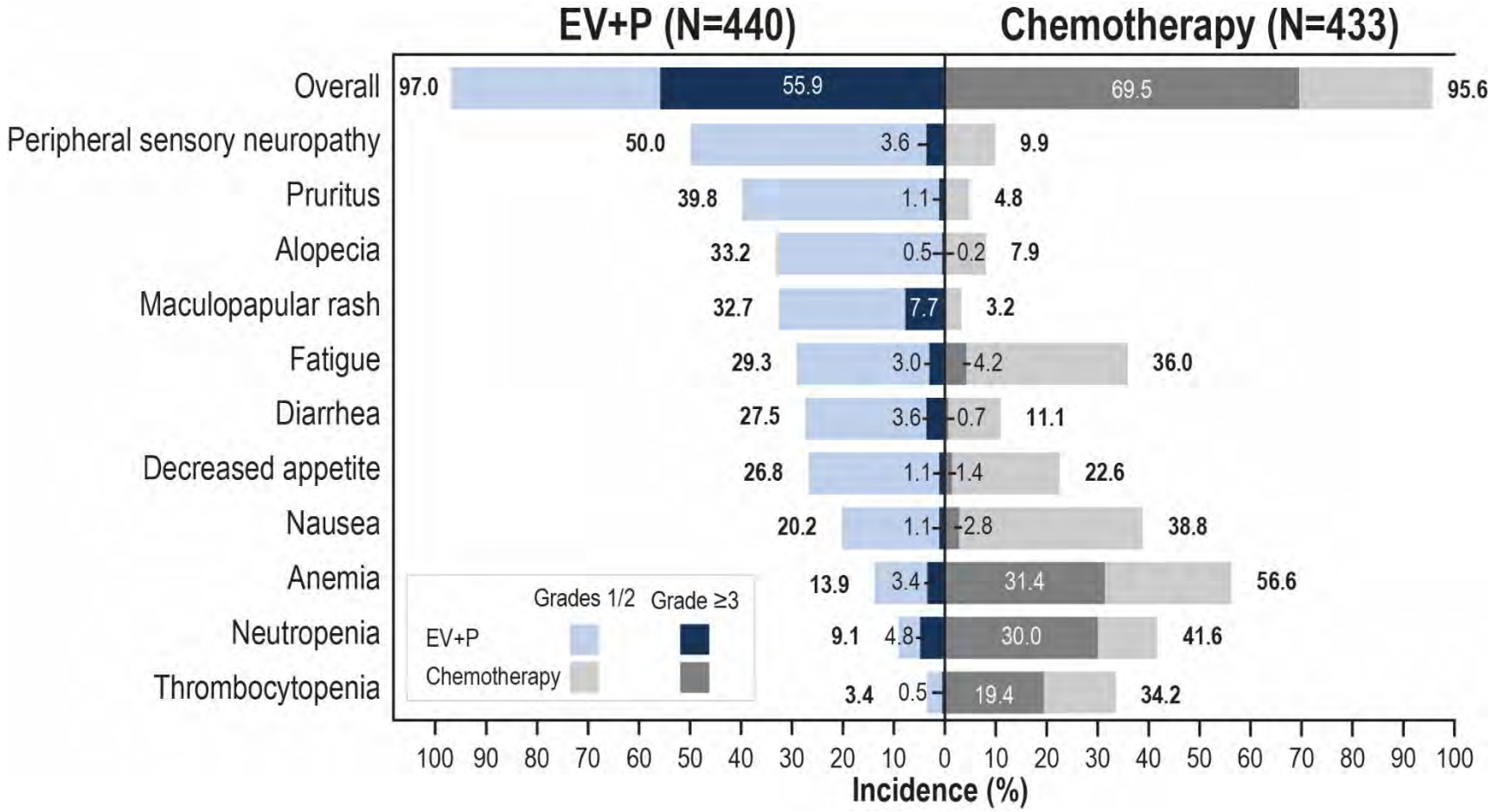
Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Are there patients in whom its not safe – or shouldn't be offered therapy?

Data cutoff: 08 Aug 2023

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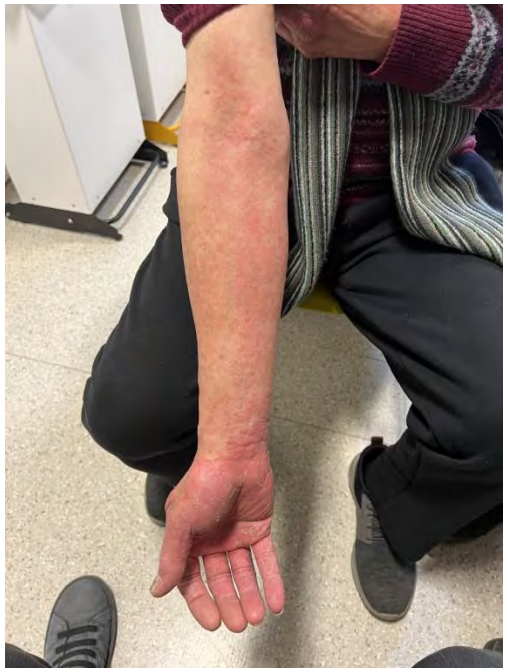
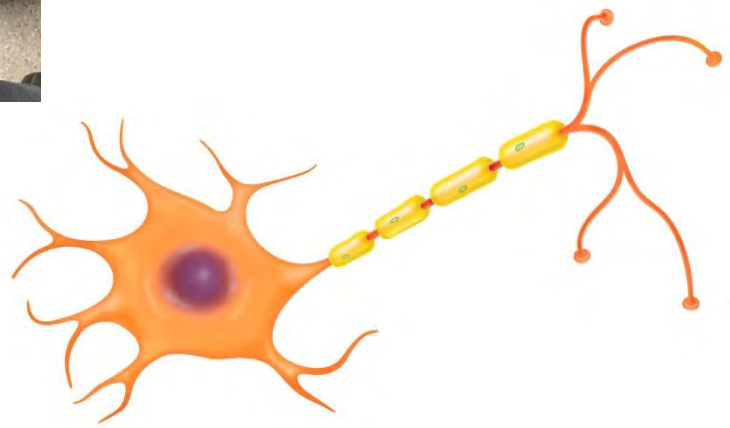
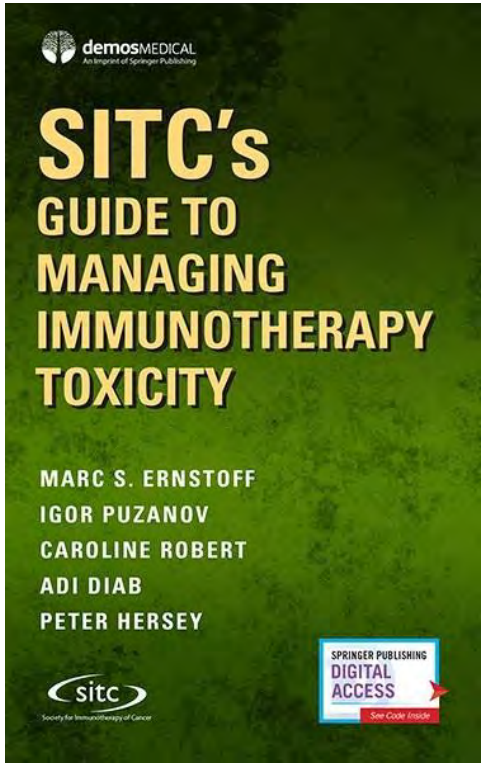
How to select patients for EVP toxicity and minimise toxicity



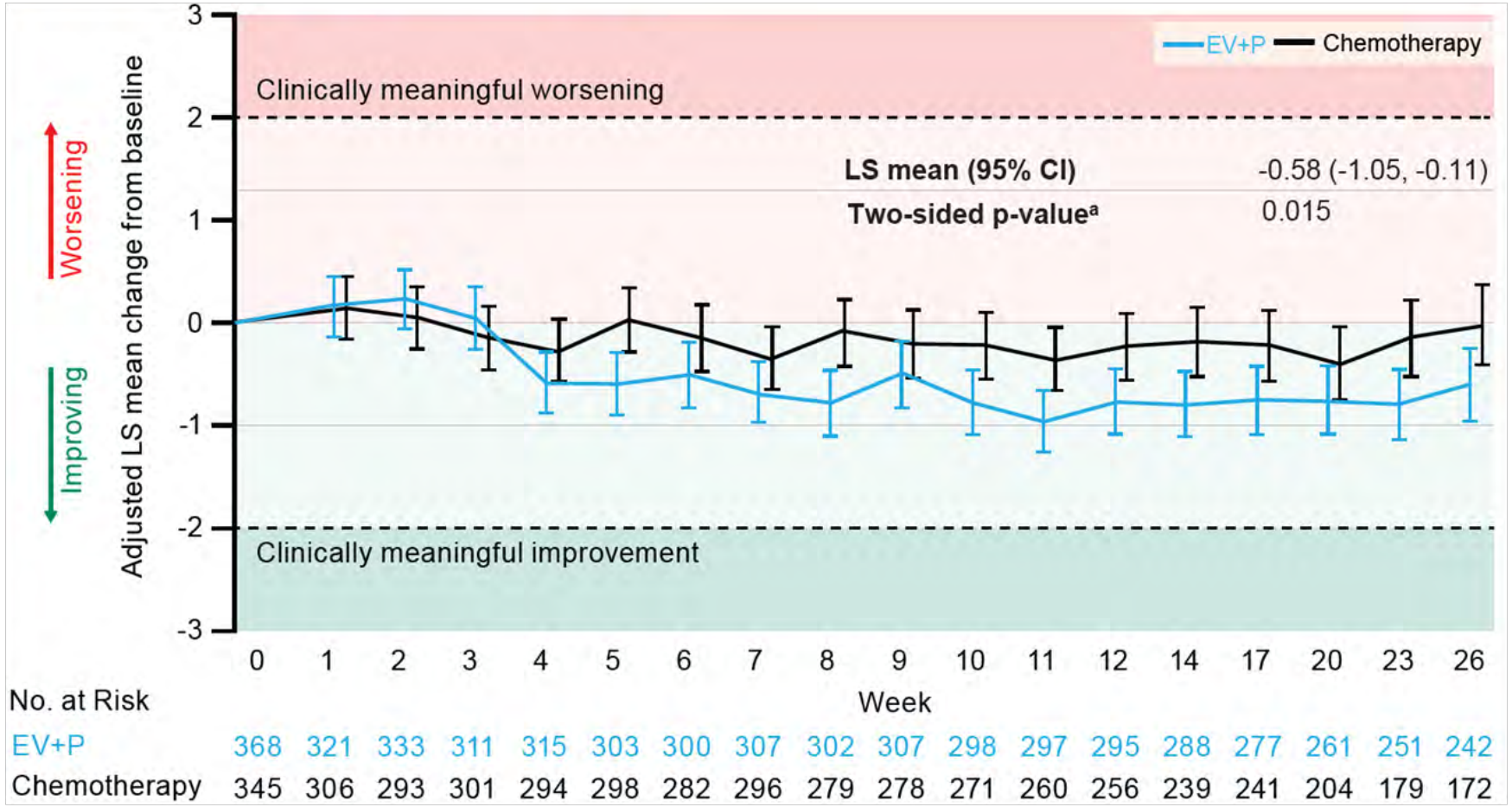




Change in Worst Pain (BPI-SF)

"Please rate your pain from 0 (no pain) to 10 (pain as bad as you can imagine) that best describes your pain at its worst in the last 24 hours."

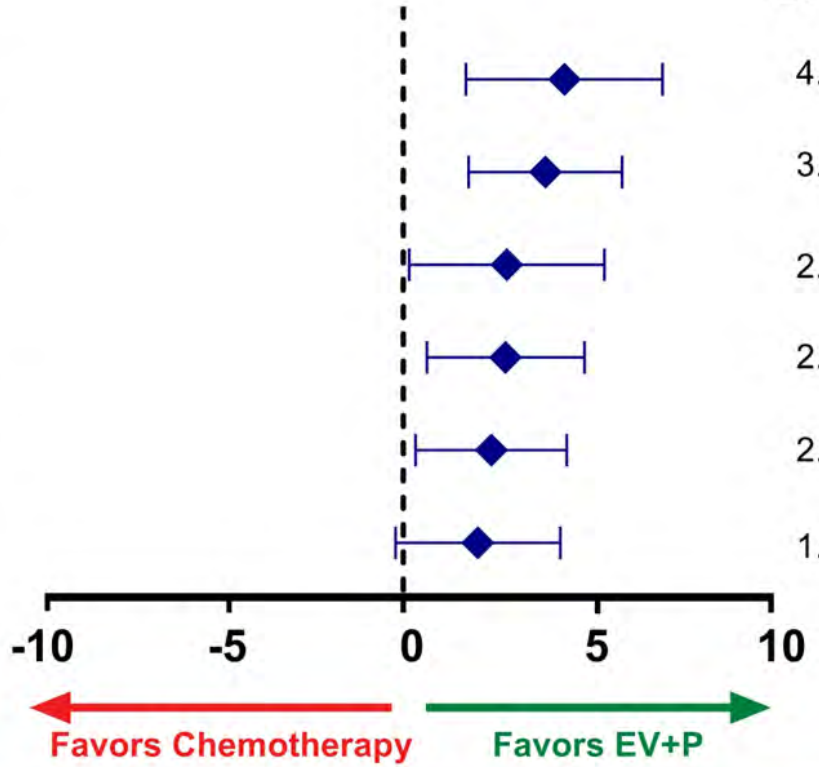
- Although pre-defined clinically meaningful thresholds were not met in either treatment arm:
  - Patients in the EV+P arm reported improved pain compared to baseline.
  - Larger improvements in pain were demonstrated in the EV+P arm than in the CT arm.



[a]Nominal p-value.
BPI-SF, Brief Pain Inventory-Short Form; CT. chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; LS, least-squares; PRO, patient reported outcome. .

Change in EORTC QLQ-C30 Functioning Domains

Functioning domain	EV+P LS mean (SE)	Chemotherapy LS mean (SE)	EV+P - Chemotherapy LS mean (95% CI)	p-value
Role functioning	-5.36 (1.23)	-9.49 (1.26)	4.13 (1.47, 6.79)	0.0024
Physical functioning	-2.63 (0.96)	-6.25 (0.99)	3.62 (1.54, 5.70)	0.0007
Social functioning	-2.94 (1.22)	-5.52 (1.25)	2.57 (-0.07, 5.22)	0.0561
Global health status/QoL	-0.59 (0.99)	-3.12 (1.01)	2.54 (0.41, 4.67)	0.0197
Cognitive functioning	-0.54 (0.95)	-2.69 (0.97)	2.15 (0.10, 4.20)	0.0400
Emotional functioning	3.85 (0.97)	1.96 (0.98)	1.89 (-0.19, 3.97)	0.0750



- Patients in the EV+P arm demonstrated improved functioning across all functioning domains compared to patients in the CT arm based on change from baseline during the first 26 weeks.

CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; LS, least squares; PRO, patient reported outcome; SE, standard error.

1968P

Study EV-103 Dose Escalation/Cohort A (DE/A): 5y Follow-Up of First-Line (1L) Enfortumab Vedotin (EV) + Pembrolizumab (P) in Cisplatin (Cis)-Ineligible Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

Jonathan E. Rosenberg[1], Peter H. O' Donnell[2], Daniel Petrylak[3], Thomas W. Flaig[4], Christopher J. Hoimes[5], Shilpa Gupta[6], Nataliya Mar[7], Terence W. Friedlander[8], Scott Tagawa[9], Mehmet Asim Bilen[10], Jason Brown[11], Rana R. McKay[12], Jaime R. Merchan[13], Sandy Srinivas[14], Aditya Shetty[15], Blanca Homet Moreno[16], Griffith Davis[17], Heidi S. Wirtz[17], Yalin Zhu[17], Matthew I. Milowsky[18]

Time to response and DOR in patients achieving confirmed CR or PR by BICR

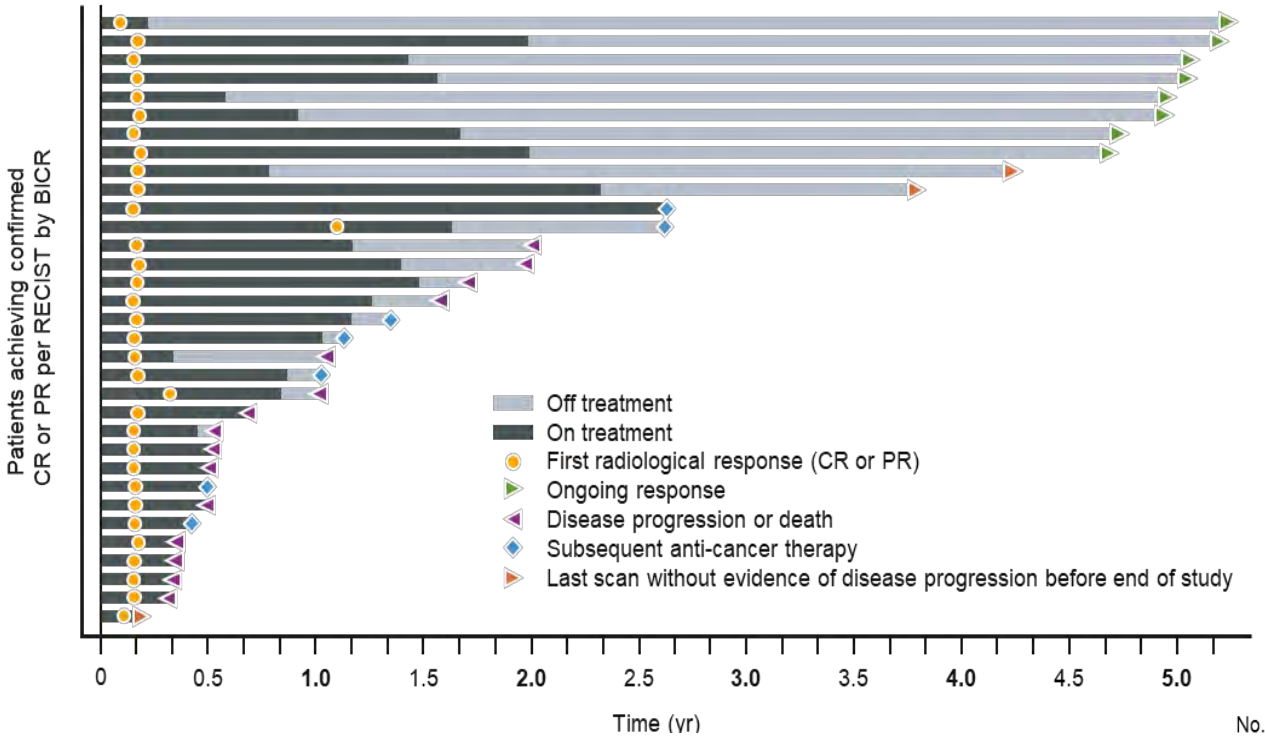
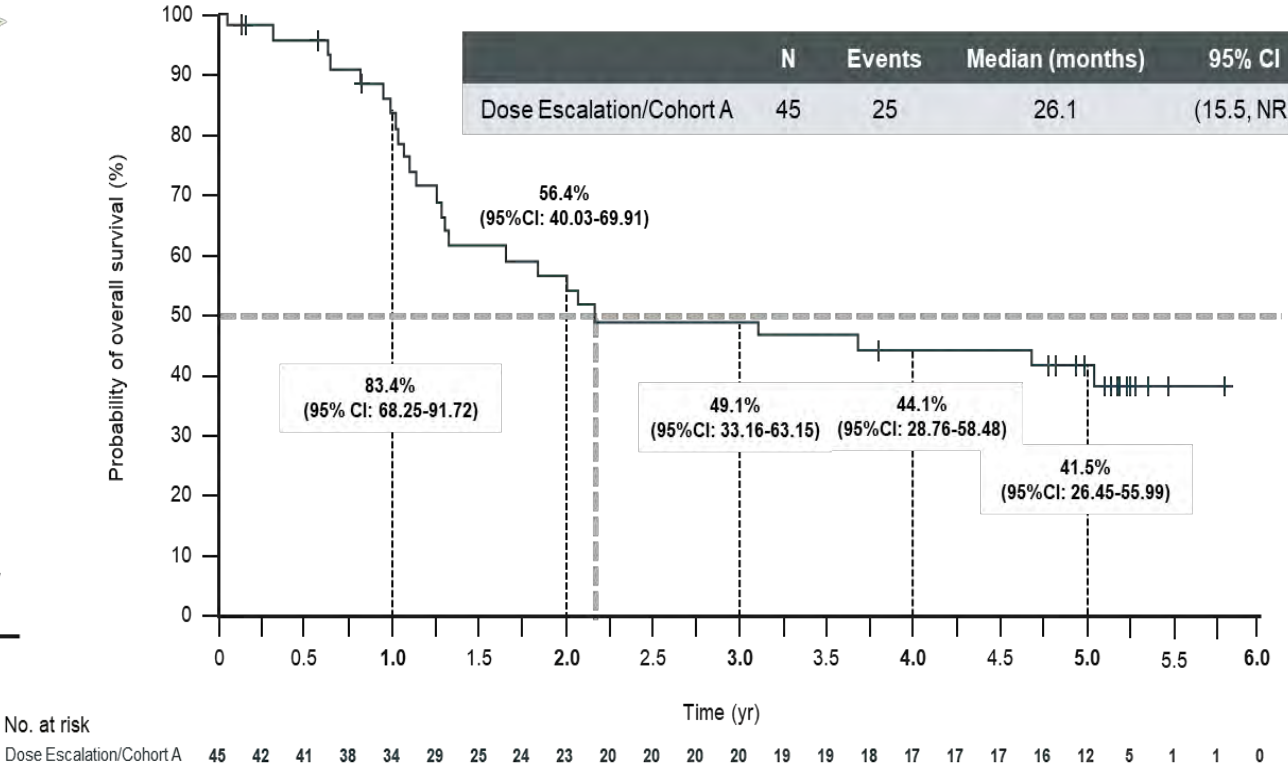


Figure 5. OS



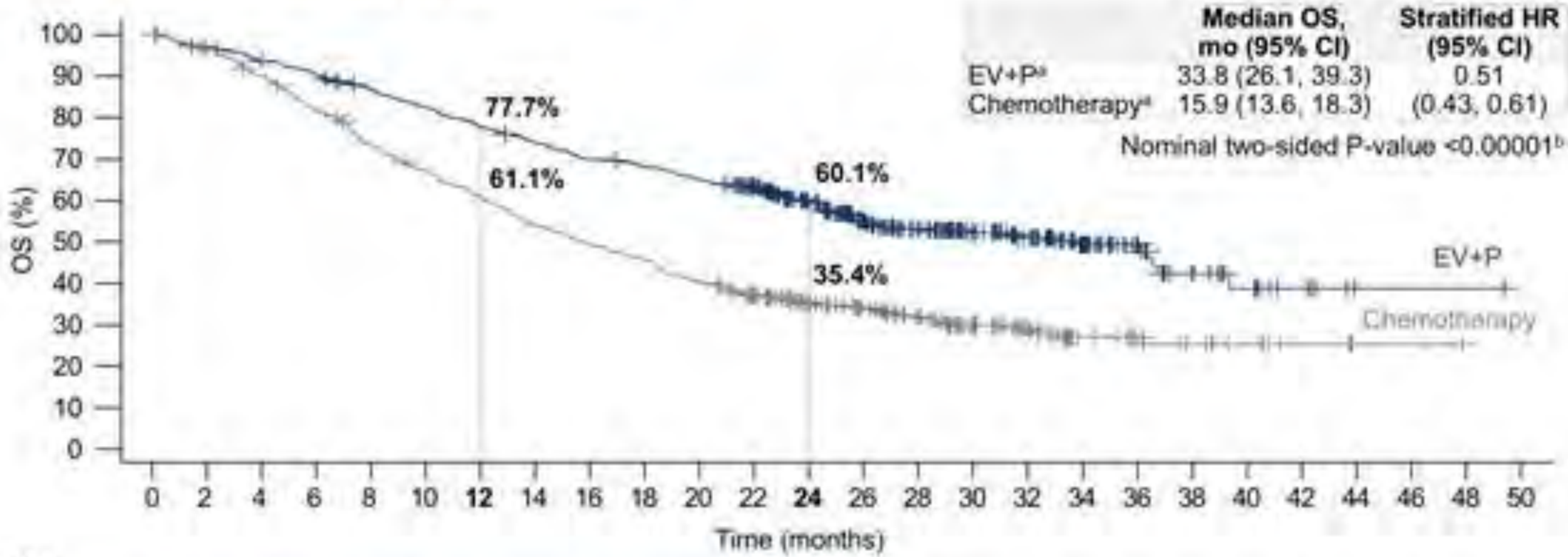
	N	Events	Median (months)	95% CI
Dose Escalation/Cohort A	45	25	26.1	(15.5, NR)

No. at risk

Dose Escalation/Cohort A	45	42	41	38	34	29	25	24	23	20	20	20	20	19	19	18	17	17	17	16	12	5	1	1	0

OS in the Overall Population

Risk of death was reduced by almost 50%



	Median OS, mo (95% CI)	Stratified HR (95% CI)
EV+P[a]	33.8 (26.1, 39.3)	0.51 (0.43, 0.61)
Chemotherapy[a]	15.9 (13.6, 18.3)	

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

No. at risk																								
EV+P	442	426	409	394	375	356	336	319	302	293	280	252	206	161	133	102	79	52	32	19	11	6	1	1	1
Chemotherapy	444	423	393	356	317	290	263	233	214	197	176	148	121	102	81	59	43	24	18	13	9	5	2	2	

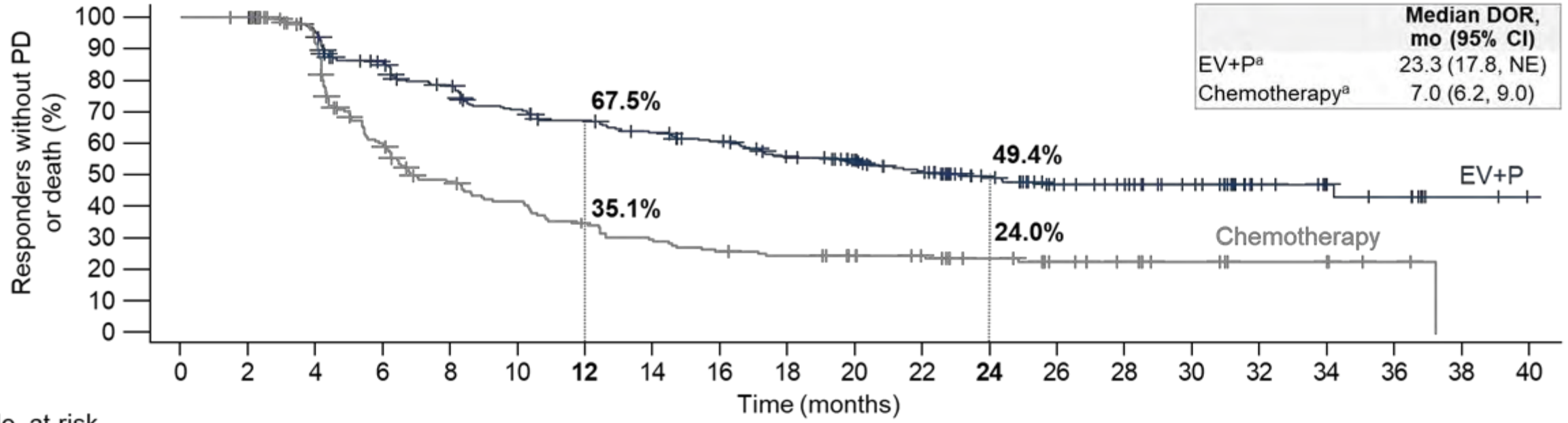
Data cutoff: August 8, 2024.

EV, enfortumab vedotin; P, pembrolizumab; OS, overall survival.

[a]Events/N were 203/442 for EV+P and 297/444 for chemotherapy. [b]P value is nominal and descriptive.

Duration of Response (CR or PR) by BICR

Among responders, the probability of maintained response at 24 months was ~50% with EV+P



	Median DOR, mo (95% CI)
EV+P[a]	23.3 (17.8, NE)
Chemotherapy[a]	7.0 (6.2, 9.0)

No. at risk

EV+P	295	295	274	238	213	190	177	165	154	137	125	107	78	58	53	40	20	14	10	4
Chemotherapy	195	194	162	102	78	67	55	47	41	38	34	30	23	16	13	9	5	5	2	

	EV+P (n=437)	Chemotherapy (n=441)	Nominal two-sided P-value
Confirmed ORR (CR or PR), n (%) [95% CI]	295 (67.5) [62.9, 71.9]	195 (44.2) [39.5, 49.0]	<0.00001[b]
Best overall response, n (%)			
CR	133 (30.4)	64 (14.5)	
PR	162 (37.1)	131 (29.7)	
SD	83 (19.0)	149 (33.8)	

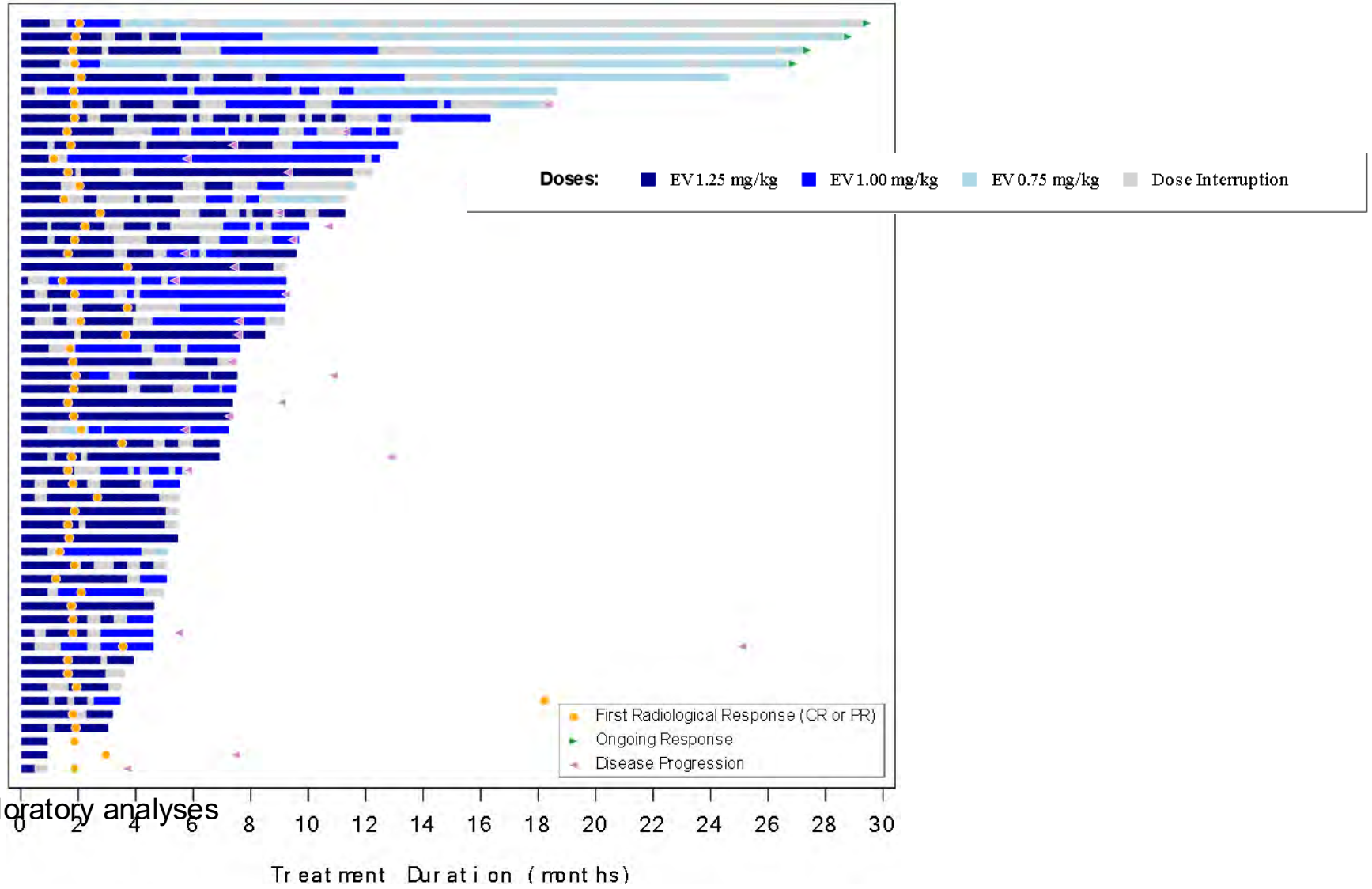
Data cutoff: August 8, 2024.

CR, complete response; EV, enfortumab vedotin; NE, not estimable; P, pembrolizumab; PR, partial response; ORR, objective response rate; SD, stable disease.

[a]Events/N were 137/295 for EV+P and 129/195 for chemotherapy. [b]P-value is nominal and descriptive.

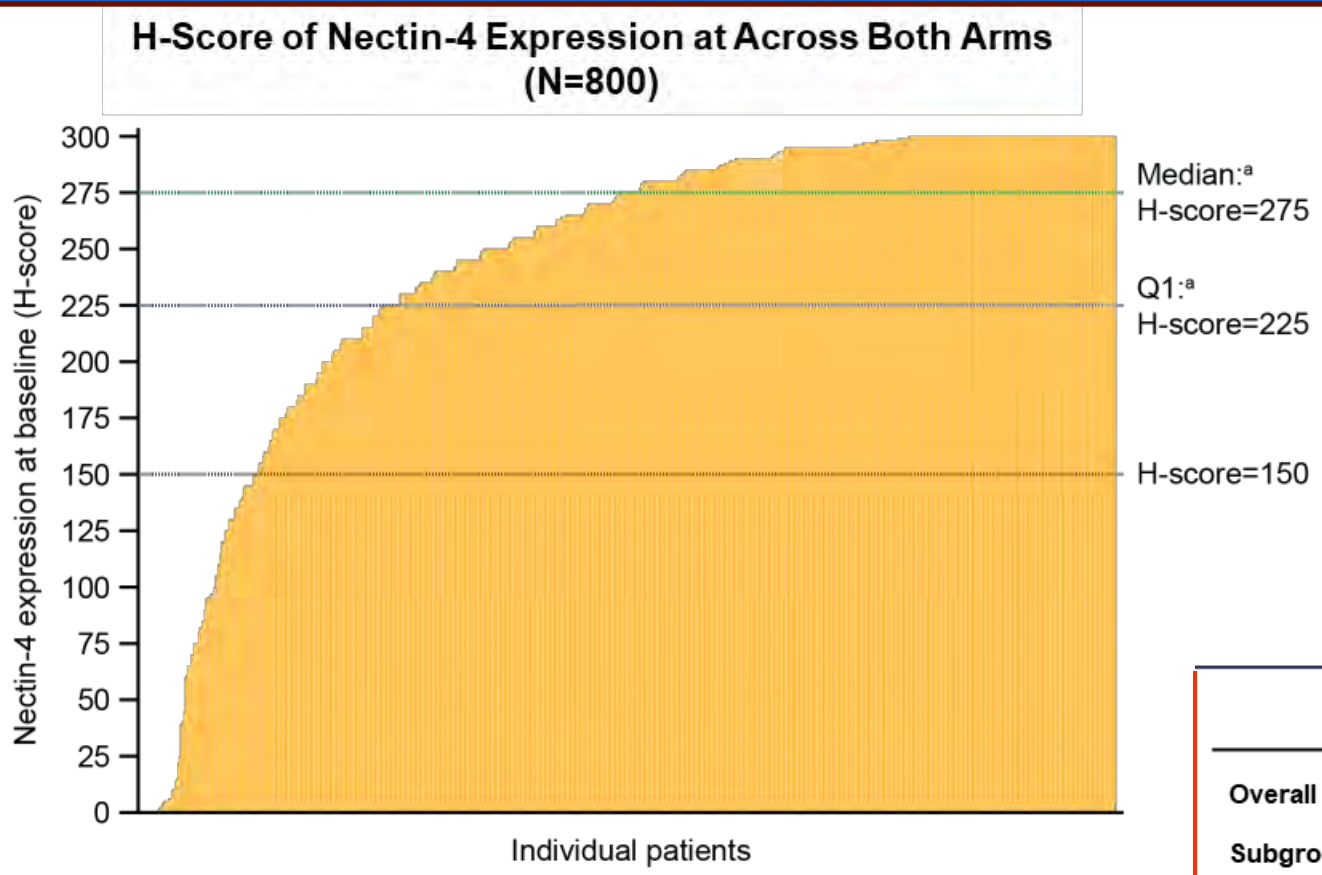
Patients often resumed treatment and continued to benefit following dose interruptions and reductions

Patients who responded to EV in EV-201 Cohort 1 (ORR 45%)



All data presented are post-hoc, exploratory analyses

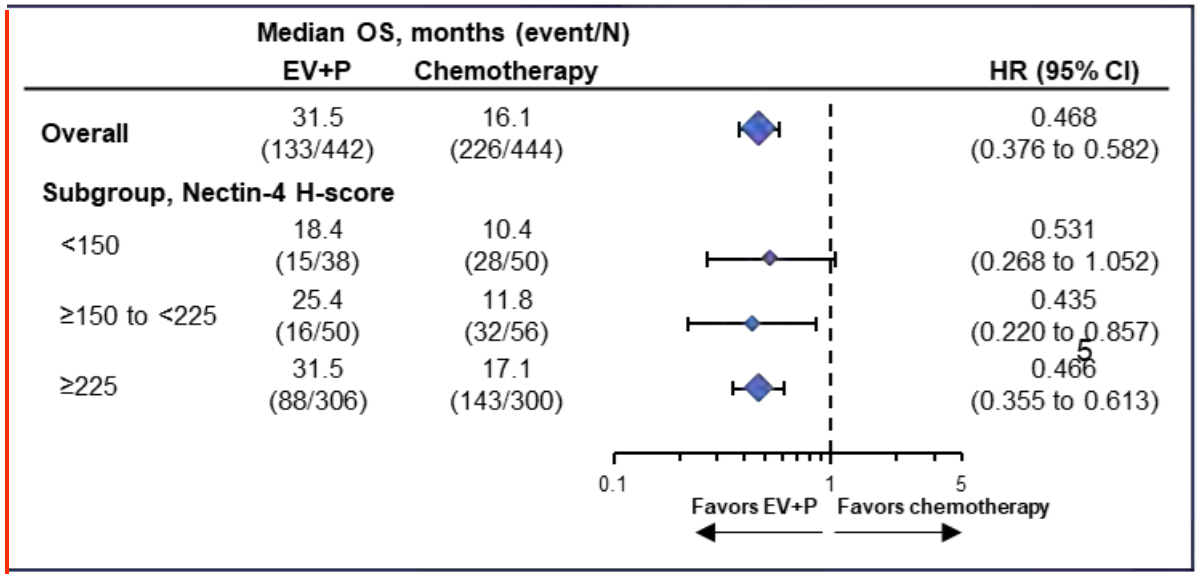
NECTIN-4 as a biomarker for enfortumab vedotin and pembrolizumab vs chemotherapy in the EV302 study.



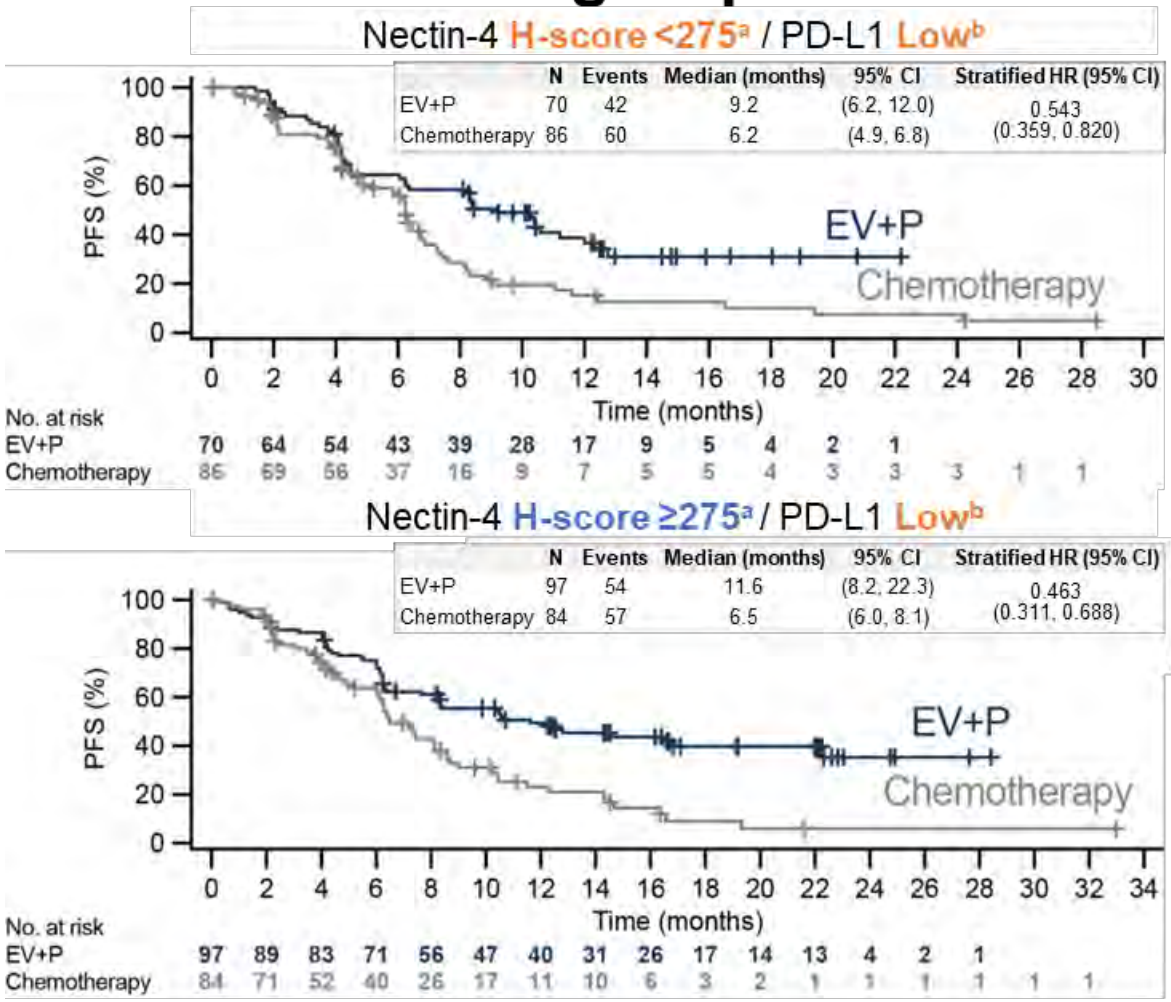
Variable	EV+P (n=394)	Chemotherapy (n=406)
H-score, median (IQR)	280 (230-298)	270 (215-297)
Subgroup, H-score, n (%)		
<150	38 (9.6)	50 (12.3)
≥150 to <225	50 (12.7)	56 (13.8)
≥225	306 (77.7)	300 (73.9)
Patients with H-score 0, n (%)	3 (0.8)	6 (1.5)

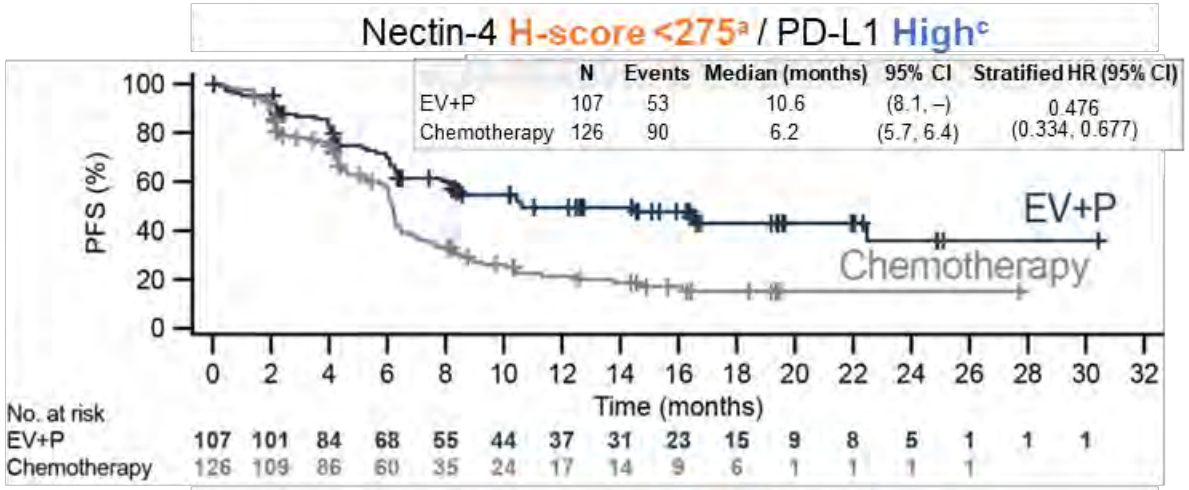
Data cutoff: 8 August 2023.
EV, enfortumab vedotin; IQR, interquartile range; P, pembrolizumab.
[a]Including all patients across both arms.

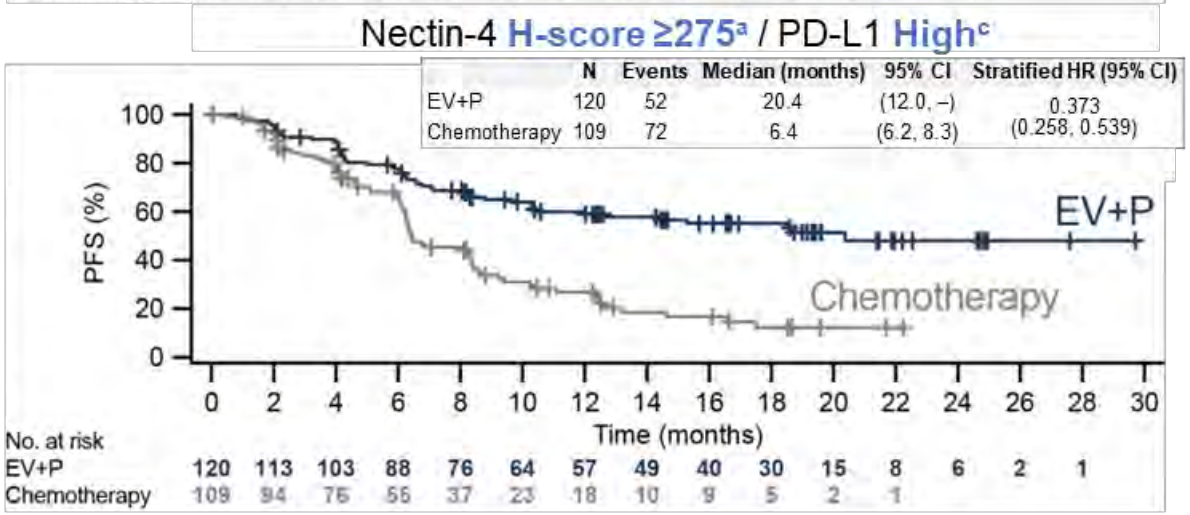
OS



Consistent PFS Benefit with EV+P Across Nectin-4 and PD-L1 Subgroups





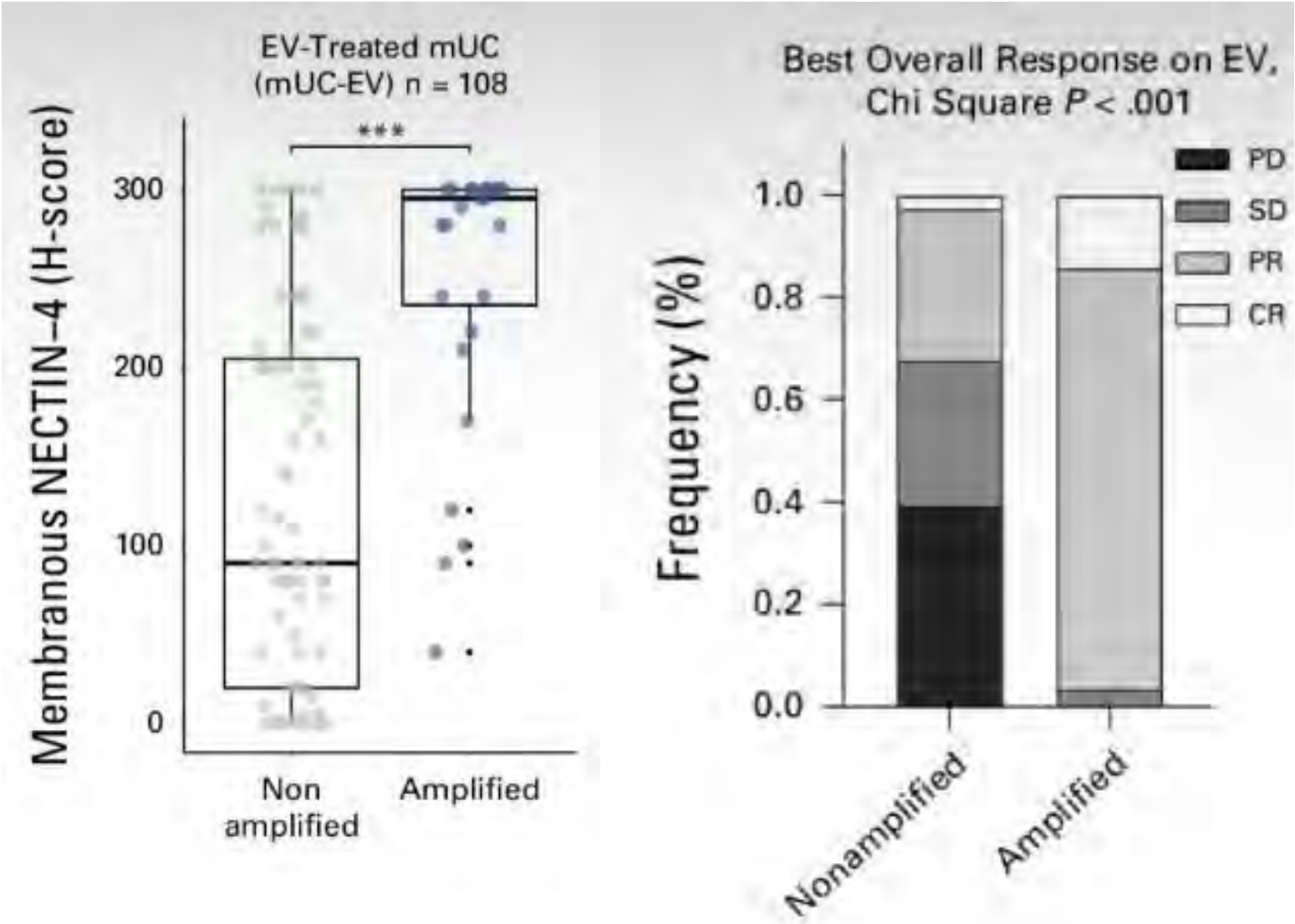


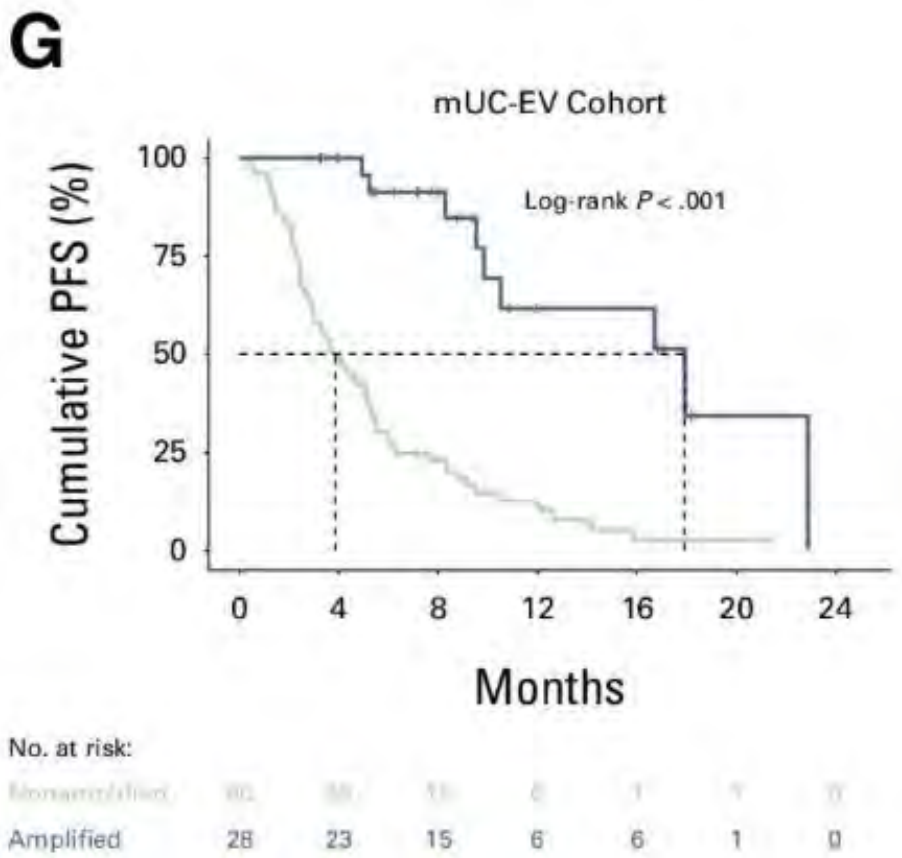
Data cutoff: 8 August 2023.

CPS, combined positive score; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1.

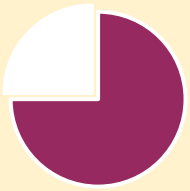
[a]The median Nectin-4 H-score was 275 across patients in both arms. [b]CPS <10. [c]CPS ≥10.

NECTIN4 amplification and response to EV monotherapy

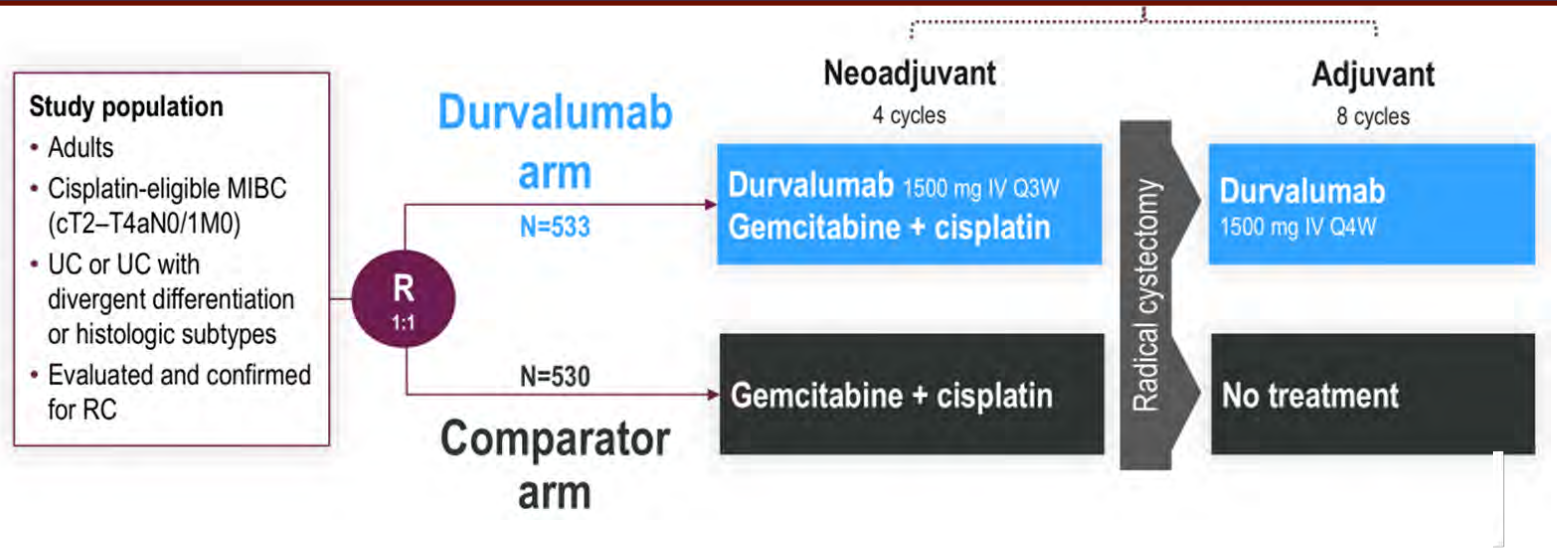


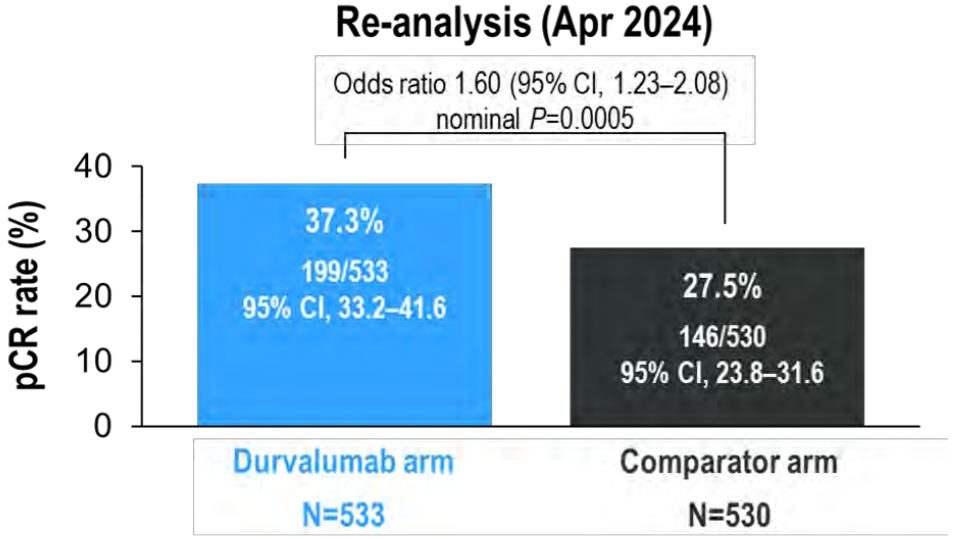


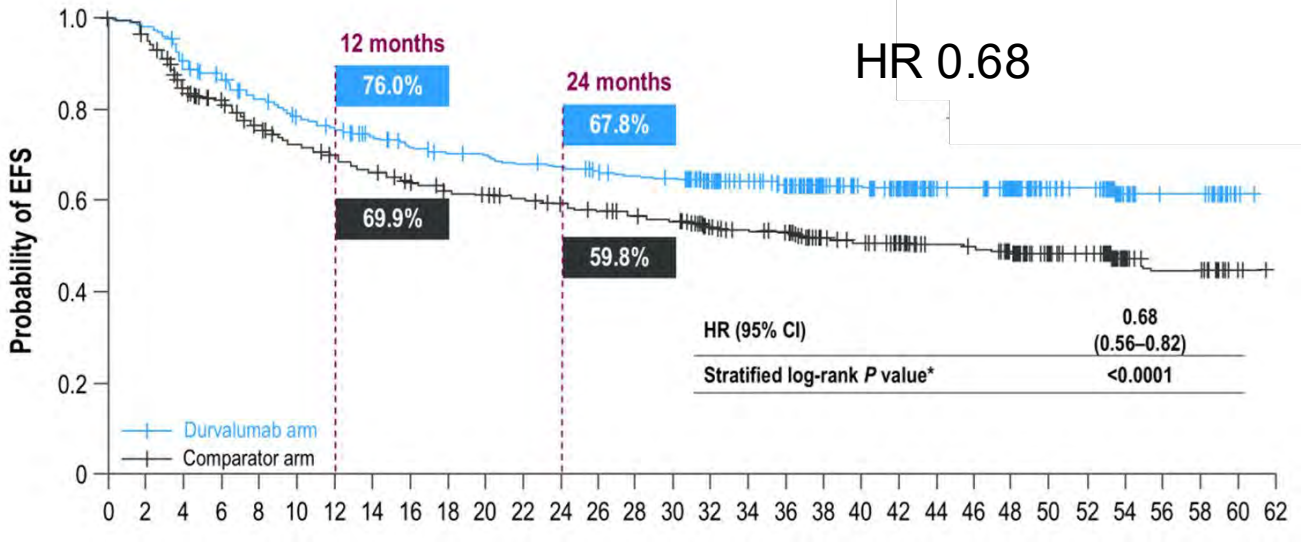
Klumper JCO 2024

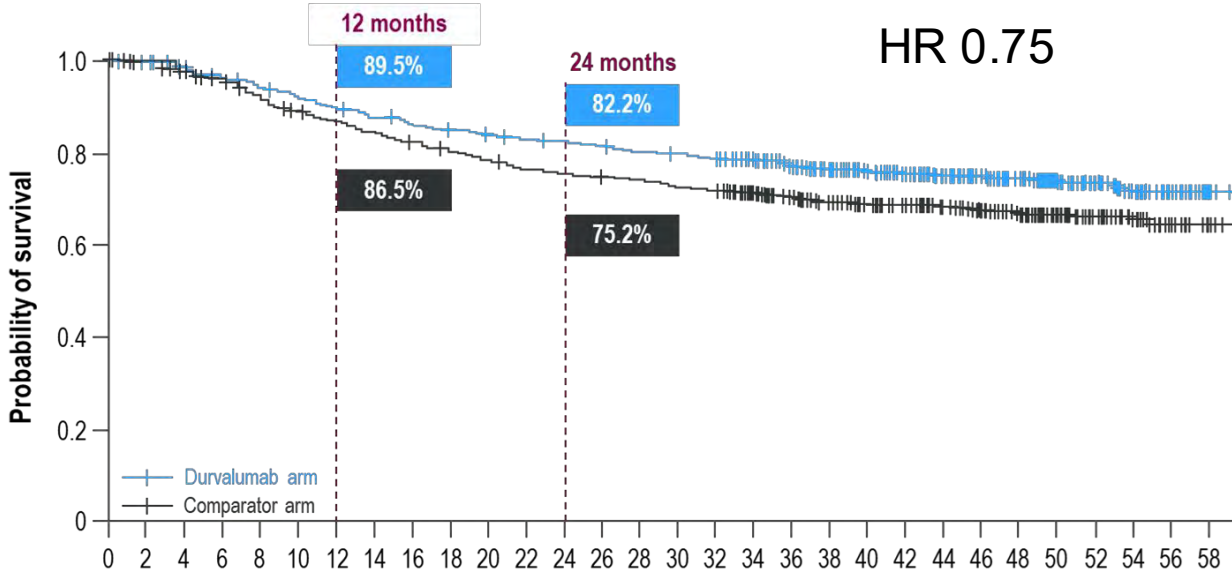
ADC in platinum advanced bladder cancer	Enfortumab Vedotin	sacituzumab Govitcan (n=113)	Disitimab Vedotin (n=109)	T-DXD (n=16)	BT8009 (n=45)	BL-B01D1 (n=27)
Target	NECTIN4	TROP-2	HER-2	HER-2	NECTIN-4	HER3/EGFR
Payload	MMAE	TOPO-1	MMAE	TOPO-1	MMAE	TOPO-1
Biomarker selection	None	None	1-3+	3+	None	None
Randomised phase III studies	*301, 302,303,304 VOLGA*	TROPICS-4	1st line R3 (China and Global)	None	1st line R3 Global	Planned (China)
Grade 3+ TRAEs	*51%*	65%	45%	45-55%	22%	52%
Response rates in platinum refractory disease	 *41%*	 *28%*	 *50%*	 *56%*	 *45%*	 *41%*
Response rates in combination with PD-1 therapy	 **68% (420)**	 **34% (41)**	 **75% (20)**	 **36% (26)**		

Summary of the Niagara trial

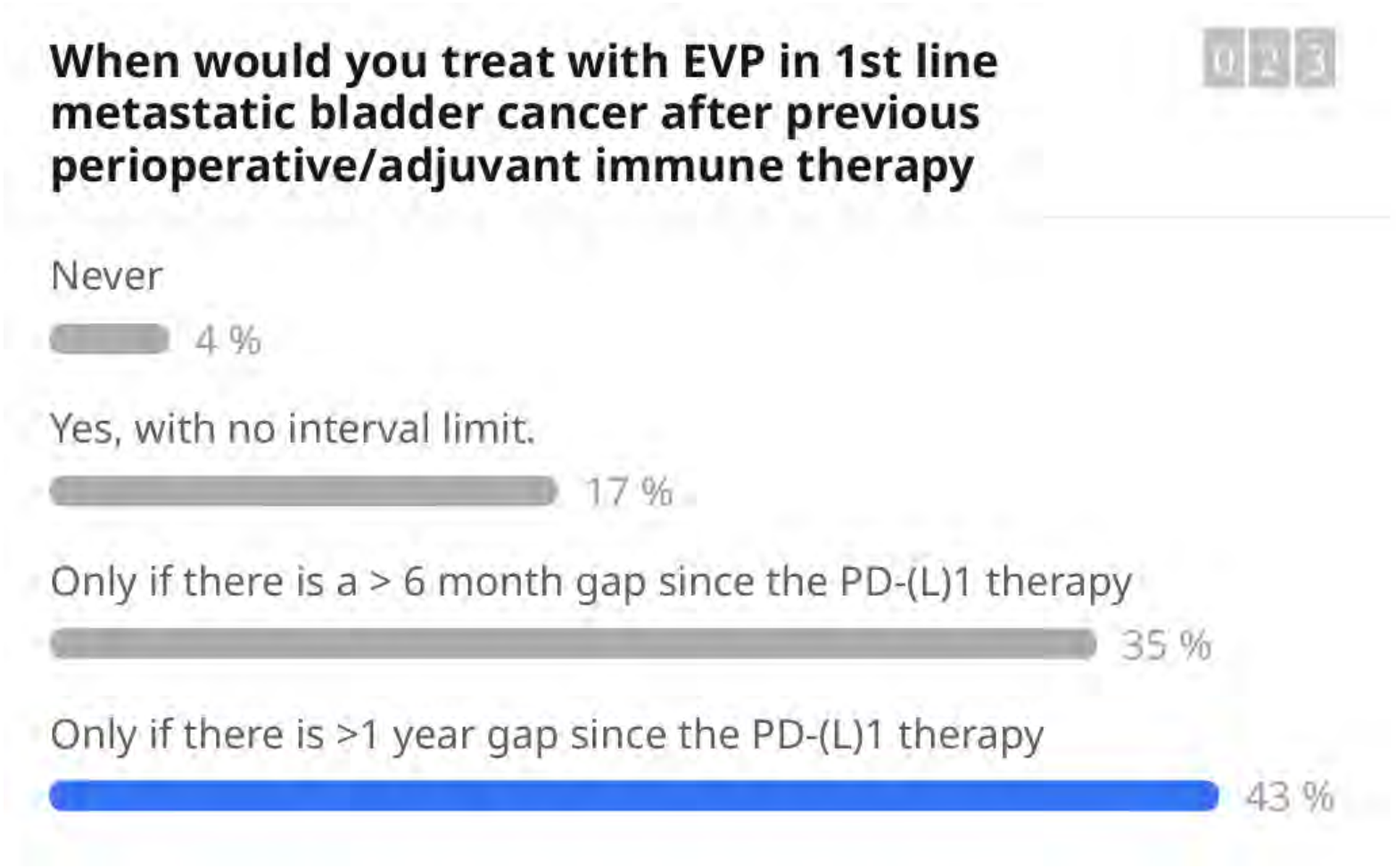








At #UromigosLive24 we asked about PD-1 rechallenge for EVP post perioperative therapy.

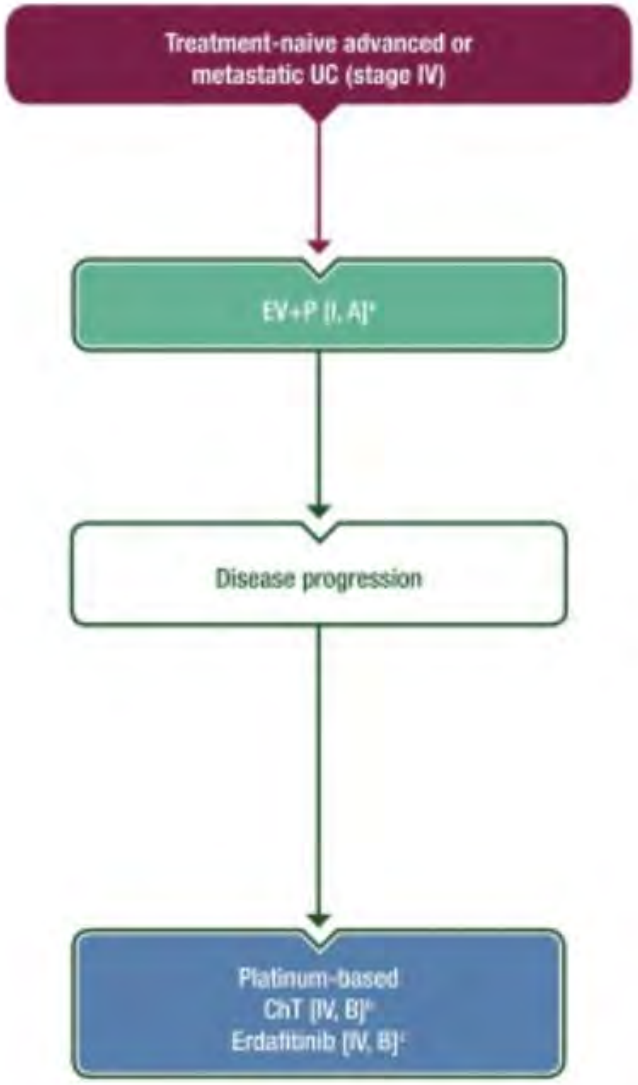


Ongoing Phase 3 Neoadjuvant IO-based Trials in MIBC

	Clinical Trial	N	Treatment Arms	Eligibility
CISPLATIN ELIGIBLE	KEYNOTE-866	870	Pembro + GC vs GC	T2-4aN0M0
	KEYNOTE-B15/EV-304	784	Pembro +EV vs GC	T2-T4aN0M0 T1-T4aN1M0
	NIAGARA	1050	Durva+ GC vs GC	T2-4aN0M0
	ENERGIZE	1200	Nivo + GC vs GC	T2-4aN0M0
CISPLATIN-INELIGIBLE	KEYNOTE-905/ EV-303	836	RC vs Pembro+EV vs Pembro	T2-4aN0M0
	VOLGA	830	RC vs Druva/Tremi+EV vs Durva+EV	T2-4aN0M0
	SWOG GAP	196	Surgery vs Gem-Carbo+ Avelumab	T2-4aN0M0

There are also RIII trials with TMT and ICI therapy: These studies may have wider influences.

New ESMO guidelines



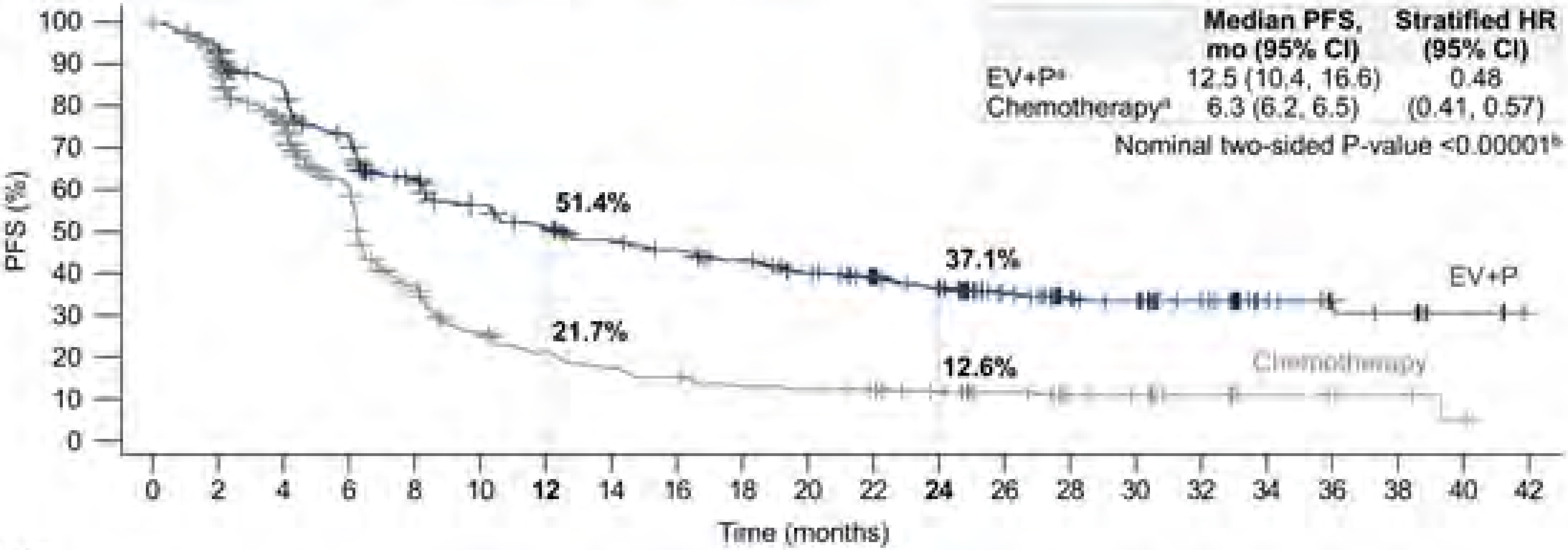
Highlights

- This ESMO Clinical Practice Guideline eUpdate addresses developments in first-line therapy in advanced urothelial carcinoma.
- EV+P is the new standard of care in first-line advanced urothelial carcinoma.
- Nivolumab–cisplatin–gemcitabine or platinum-based ChT and maintenance avelumab are alternatives if EV+P is not possible.

Powles T el al Annals 2024

PFS by BICR in the Overall Population

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



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.

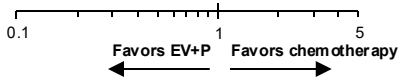
[a]Events/N were 282/442 for EV+P and 317/444 for chemotherapy. [b]P-value is nominal and descriptive.

OS in Prespecified Subgroups

OS benefit was consistent across prespecified subgroups

	Median OS, months (event/N) EV+P	Chemotherapy	HR (95% CI)
Overall	33.8 (203/442)	15.9 (297/444)	0.513 (0.428, 0.614)
Age			
<65 years	39.3 (59/144)	18.7 (87/135)	0.434 (0.307, 0.614)
≥65 years	27.1 (144/298)	14.6 (210/309)	0.544 (0.439, 0.674)
Race			
White	26.1 (158/308)	15.1 (207/290)	0.521 (0.422, 0.644)
Other	36.3 (45/134)	19.1 (90/154)	0.436 (0.302, 0.629)
Region			
North America	25.7 (57/103)	21.0 (54/85)	0.672 (0.451, 1.000)
Europe	25.6 (90/172)	14.6 (140/197)	0.522 (0.397, 0.687)
Rest of world	NR (56/167)	15.5 (103/162)	0.386 (0.277, 0.539)
Sex			
Female	25.4 (46/98)	14.6 (70/108)	0.549 (0.371, 0.811)
Male	33.8 (157/344)	16.4 (227/336)	0.501 (0.407, 0.617)
ECOG PS			
0	36.5 (77/223)	18.7 (136/215)	0.394 (0.296, 0.524)
1-2	22.8 (126/219)	13.3 (160/227)	0.621 (0.490, 0.787)
Primary disease site of origin			
Upper tract	36.5 (60/135)	18.3 (63/104)	0.538 (0.371, 0.781)
Lower tract	32.9 (142/305)	15.6 (233/339)	0.504 (0.408, 0.623)

	Median OS, months (event/N) EV+P	Chemotherapy	HR (95% CI)
Overall	33.8 (203/442)	15.9 (297/444)	0.513 (0.428, 0.614)
Liver metastases			
Present	19.1 (68/100)	10.1 (82/99)	0.556 (0.399, 0.776)
Absent	39.3 (135/342)	18.3 (215/345)	0.496 (0.400, 0.615)
PD-L1 expression			
Low (CPS <10)	31.2 (91/184)	15.1 (136/185)	0.472 (0.361, 0.618)
High (CPS ≥10)	36.5 (111/254)	17.1 (158/254)	0.550 (0.431, 0.703)
Cisplatin eligibility			
Eligible	36.7 (101/244)	18.7 (143/234)	0.541 (0.419, 0.699)
Ineligible	25.6 (102/198)	12.7 (154/210)	0.498 (0.386, 0.642)
Metastatic disease site			
Visceral metastases	25.7 (163/318)	13.5 (235/318)	0.505 (0.412, 0.619)
Lymph node only	NR (34/103)	24.4 (54/104)	0.512 (0.332, 0.789)
Renal function			
Normal	39.3 (33/84)	18.6 (61/95)	0.496 (0.318, 0.773)
Mild	36.5 (69/165)	18.4 (101/162)	0.502 (0.365, 0.689)
Moderate/severe	25.6 (101/193)	13.3 (135/187)	0.528 (0.405, 0.689)

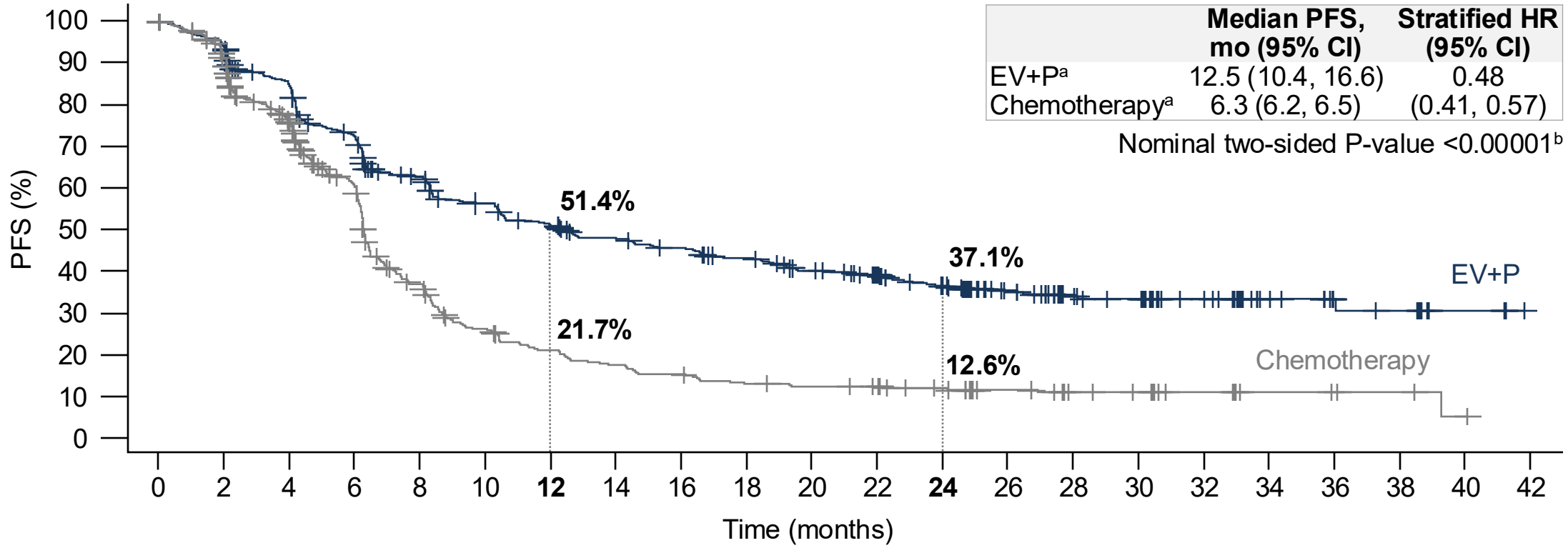


Data cutoff: August 8, 2024.

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1; OS, overall survival.

PFS by BICR in the Overall Population

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.

Declaration of Interests

Prof Tom Powles has the following to disclose:

- **Research grants (institution)**: Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Eisai, EMD Serono Inc., Exelixis, F. Hoffmann-La Roche, Gilead Sciences Inc., Ipsen Biopharm Limited, Johnson & Johnson Health Care Systems Inc., Merck, MSD, Novartis, Pfizer, Seagen
- **Research grants (individual)**: Mashup Communications
- **Consultancy/honoraria**: Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Eisai, EMD Serono Inc., Exelixis, F. Hoffmann-La Roche, Gilead Sciences Inc., Incyte Corporation, Ipsen Biopharm Limited, Johnson & Johnson Health Care Systems Inc., Mashup Communications, Merck, MSD, Novartis, Pfizer, Seagen
- **Travel and accommodation expenses**: AstraZeneca, F. Hoffmann-La Roche, Gilead Sciences Inc, Ipsen Biopharm Limited, Mashup Communications, Merck, MSD, Pfizer

Key Takeaway Points/Conclusions

We present updated results for EV-302/KEYNOTE-A39 with 1 year of additional follow-up (~2.5 years of median follow-up) and an exploratory analysis of patients with confirmed complete response (cCR)

- First-line EV+P continued to demonstrate superior efficacy compared with chemotherapy in the broad patient population and across prespecified subgroups; median OS was more than 2.5 years
- The response to EV+P was durable, with a median DOR of nearly 2 years; there was also a 74% probability of remaining in cCR at 24 months with EV+P
- Frequency and grade of TRAEs and AESIs in the EV+P arm remained consistent with the previously reported primary analysis,[1] with no new safety signals
- These results reinforce EV+P as the SOC for the first-line treatment of patients with la/mUC

AESI, adverse event of special interest; DOR, duration of response; EV, enfortumab vedotin; la/mUC, locally advanced or metastatic urothelial cancer; P, pembrolizumab; SOC, standard of care; TRAE, treatment-related adverse event.

1. Powles T, et al. N Engl J Med. 2024;390(10):875-88.

Background

- In the EV-302 primary analysis, EV+P nearly doubled mPFS and mOS in patients with previously untreated la/mUC versus platinum-based chemotherapy[1]
  - mPFS was 12.5 months (95% CI: 10.4, 16.6) with EV+P vs 6.3 months (95% CI: 6.2, 6.5) with platinum-based chemotherapy[1]
  - mOS was 31.5 months (95% CI: 25.4, NE) in the EV+P arm vs 16.1 months (95% CI: 13.9, 18.3) in the platinum-based chemotherapy arm[1]
- Based on these results, EV+P received approvals in many countries globally[2-5] and is the SOC in global treatment guidelines for patients with untreated la/mUC[6,7]

Here, we present 1 year of additional follow-up for EV-302 (~2.5 years of median follow-up) and an exploratory analysis of patients with confirmed complete response

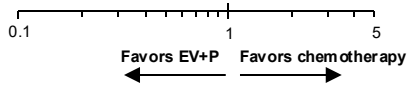
EV, enfortumab vedotin; la/mUC, locally advanced or metastatic urothelial cancer; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; P, pembrolizumab; SOC, standard of care.

1. Powles T, et al. N Engl J Med. 2024;390(10):875-88. 2. PADCEV. Highlights of Prescribing Information. 2023. 3. Padcev. Summary of Product Characteristics. 2024. 4. Astellas Pharma Inc. Japan's Ministry of Health, Labour and Welfare approves PADCEV (enfortumab vedotin) with KEYTRUDA (pembrolizumab) for first-line treatment of radically unresectable urothelial carcinoma. News release. Accessed January 23, 2025. https://www.astellas.com/en/news/29451. 5. Pfizer Canada. Padcev (enfortumab vedotin) in combination with pembrolizumab approved by Health Canada to treat advanced bladder cancer. News release. Accessed January 23, 2025. https://www.newswire.ca/news-releases/padcev-r-enfortumab-vedotin-in-combination-with-pembrolizumab-approved-by-health-canada-to-treat-advanced-bladder-cancer-862646661.html. 6. Powles T, et al. ESMO Clinical Practice Guideline. Ann Oncol. 2024;35(6):485-90. 7. Witjes J, et al. Eur Urol. 2024;85(1):17-31.

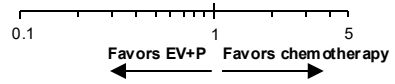
PFS by BICR in Prespecified Subgroups

PFS benefit was consistent across prespecified subgroups

	Median PFS, months (event/N) EV+P	Chemotherapy	HR (95% CI)
Overall	12.5 (262/442)	6.3 (317/444)	0.481 (0.407, 0.570)
Age			
<65 years	14.6 (87/144)	6.4 (90/135)	0.490 (0.358, 0.670)
≥65 years	12.3 (175/298)	6.2 (227/309)	0.478 (0.390, 0.585)
Race			
White	10.5 (191/308)	6.2 (214/290)	0.492 (0.401, 0.604)
Other	19.2 (71/134)	6.5 (103/154)	0.461 (0.335, 0.633)
Region			
North America	10.3 (72/103)	6.3 (57/85)	0.605 (0.418, 0.876)
Europe	10.4 (102/172)	6.3 (149/197)	0.523 (0.403, 0.678)
Rest of world	19.3 (88/167)	6.2 (111/162)	0.376 (0.279, 0.508)
Sex			
Female	10.4 (59/98)	6.1 (75/108)	0.505 (0.351, 0.727)
Male	14.0 (203/344)	6.3 (242/336)	0.468 (0.385, 0.569)
ECOG PS			
0	17.3 (121/223)	6.7 (151/215)	0.404 (0.314, 0.520)
1-2	9.3 (141/219)	6.1 (166/227)	0.555 (0.440, 0.699)
Primary disease site of origin			
Upper tract	12.3 (81/135)	6.2 (70/104)	0.542 (0.384, 0.763)
Lower tract	12.8 (179/305)	6.3 (246/339)	0.462 (0.379, 0.564)



	Median PFS, months (event/N) EV+P	Chemotherapy	HR (95% CI)
Overall	12.5 (262/442)	6.3 (317/444)	0.481 (0.407, 0.570)
Liver metastases			
Present	8.1 (74/100)	6.0 (80/99)	0.548 (0.392, 0.766)
Absent	16.4 (188/342)	6.4 (237/345)	0.458 (0.376, 0.557)
PD-L1 expression			
Low (CPS <10)	10.5 (122/184)	6.3 (131/185)	0.517 (0.400, 0.667)
High (CPS ≥10)	16.4 (138/254)	6.2 (182/254)	0.459 (0.365, 0.576)
Cisplatin eligibility			
Eligible	15.0 (140/244)	6.5 (155/234)	0.518 (0.409, 0.655)
Ineligible	10.6 (122/198)	6.1 (162/210)	0.455 (0.357, 0.580)
Metastatic disease site			
Visceral metastases	10.4 (203/318)	6.2 (242/318)	0.477 (0.393, 0.579)
Lymph node only	22.1 (50/103)	8.3 (60/104)	0.473 (0.317, 0.704)
Renal function			
Normal	18.7 (47/84)	6.7 (64/95)	0.520 (0.350, 0.774)
Mild	12.7 (91/165)	6.3 (118/162)	0.477 (0.358, 0.636)
Moderate/severe	10.5 (124/193)	6.2 (135/187)	0.493 (0.381, 0.637)

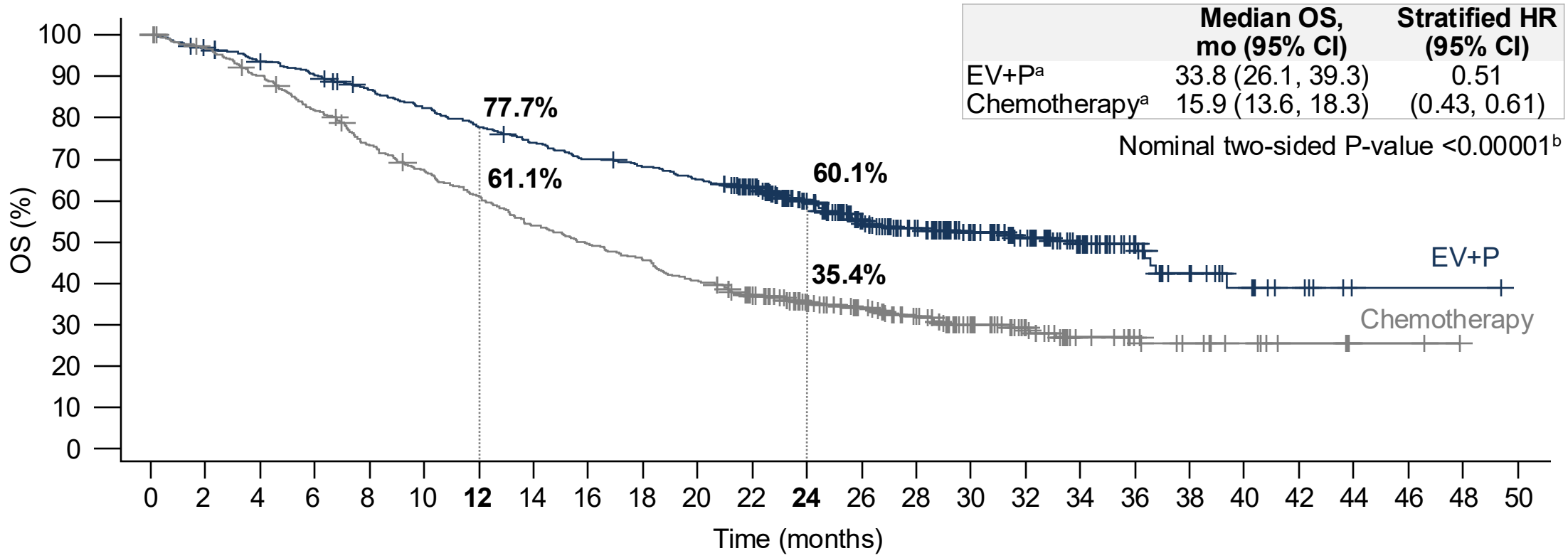


Data cutoff: August 8, 2024.

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1; PFS, progression-free survival.

OS in the Overall Population

Risk of death was reduced by almost 50%



	Median OS, mo (95% CI)	Stratified HR (95% CI)
EV+P[a]	33.8 (26.1, 39.3)	0.51
Chemotherapy[a]	15.9 (13.6, 18.3)	(0.43, 0.61)

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

No. at risk

EV+P	442	426	409	394	375	356	336	319	302	293	280	252	206	161	133	102	79	52	32	19	11	6	1	1	1
Chemotherapy	444	423	393	356	317	290	263	233	214	197	176	148	121	102	81	59	43	24	18	13	9	5	2	2	

Data cutoff: August 8, 2024.

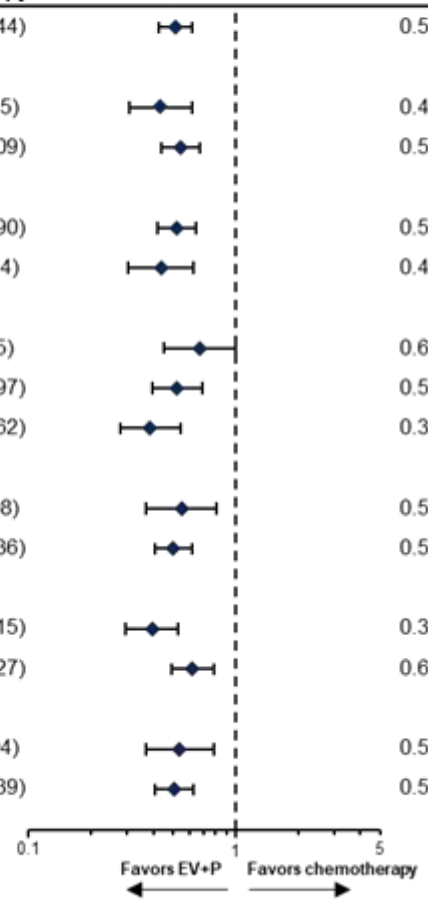
EV, enfortumab vedotin; P, pembrolizumab; OS, overall survival.

[a]Events/N were 203/442 for EV+P and 297/444 for chemotherapy. [b]P-value is nominal and descriptive.

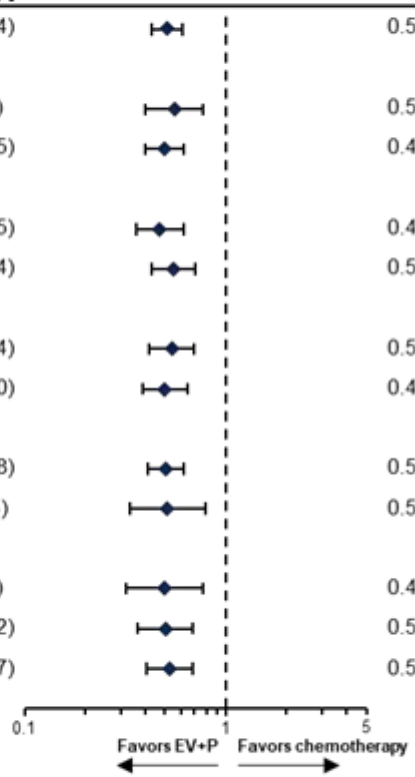
OS in Prespecified Subgroups

OS benefit was consistent across prespecified subgroups

	Median OS, months (event/N) EV+P	Chemotherapy	HR (95% CI)
Overall	33.8 (203/442)	15.9 (297/444)	0.513 (0.428, 0.614)
Age			
<65 years	39.3 (59/144)	18.7 (87/135)	0.434 (0.307, 0.614)
≥65 years	27.1 (144/298)	14.6 (210/309)	0.544 (0.439, 0.674)
Race			
White	26.1 (158/308)	15.1 (207/290)	0.521 (0.422, 0.644)
Other	36.3 (45/134)	19.1 (90/154)	0.436 (0.302, 0.629)
Region			
North America	25.7 (57/103)	21.0 (54/85)	0.672 (0.451, 1.000)
Europe	25.6 (90/172)	14.6 (140/197)	0.522 (0.397, 0.687)
Rest of world	NR (56/167)	15.5 (103/162)	0.386 (0.277, 0.539)
Sex			
Female	25.4 (46/98)	14.6 (70/108)	0.549 (0.371, 0.811)
Male	33.8 (157/344)	16.4 (227/336)	0.501 (0.407, 0.617)
ECOG PS			
0	36.5 (77/223)	18.7 (136/215)	0.394 (0.296, 0.524)
1-2	22.8 (126/219)	13.3 (160/227)	0.621 (0.490, 0.787)
Primary disease site of origin			
Upper tract	36.5 (60/135)	18.3 (63/104)	0.538 (0.371, 0.781)
Lower tract	32.9 (142/305)	15.6 (233/339)	0.504 (0.408, 0.623)



	Median OS, months (event/N) EV+P	Chemotherapy	HR (95% CI)
Overall	33.8 (203/442)	15.9 (297/444)	0.513 (0.428, 0.614)
Liver metastases			
Present	19.1 (68/100)	10.1 (82/99)	0.556 (0.399, 0.776)
Absent	39.3 (135/342)	18.3 (215/345)	0.496 (0.400, 0.615)
PD-L1 expression			
Low (CPS <10)	31.2 (91/184)	15.1 (136/185)	0.472 (0.361, 0.618)
High (CPS ≥10)	36.5 (111/254)	17.1 (158/254)	0.550 (0.431, 0.703)
Cisplatin eligibility			
Eligible	36.7 (101/244)	18.7 (143/234)	0.541 (0.419, 0.699)
Ineligible	25.6 (102/198)	12.7 (154/210)	0.498 (0.386, 0.642)
Metastatic disease site			
Visceral metastases	25.7 (163/318)	13.5 (235/318)	0.505 (0.412, 0.619)
Lymph node only	NR (34/103)	24.4 (54/104)	0.512 (0.332, 0.789)
Renal function			
Normal	39.3 (33/84)	18.6 (61/95)	0.496 (0.318, 0.773)
Mild	36.5 (69/165)	18.4 (101/162)	0.502 (0.365, 0.689)
Moderate/severe	25.6 (101/193)	13.3 (135/187)	0.528 (0.405, 0.689)



Data cutoff: August 8, 2024.

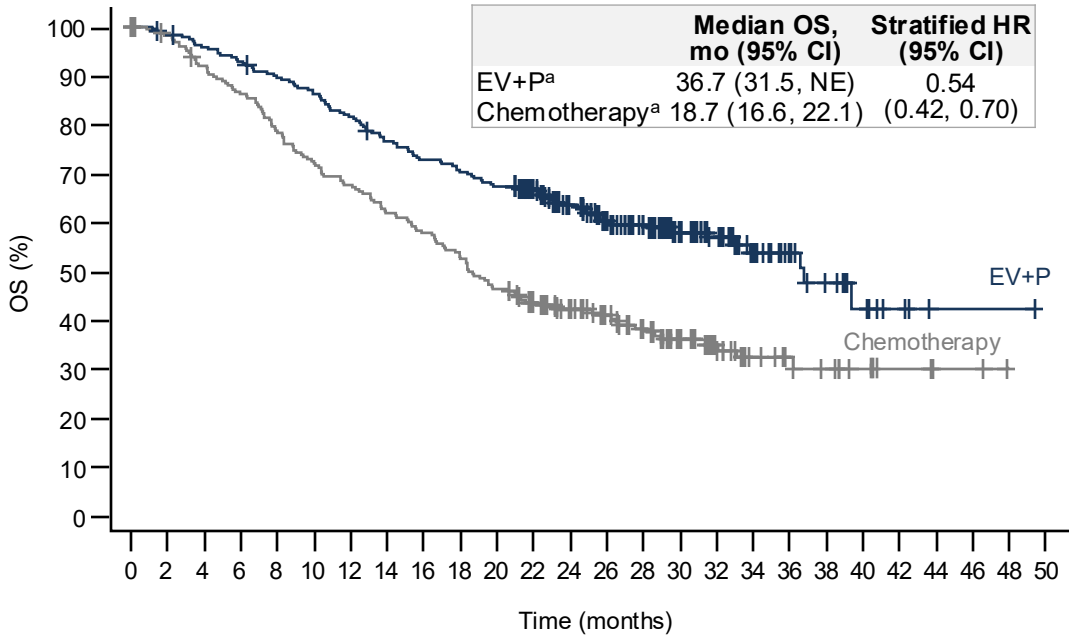
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1; OS, overall survival.

47

OS Subgroup Analysis: Cisplatin Eligibility

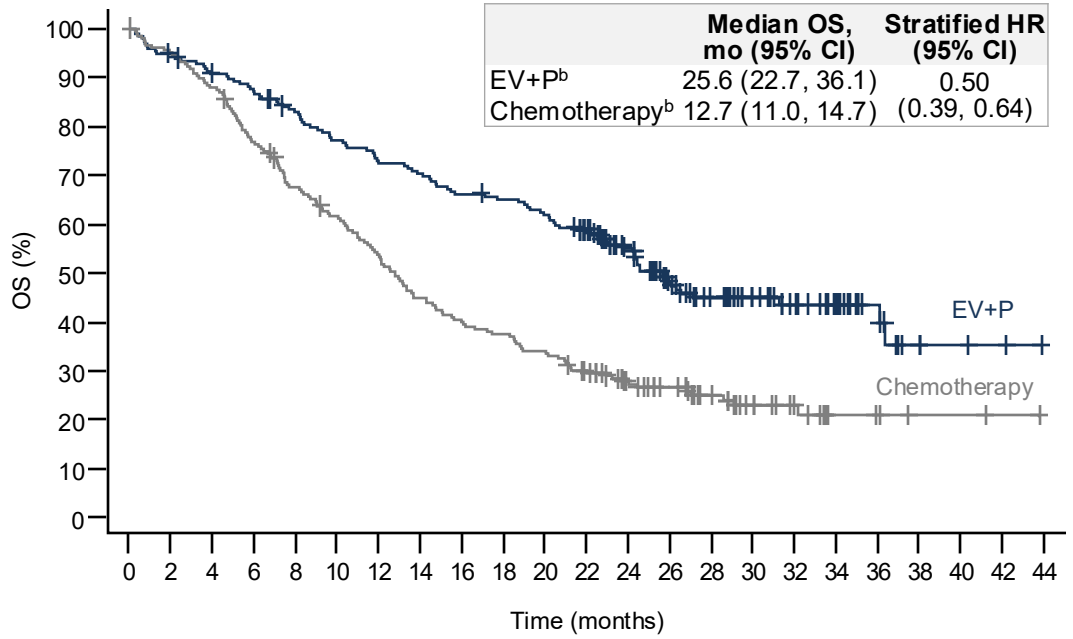
OS benefit was consistent with the overall population regardless of cisplatin eligibility

Cisplatin Eligible



No. at risk																								
EV+P	244	239	232	225	216	208	197	184	175	169	162	147	121	98	83	64	50	30	20	14	8	4	1	1	1
Chemotherapy	234	224	209	196	178	164	154	141	132	120	106	90	77	65	54	41	30	19	14	11	7	4	2	2	

Cisplatin Ineligible



No. at risk																								
EV+P	198	187	177	169	159	148	139	135	127	124	118	105	85	63	50	38	29	22	12	5	3	2		
Chemotherapy	210	199	184	160	139	126	109	92	82	77	70	58	44	37	27	18	13	5	4	2	2	1		

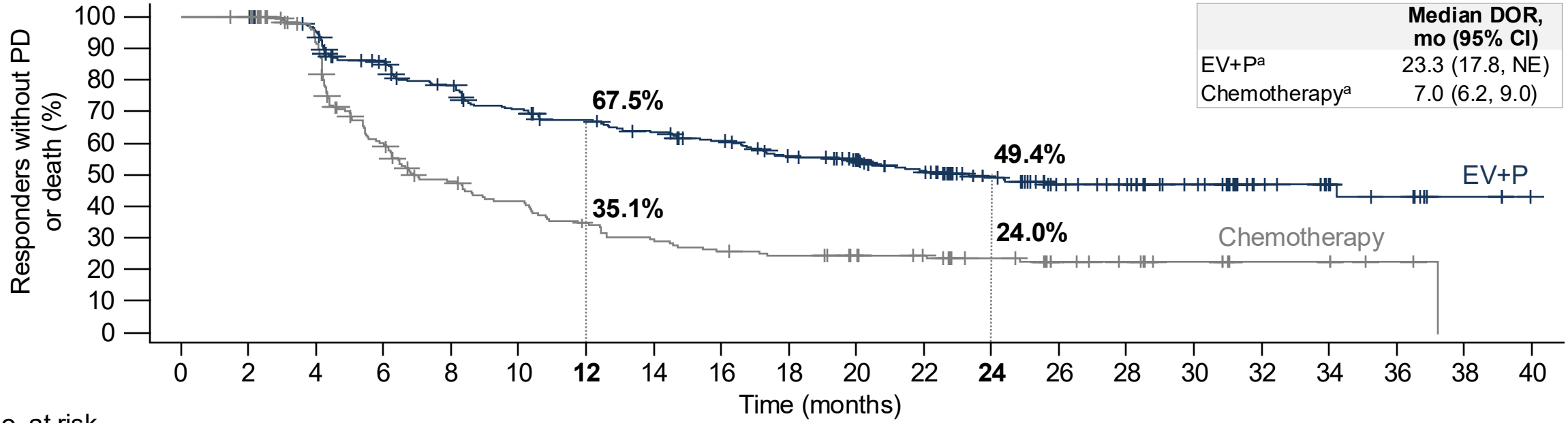
Data cutoff: August 8, 2024.

EV, enfortumab vedotin; NE, not estimable; OS, overall survival; P, pembrolizumab.

[a]Events/N in the cisplatin-eligible population were 101/244 for EV+P and 143/234 for chemotherapy. [b]Events/N in the cisplatin-ineligible population were 102/198 for EV+P and 154/210 for chemotherapy.

Duration of Response (CR or PR) by BICR

Among responders, the probability of maintained response at 24 months was ~50% with EV+P



	Median DOR, mo (95% CI)
EV+P[a]	23.3 (17.8, NE)
Chemotherapy[a]	7.0 (6.2, 9.0)

No. at risk

EV+P	295	295	274	238	213	190	177	165	154	137	125	107	78	58	53	40	20	14	10	4
Chemotherapy	195	194	162	102	78	67	55	47	41	38	34	30	23	16	13	9	5	5	2	

	EV+P (n=437)	Chemotherapy (n=441)	Nominal two-sided P-value
Confirmed ORR (CR or PR), n (%) [95% CI]	295 (67.5) [62.9, 71.9]	195 (44.2) [39.5, 49.0]	<0.00001[b]
Best overall response, n (%)			
CR	133 (30.4)	64 (14.5)	
PR	162 (37.1)	131 (29.7)	
SD	83 (19.0)	149 (33.8)	

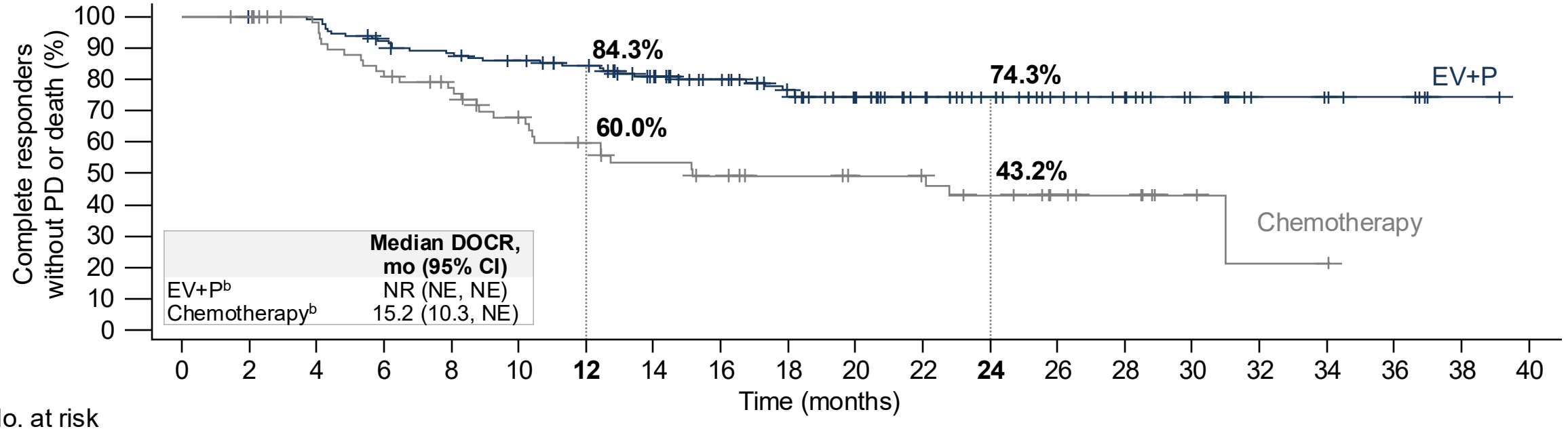
Data cutoff: August 8, 2024.

CR, complete response; EV, enfortumab vedotin; NE, not estimable; P, pembrolizumab; PR, partial response; ORR, objective response rate; SD, stable disease.

[a]Events/N were 137/295 for EV+P and 129/195 for chemotherapy. [b]P-value is nominal and descriptive.

Duration of Confirmed Completed Response (cCR)[a] by BICR

Probability of maintained CR at 24 months was 74% with EV+P



No. at risk

EV+P	133	132	129	118	112	107	101	89	78	68	55	44	36	27	23	16	8	7	5	1
Chemotherapy	64	63	57	48	42	35	29	25	22	19	17	16	13	9	7	3	1	1		

- For patients with cCR:
  - PFS HR=0.36; 95% CI: 0.21, 0.61; estimated 24-month PFS rate: 78.2% for EV+P vs 53.7% for chemotherapy
  - OS HR=0.37; 95% CI: 0.17, 0.80; estimated 24-month OS rate: 95.4% for EV+P vs 85.8% for chemotherapy

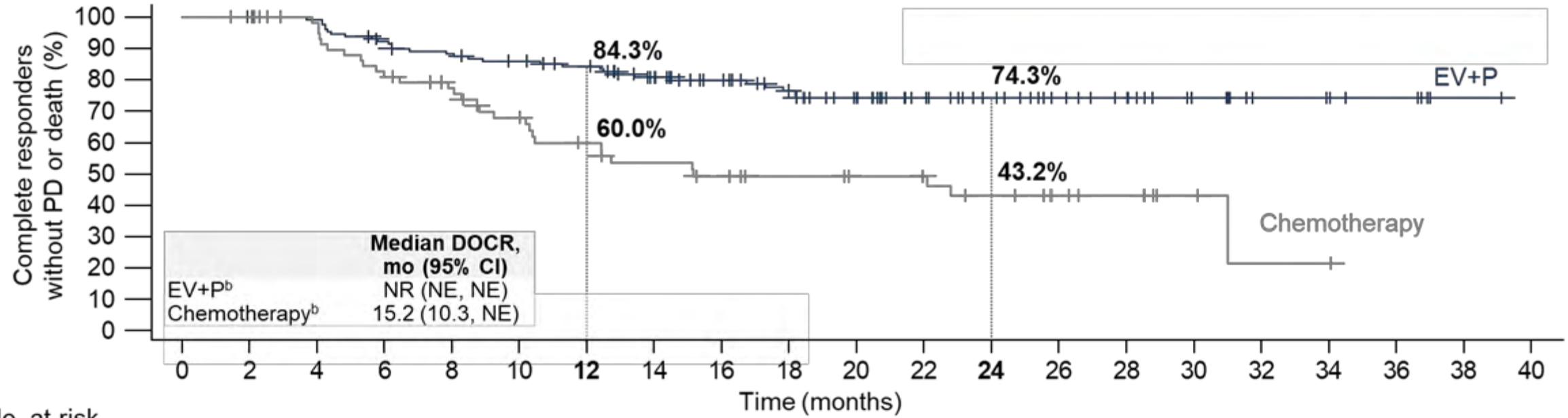
Data cutoff: August 8, 2024.

DOCR, duration of complete response; EV, enfortumab vedotin; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival; P, pembrolizumab; PD, disease progression; PFS, progression-free survival.

[a]For patients with a best overall response of confirmed CR. [b]Events/N were 30/133 for EV+P and 30/64 for chemotherapy.

Duration of Confirmed Completed Response (cCR)[a] by BICR

Probability of maintained CR at 24 months was 74% with EV+P



No. at risk

EV+P	133	132	129	118	112	107	101	89	78	68	55	44	36	27	23	16	8	7	5	1
Chemotherapy	64	63	57	48	42	35	29	25	22	19	17	16	13	9	7	3	1	1		

- For patients with cCR:
  - PFS HR=0.36; 95% CI: 0.21, 0.61; estimated 24-month PFS rate: 78.2% for EV+P vs 53.7% for chemotherapy
  - OS HR=0.37; 95% CI: 0.17, 0.80; estimated 24-month OS rate: 95.4% for EV+P vs 85.8% for chemotherapy

Data cutoff: August 8, 2024.

DOCR, duration of complete response; EV, enfortumab vedotin; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival; P, pembrolizumab; PD, disease progression; PFS, progression-free survival.
[a]For patients with a best overall response of confirmed CR. [b]Events/N were 30/133 for EV+P and 30/64 for chemotherapy.

ESMO WEBINARS

ADVANCED UROTHELIAL CARCINOMA

2nd and later line therapies: practice- and biology- informed selection of strategy

Viktor Grünwald, MD, PhD

Carolus-endowed Professorship for interdisciplinary GU Oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

DOI

Financial Interests

Invited Speaker, Personal: Amgen, AstraZeneca, Astellas, BMS, EISAI, Ipsen, Johnson & Johnson, Merck, MSD, Pfizer, Novartis/AAA, Telix Pharmaceutical, Roche

Advisory Board, Personal: BMS, EISAI, Ipsen, Debiopharm, Gilead, Johnson & Johnson, Merck, MSD, Novartis, Oncorena, Recordati, Synthekine

Stocks/Shares, Personal: Amgen, AstraZeneca, BMS, Bicycle Therapeutics, MSD, Genmab

Steering Committee Member: Amgen, BMS, EISAI, Ipsen

Research Grant, Financial interest, Institutional: AstraZeneca, BMS, MSD, Ipsen, Pfizer

Travel support: Ipsen, Johnson & Johnson, Merck, Pfizer

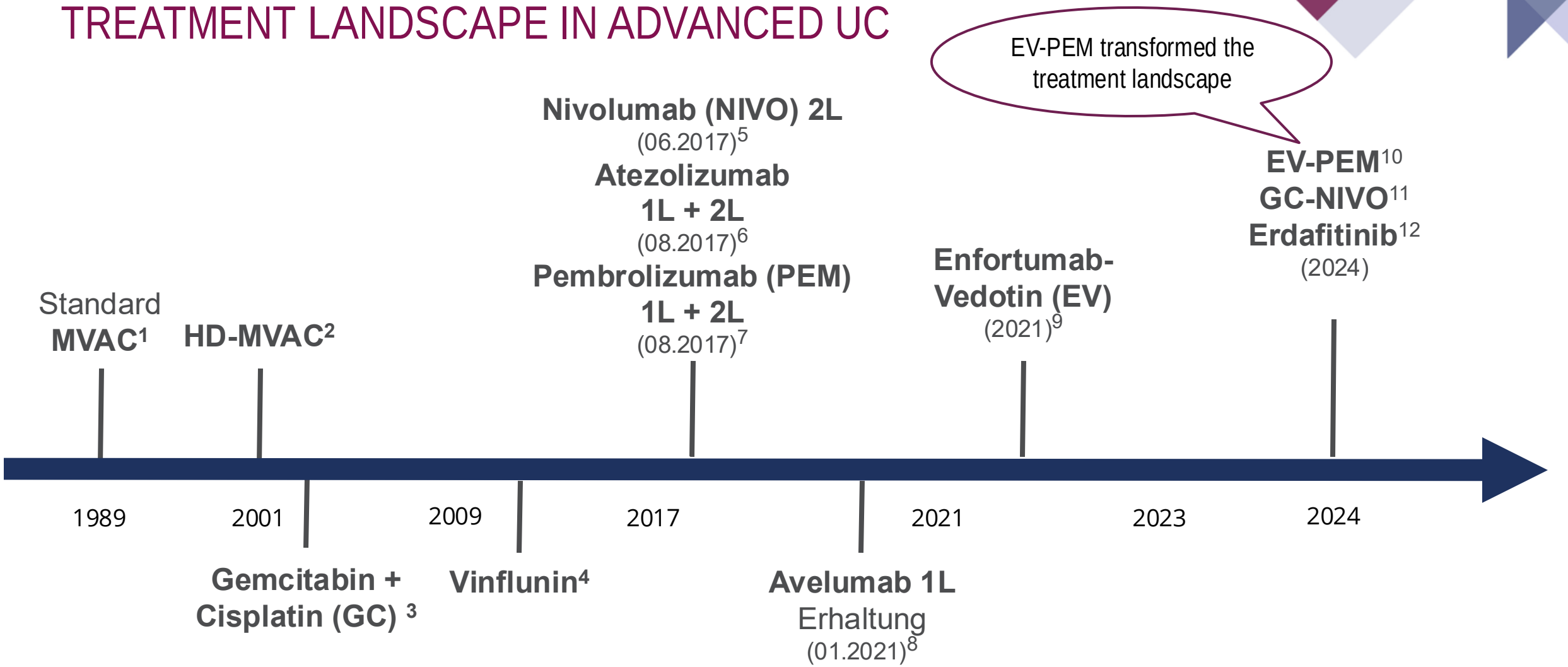
Non-Financial Interests

Membership: ASCO, ESMO, German medical Oncology and Hematology Society

Advisory role: German Cancer Society

Leadership role: Working Group medical oncology (AIO)

TREATMENT LANDSCAPE IN ADVANCED UC

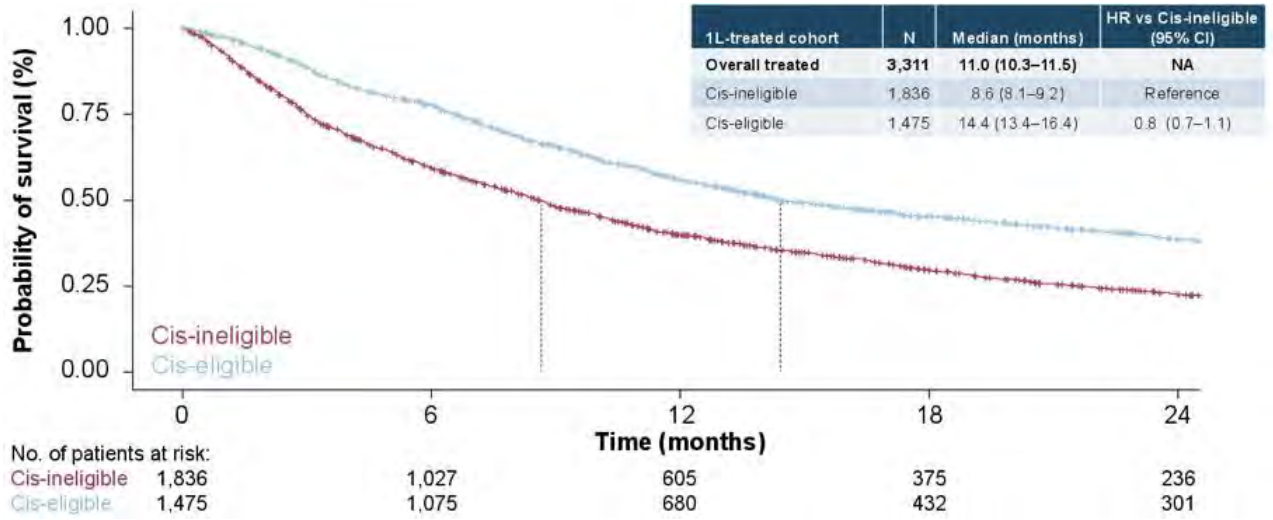


HD-MVAC = dosisintensiviertes Methotrexat, Vinblastin, Adriamycin und Cisplatin, 1L: Erstlinientherapie, 2L: Zweitlinientherapie

1. Sternberg C.N. et al. Cancer 1989 Dec 15;64(12):2448-58; 2. Sternberg C.N. et al. J Clin Oncol 2001 May 15;19(10):2638-46; 3. Gemzar, https://www.ema.europa.eu/en/documents/referral/gemzar-article-30-referral-annex-i-ii-iii_de.pdf; 4. Javlor, https://www.ema.europa.eu/en/documents/product-information/javlor-epar-product-information_en.pdf; 5. Opdivo, https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf; 6. Tecentriq, https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf; 7. Keytruda, https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf; 8. Bavencio, https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf; 9. Powles T., N Engl J Med 2021; 384:1125-1135, DOI: 10.1056/NEJMoa2035807, 25. März 2021.. 10. Powles et al. ESMO2023: LBA6. 11. van der Heijden eet al, ESMO 2023_ LBA7. 12. Loriot et al. N Engl J Med 2023;389:1961-1971
DOI: 10.1056/NEJMoa2308849

SUBSEQUENT THERAPIES

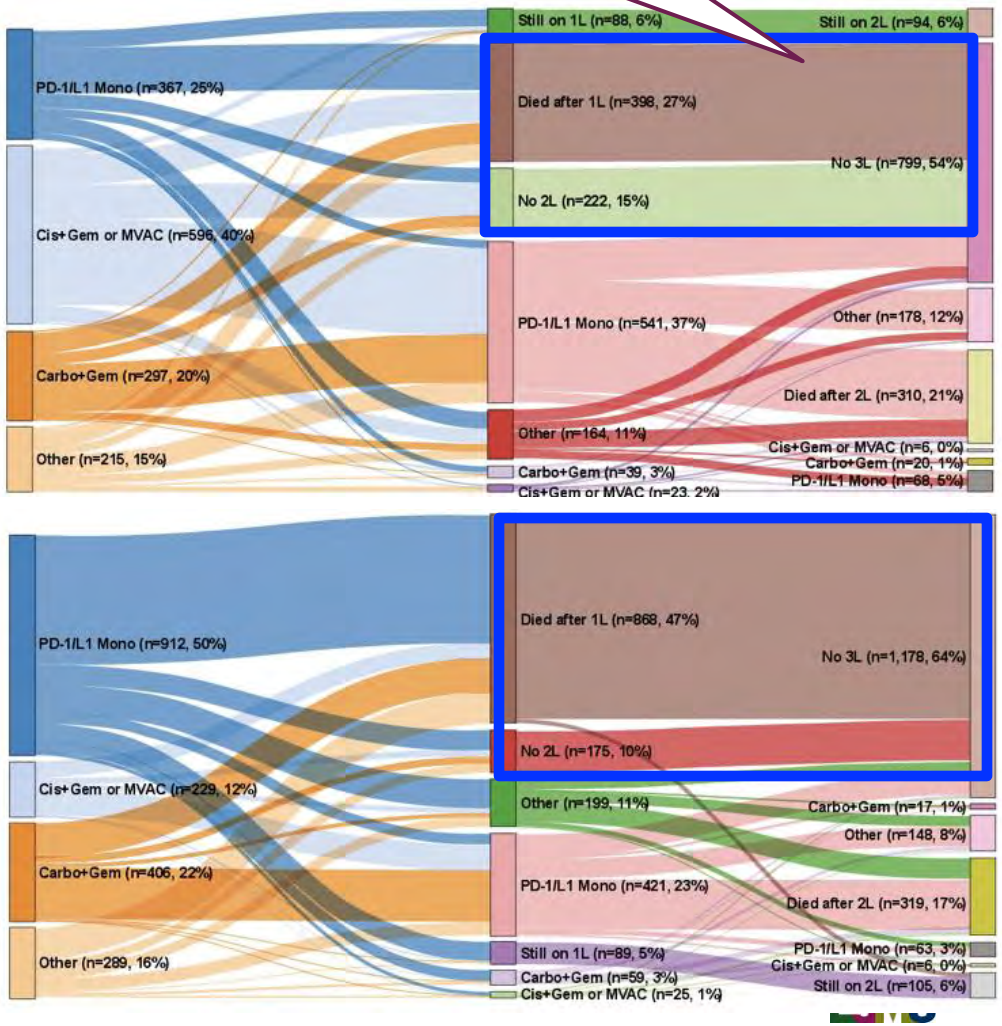
Many patients do not receive 2nd line therapy



1L-treated cohort	N	Median (months)	HR vs Cis-ineligible (95% CI)
Overall treated	3,311	11.0 (10.3–11.5)	NA
Cis-ineligible	1,836	8.6 (8.1–9.2)	Reference
Cis-eligible	1,475	14.4 (13.4–16.4)	0.8 (0.7–1.1)

23% received no 1st line treatment

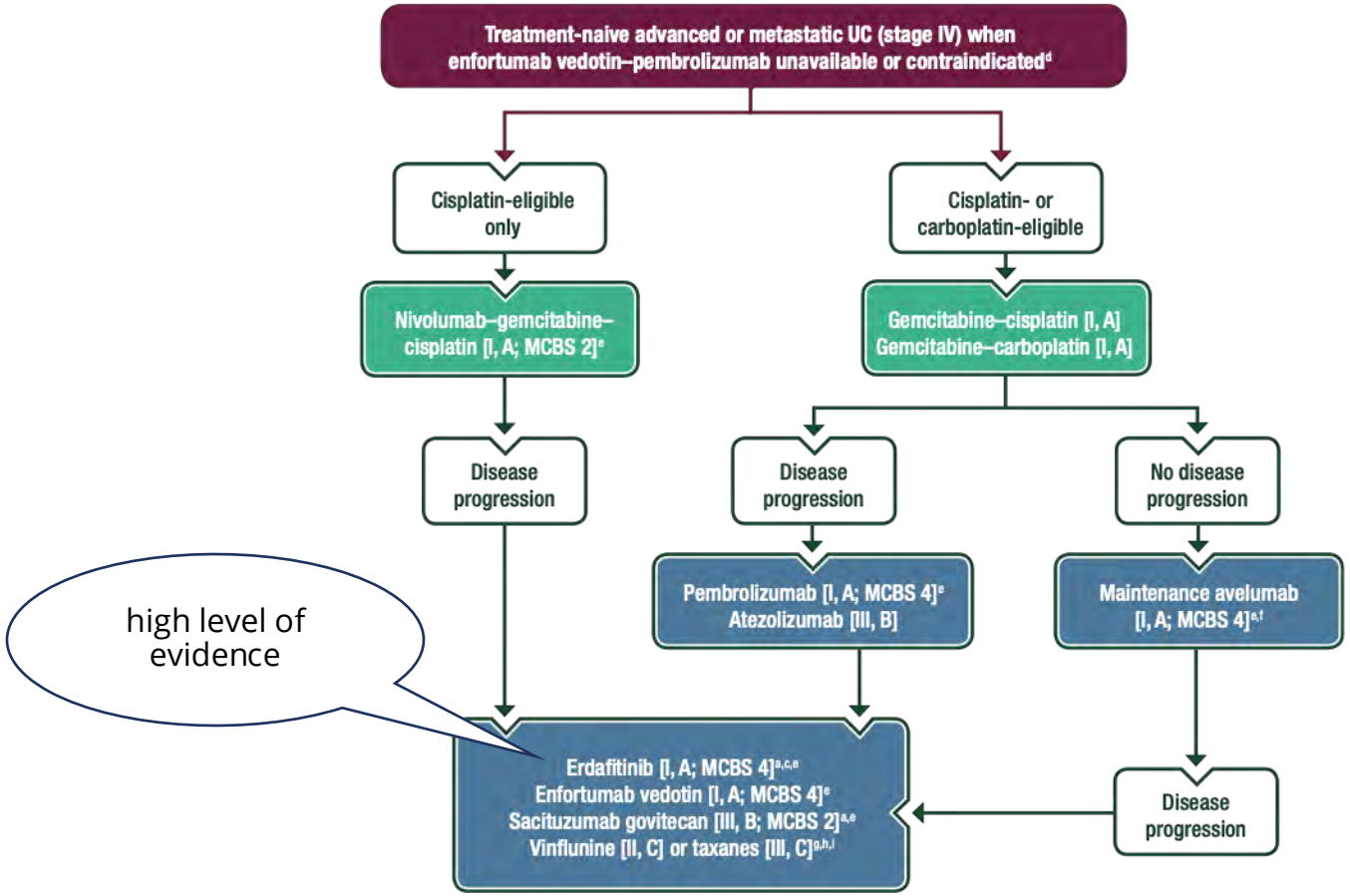
will this change with current options?



Sonpavde et al. ASCO22: 4565

ESMO GUIDELINES FOR UROTHELIAL CARCINOMA

After platin-based therapy

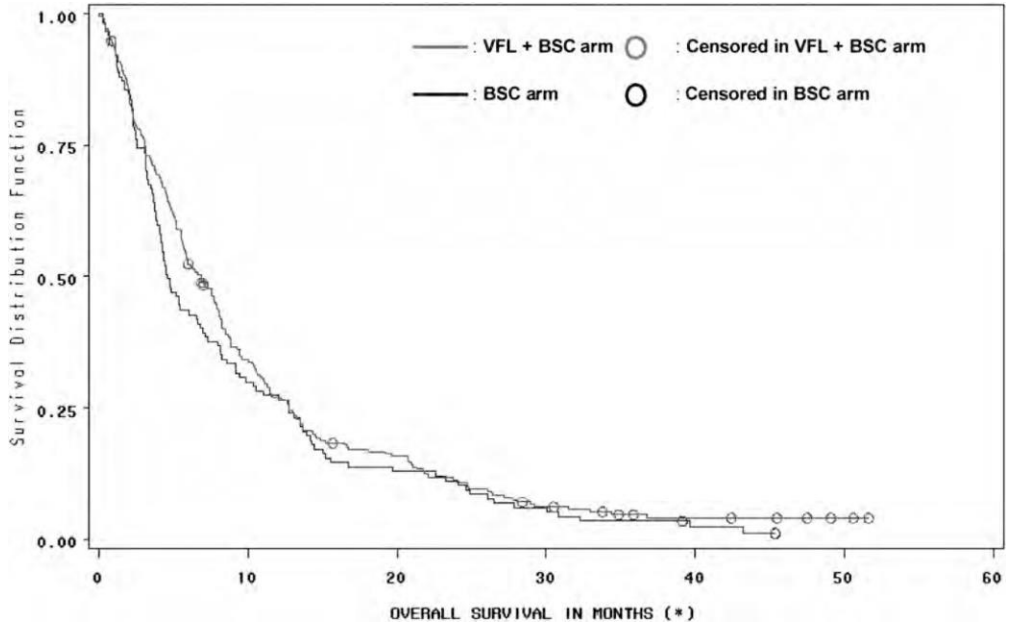


Powles et al. Ann Oncol 2024 https://doi.org/10.1016/j.annonc.2024.03.001

PHASE III TRIALS AFTER PLATINUM-FAILURE

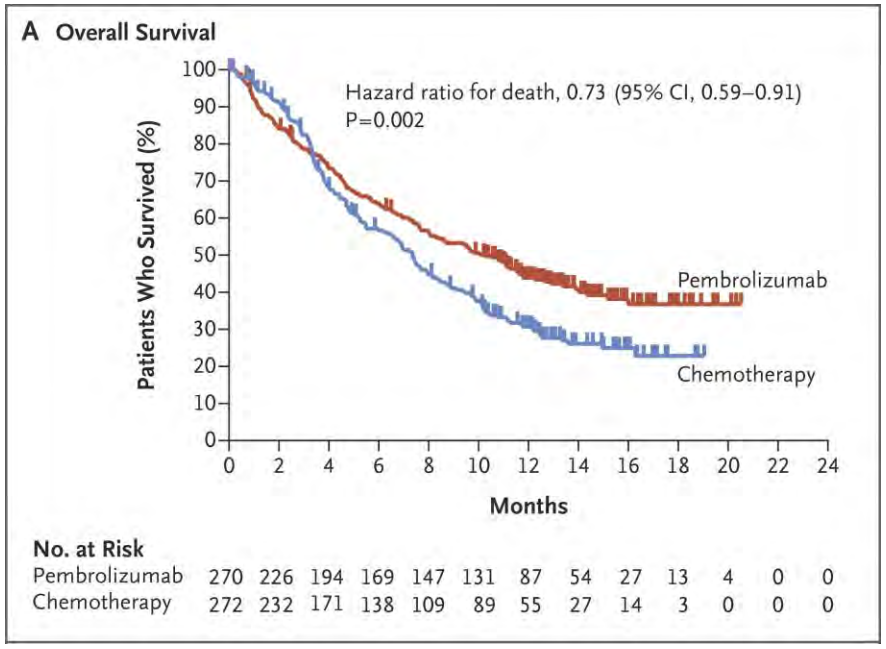
High-level of evidence support certain treatment options

Vinflunine vs. BSC



Bellmunt, J. et al. Annals of Oncology, Volume 24, Issue 6, 1466 - 1472

Pembrolizumab vs. Chemo

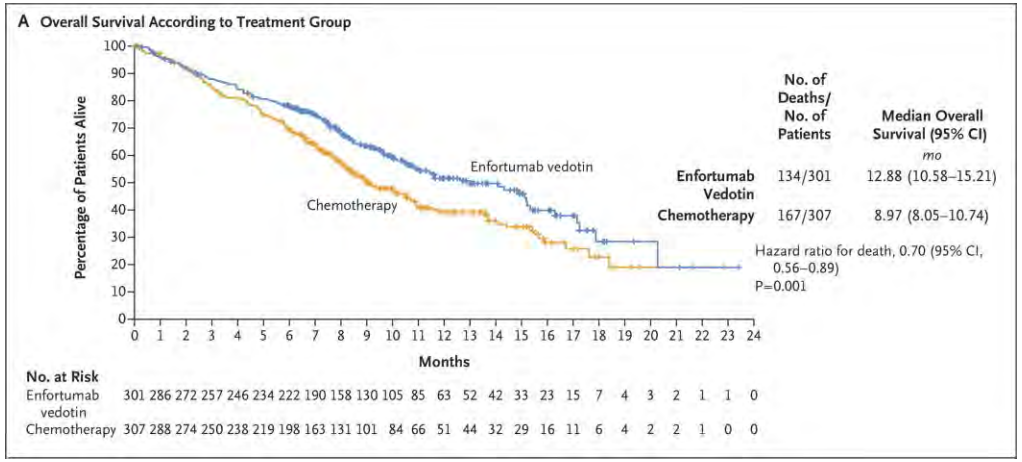


Bellmunt et al. N Engl J Med 2017;376:1015-1026
DOI: 10.1056/NEJMoa1613683

PHASE III TRIALS AFTER IO-FAILURE

Permitted more than 1 previous line of therapy

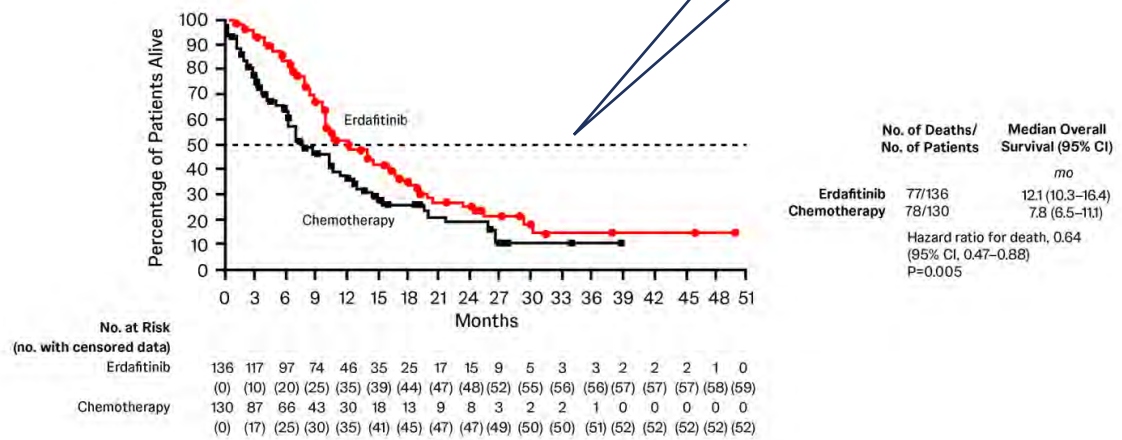
Enfortumab vedotin vs. Chemo



Powles et al. N Engl J Med 2021;384:1125-1135. DOI: 10.1056/NEJMoa2035807

Erdafitinib vs. Chemo

FGFR alterered UC only (approx.17%)



Loriot Y, et al. N Engl J Med. 2023;389(21):1961–1971.

TODAY'S PROBLEM - WHAT TO DO AFTER EV-PEM FAILURE

Case report

synchronous metastatic Urothelial-Ca of the renal pelvis (UTUC)

Biosy revealed pure UC

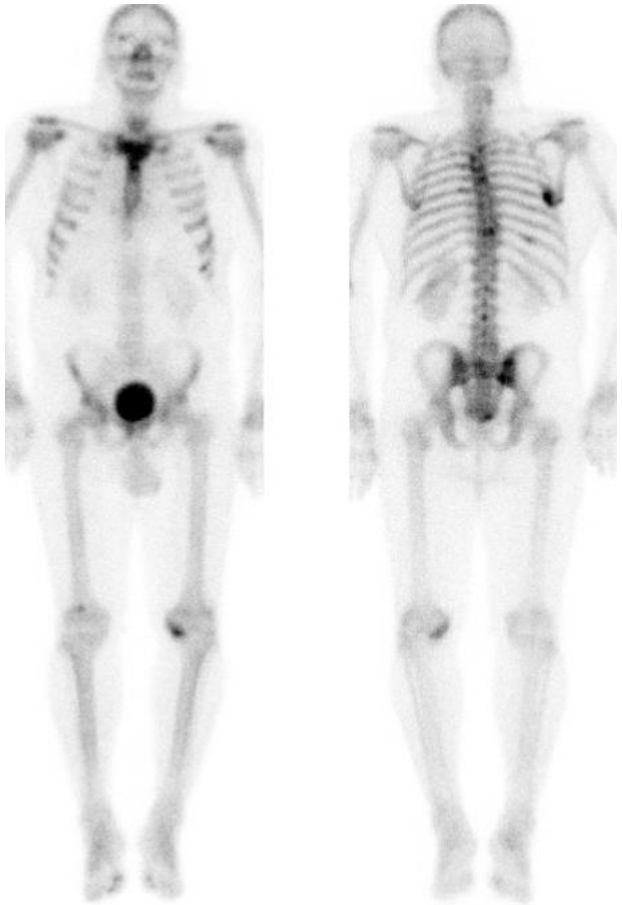
iTNM: cTx, cN0, cM1 (OSS, PUL)

Osseous PD (new lesion) after 6 mo. of Enfortumab vedotin + Pembrolizumab

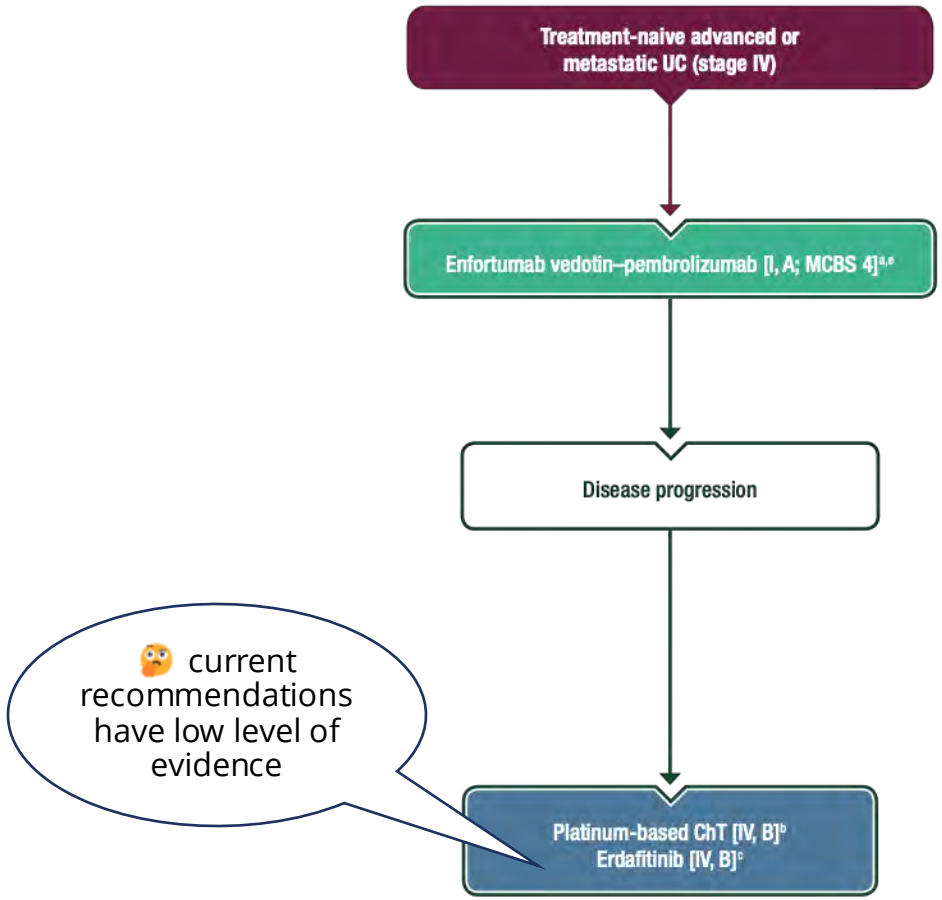
ECOG: 0

Treatment Options:

Platin-Gemcitabin	Erdafitinib	Vinflunine	Taxane	ADC with alternative targets



ESMO GUIDELINES FOR UROTHELIAL CARCINOMA



Powles et al. Ann Oncol 2024 https://doi.org/10.1016/j.annonc.2024.03.001

GENOMIC ALTERATIONS REQUIRE STANDARDIZED REPORTING

Nomenclature

- **SNVs and indels** should be reported using p. and c. notation
- **Gene fusions** should be reported listing both fused gene partners separated by a slash
- **CNVs** should be reported in table format as copy number GAIN or LOSS†
- **Numerical copy number changes** can be performed and reported when appropriate

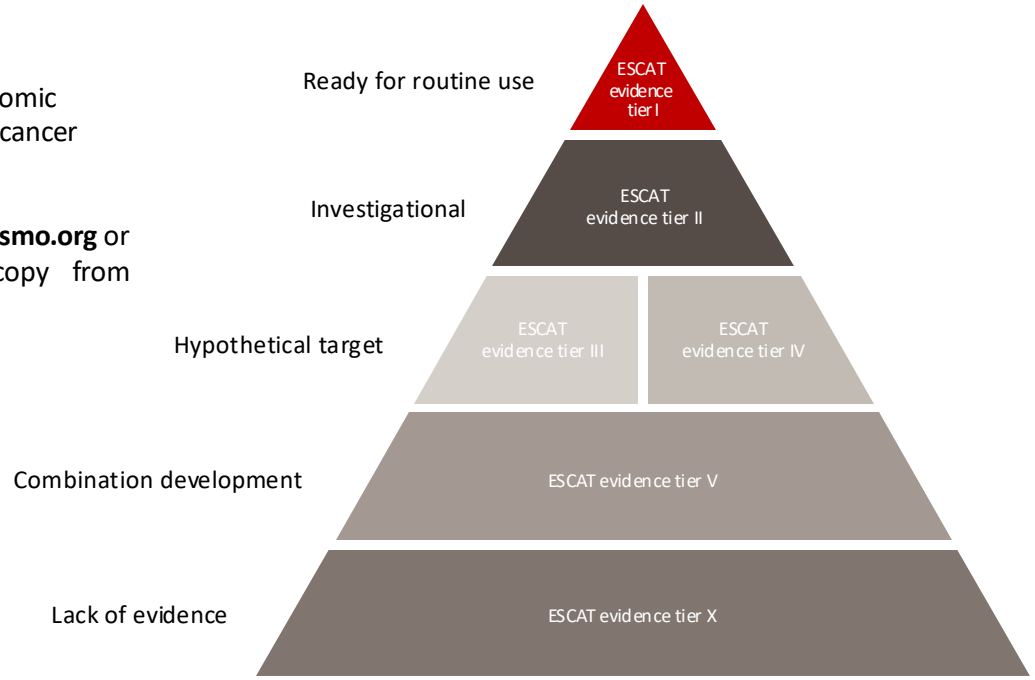
Adapted from Li et al. 2017.[1]

	ESCAT evidence tier		Required level of evidence	Clinical implication
Ready for routine use	**I** **Alteration-drug match is associated with improved outcome in clinical trials**	**I-A**	Prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point	**Access to the treatment should be considered standard of care**
		I-B	Prospective, non-randomised clinical trials show the alteration-drug match in a specific tumour type, results in a clinically meaningful benefit as defined by ESMO MCBS 1.1	
		I-C	Clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types	

Adapted from Mateo J et al. 2018.[2]

A framework to rank genomic alterations as targets for cancer precision medicine.

Read the full article on **esmo.org** or download your pdf copy from *Annals of Oncology*.



Adapted from Mateo J et al. 2018.[2]

FGFR alterations are classed as fusions and mutations[3]

CNVs, copy number variants; ESCAT, ESMO Scale for Clinical Accountability of molecular Targets; ESMO, European Society for Medical Oncology; MCBS, Magnitude of Clinical Benefit Scale; SNVs, single nucleotide variants. †CNVs generated from NGS tests. Genomic coordinates of gene/genomic locus can be included if applicable.

1. Li MM, et al. J Mol Diagn. 2017;19(1):4–23. 2. Mateo J, et al. Ann Oncol. 2018;29(9):1895–1902. 3. Mosele MF, et al. Ann Oncol. 2024;35(7):588–606.

BOTH PCR AND NGS ARE SUITABLE FOR *FGFR* ALTERATION* DETECTION[1,2]

Detects both point mutations and fusions of *FGFR3*[†]

CE-IVD RT-PCR assays:
QIAGEN Therascreen
Diatech Easy PGX

NGS:
Thermo Fisher Oncomine Dx
Illumina TSO500

Detects *FGFR2* & *3* fusions and mutations

[†]*FGFR3* mutations:
Exon7: p.R248C (c.742C>T), p.S249C (c.746C>G), p.P283S (c.847C>T), p.G299S (c.895G>A)
Exon9: p.G370C (c.1108G>T, p.S371C (c.1111A>T), p.Y373C (c.1118A>G), p.G380R (c.1138G>A), p.A391E (c.1172C>A)
Exon 14: p.K650E (c.1948A>G), p.K650M (c.1949A>T), p.K650Q (c.1948A>C), p.K650T (c.1949A>C)
FGFR3 fusions:
FGFR3: TACC3v3, *FGFR3*:TACC3v1, and *FGFR3*:BAIAP2L1

[1]35 mutations and 21 fusions (46 gene variants)
[2]523 genes variants

RT-PCR → specific targets

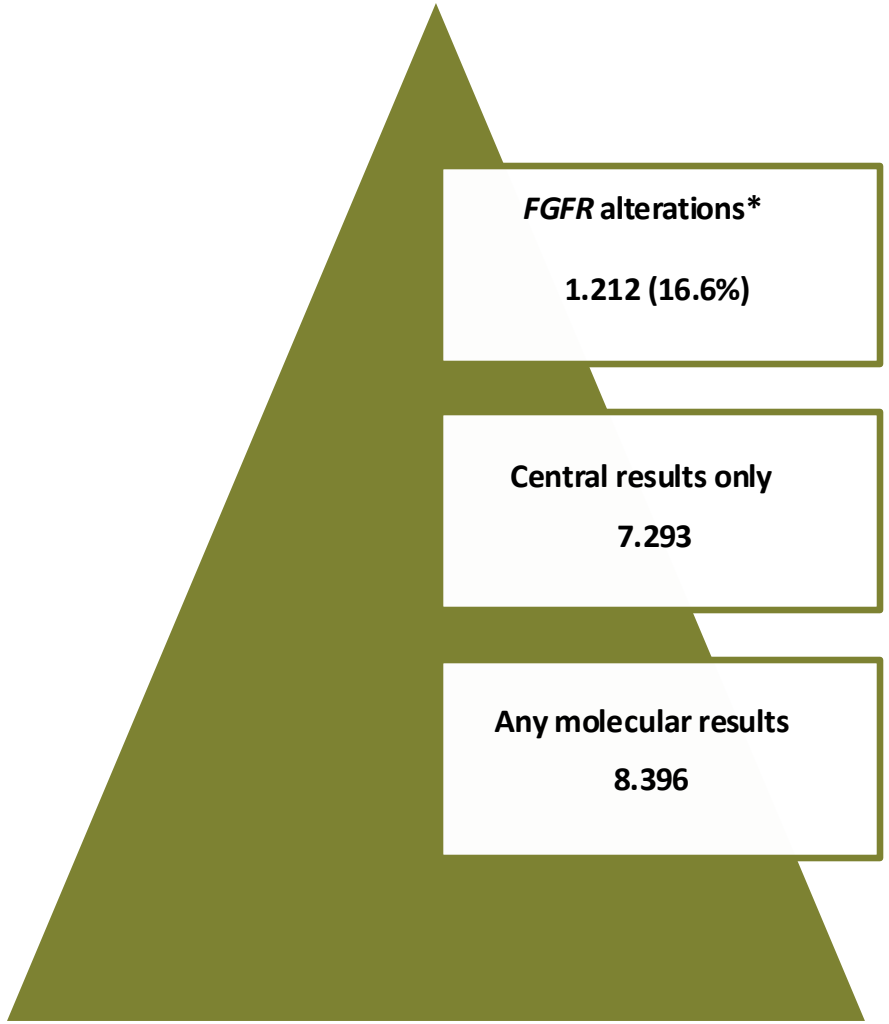
NGS → the whole picture

Speak to your pathologist for more information

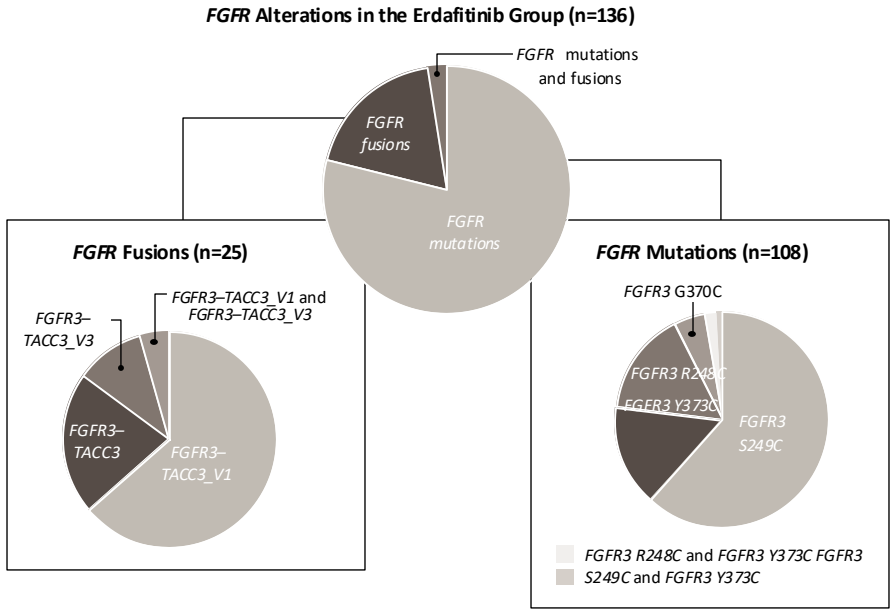
CE-IVD, CE-marked in vitro diagnostic; *FGFR,* fibroblast growth factor receptor; NGS, next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction.
**FGFR* alterations are classed as fusions and mutations.[2]

1. Major C, et al. AACR 2022 Annual Meeting. Abstract 4578. 2. Mosele MF, et al. Ann Oncol. 2024;35(7):588–606.

FGFR TESTING IN THE THOR TRIAL



Additional 108 pts. identified in local tests



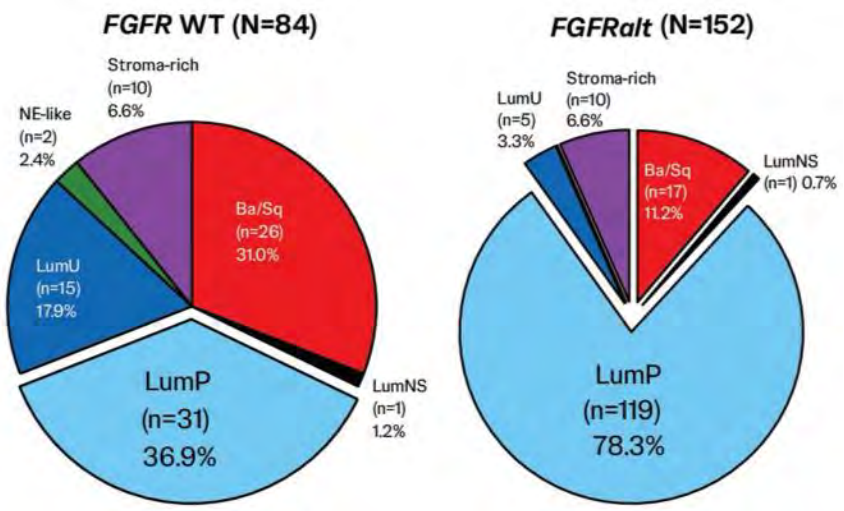
Adapted from Loriot Y et al. 2023.[1]

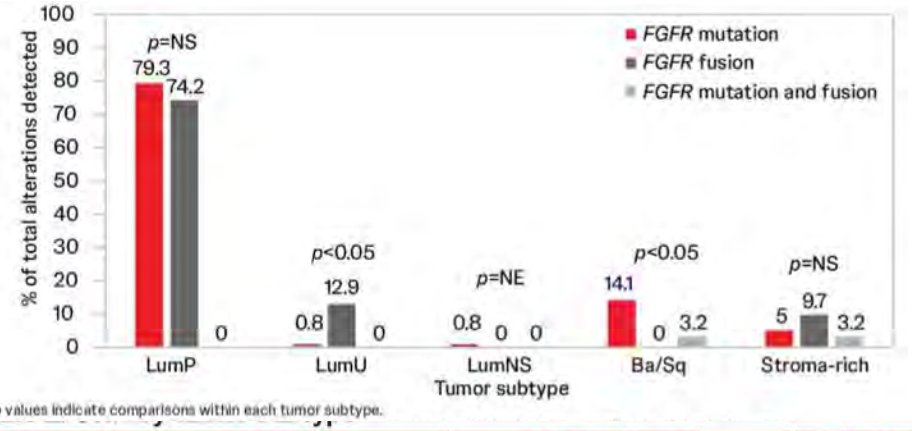
FGFR, fibroblast growth factor receptor; pts, patients.
*At least one FGFR3 mutation or FGFR2/3 fusion was required for study inclusion

1. Loriot, Y et al. N Engl J Med. 2023;389:1961–1971.

FGFR ALTERATIONS

Are enriched in the luminal-papillary subtype





p values indicate comparisons within each tumor subtype.

Subtype	Erdafitinib		Pembrolizumab		*P* value
	N	ORR (95% CI)	N	ORR (95% CI)	
Non-LumP	17	**41.2%** [18.4%, 67.1%]	16	**25.0%** [10.3%, 56.0%]	
LumP	48	**41.7%** [27.6%, 56.8%]	71	**19.7%** [11.2%, 30.9%]	0.0129
ITT[1]	175	40.0%	176	21.6%	

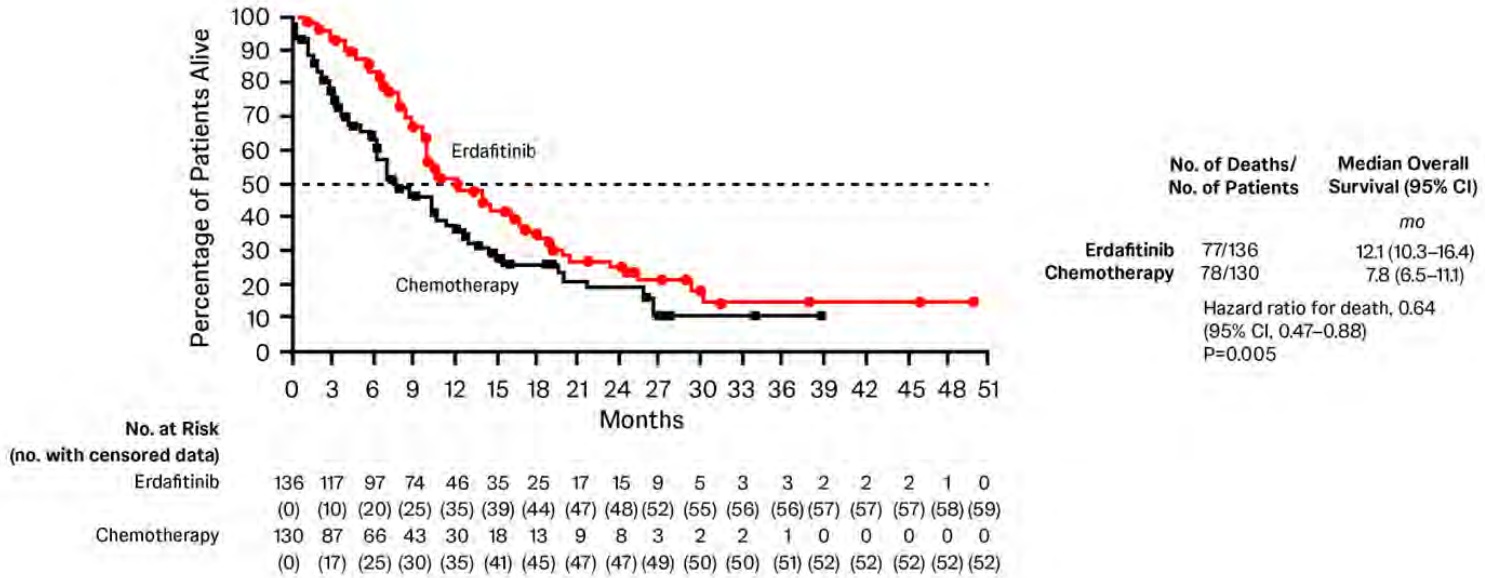
ITT, intent-to-treat; lumP, luminal papillary; non-LumP, all other subtypes excluding LumP; ORR, overall response rate.

4578 Siefker-Radtke et al. ASCO 2024

SEQUENCE MATTERS IN FGFR ALTERED UC

Erdafitinib is a standard of care after ICI failure

👍 erdafitinib is superior to chemo after ICI-failure

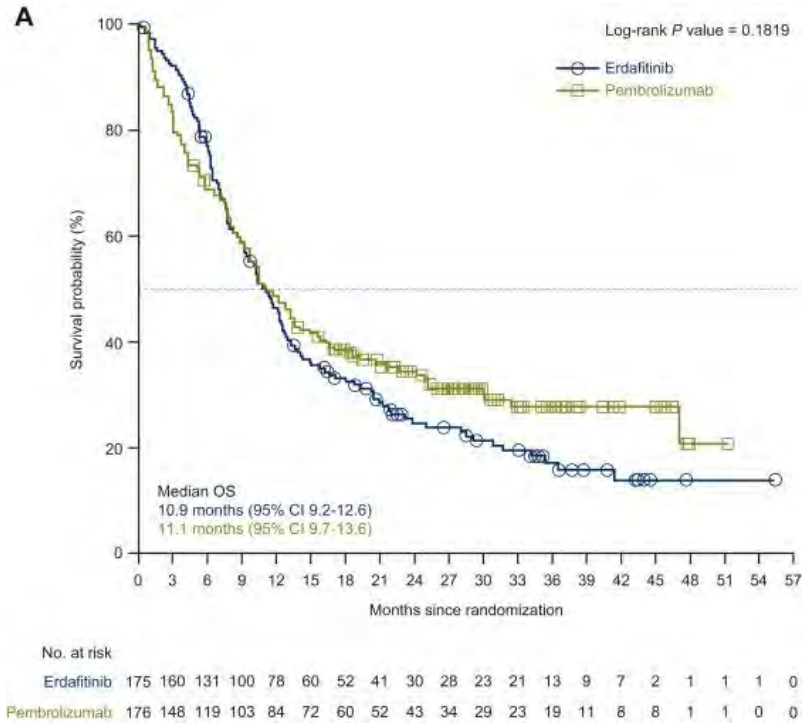


	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Erdafitinib	77/136	12.1 (10.3–16.4)
Chemotherapy	78/130	7.8 (6.5–11.1)

Hazard ratio for death, 0.64
(95% CI, 0.47–0.88)
P=0.005

Loriot Y, et al. N Engl J Med. 2023;389(21):1961–1971.

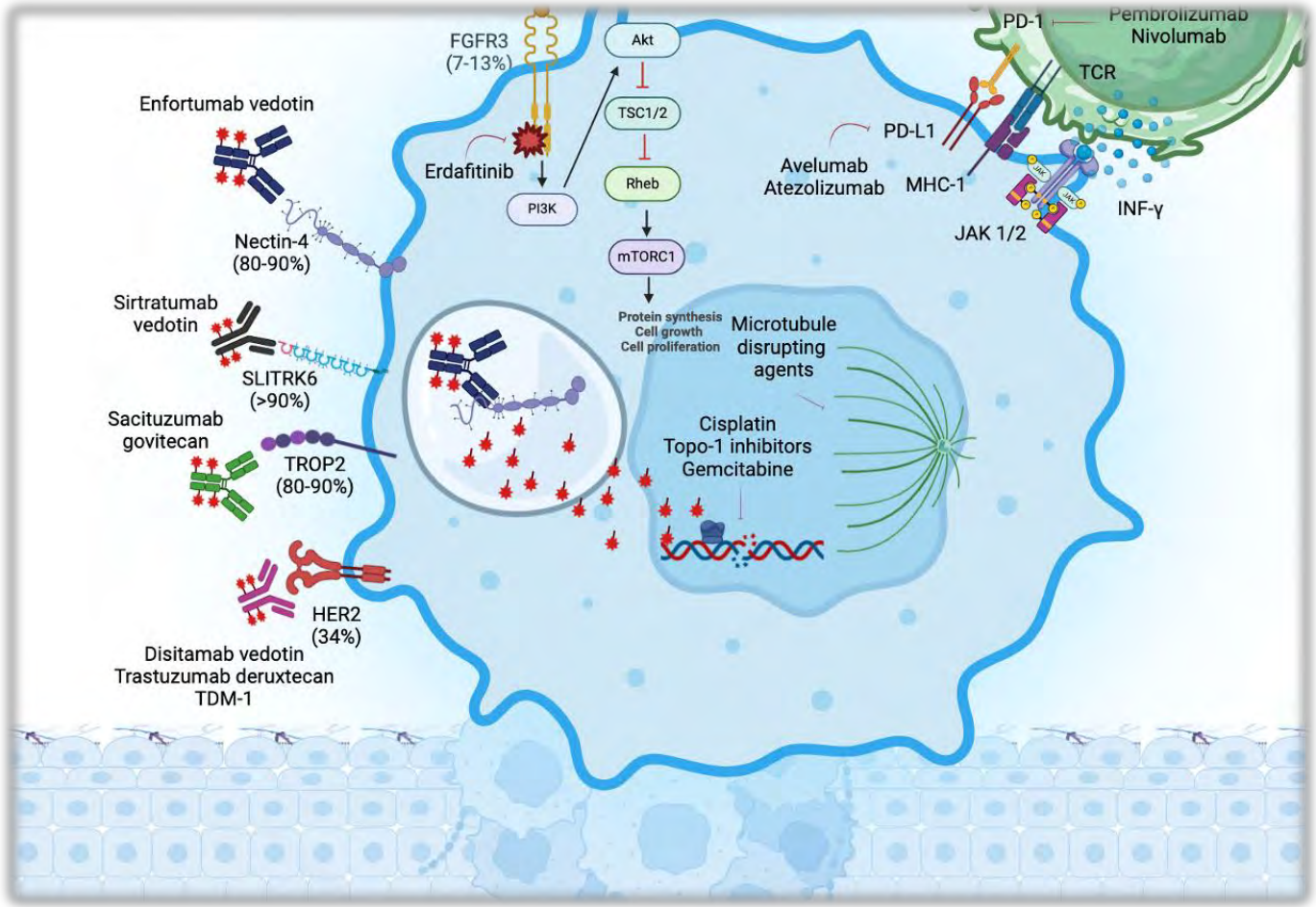
✋ erdafitinib vs. pembrolizumab without OS benefit



Siefker-Radtke et al. Ann Oncol 2024 https://doi.org/10.1016/j.annonc.2023.10.003

NEW TREATMENT OPTIONS IN UC

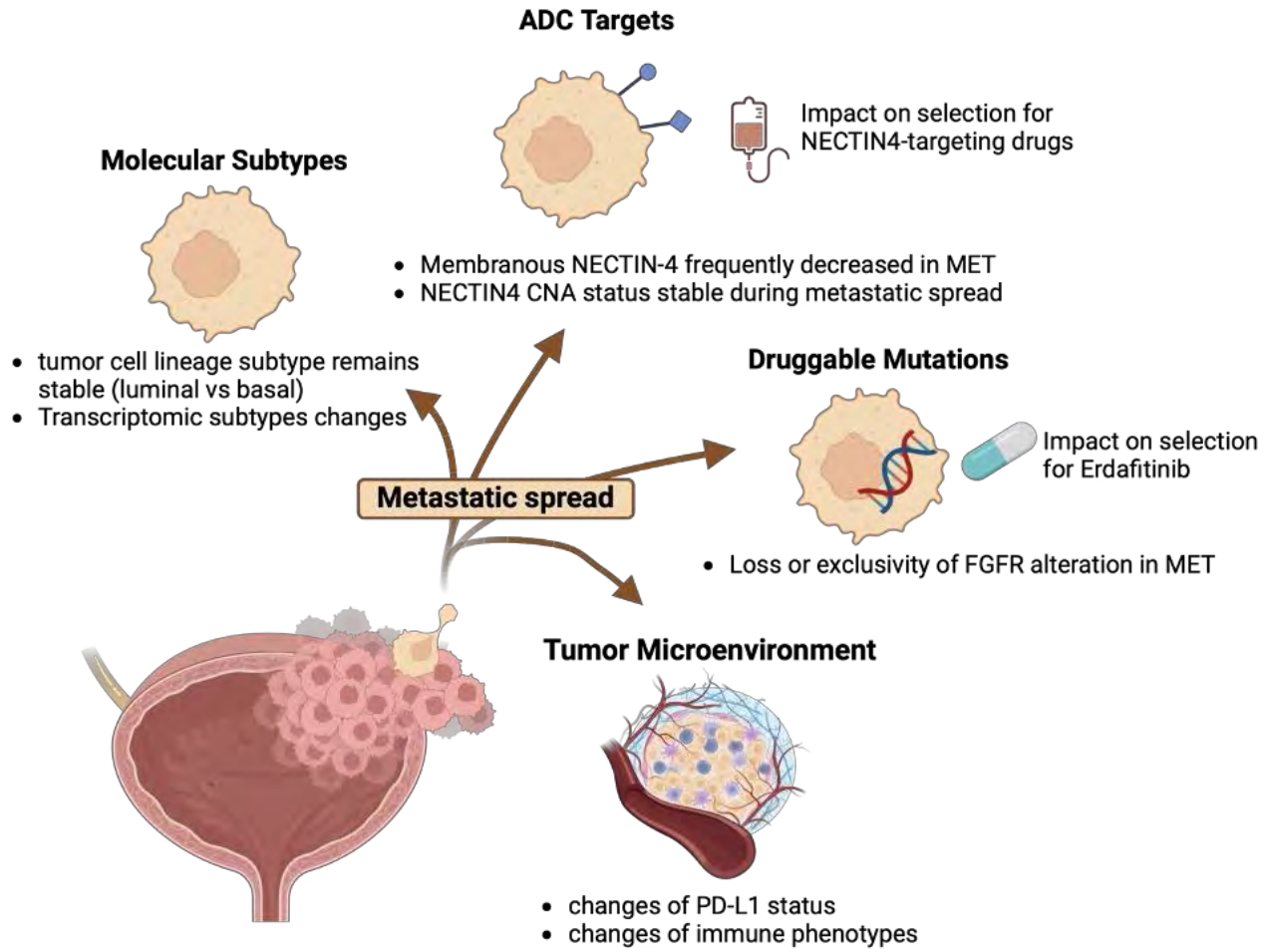
Novel agents and mechanisms of action are promising



Modified from Grande E, et al at ASCO Daily News 2024 (in press)

BIOPSY WHAT YOU TREAT

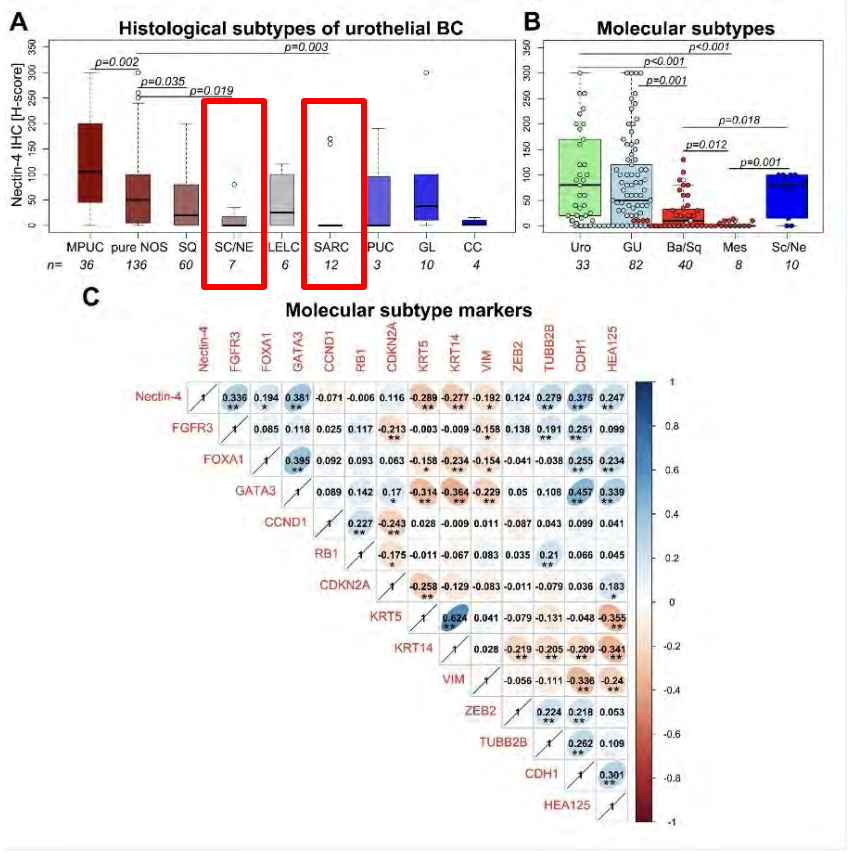
Placticity of cancer cells demands representative tissue for molecular assessment



Klümper et al. Nat Rev 2024, in Press

UC SUBTYPES EXPRESS TARGETS DIFFERENTIALLY

TROP2 and NECTIN4 expression differ between UC subtypes



(A)

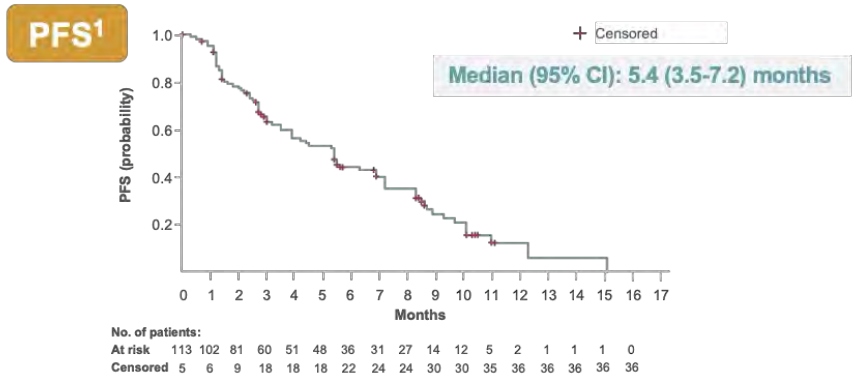
	Both markers expressed	No marker expression	Only TROP2 not expressed	Only Nectin 4 not expressed	Not available	
Total number	177	5	8	15	42	
Histology						
Neuroendocrine	2 (1.1)	4 (80.0)	4 (50.0)	0		
Sarcomatoid	11 (6.2)	1 (20.0)	2 (25.0)	3 (20.0)		
Large nested	6 (3.4)	0	0	1 (6.7)		
Squamous	46 (25.8)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

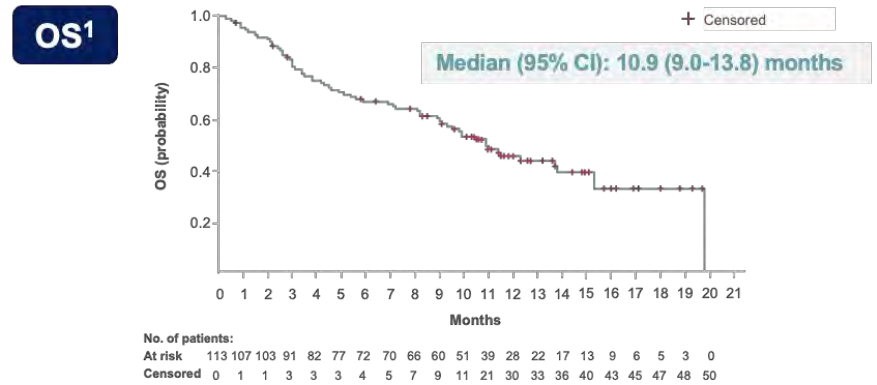
Olah et al. BJU Int 2025 doi: 10.1111/bju.16643.

Bahlinger et al. Histopathology, First published: 09 January 2024, DOI: (10.1111/his.15130)

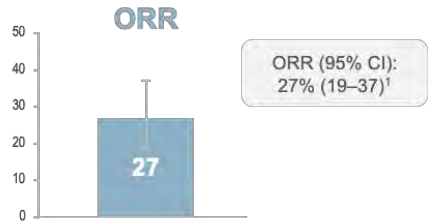
SACITUZUMAB GOVITECAN – EARLY TRIALS

Showed promising activity after platin- and ICI-failure





N=113



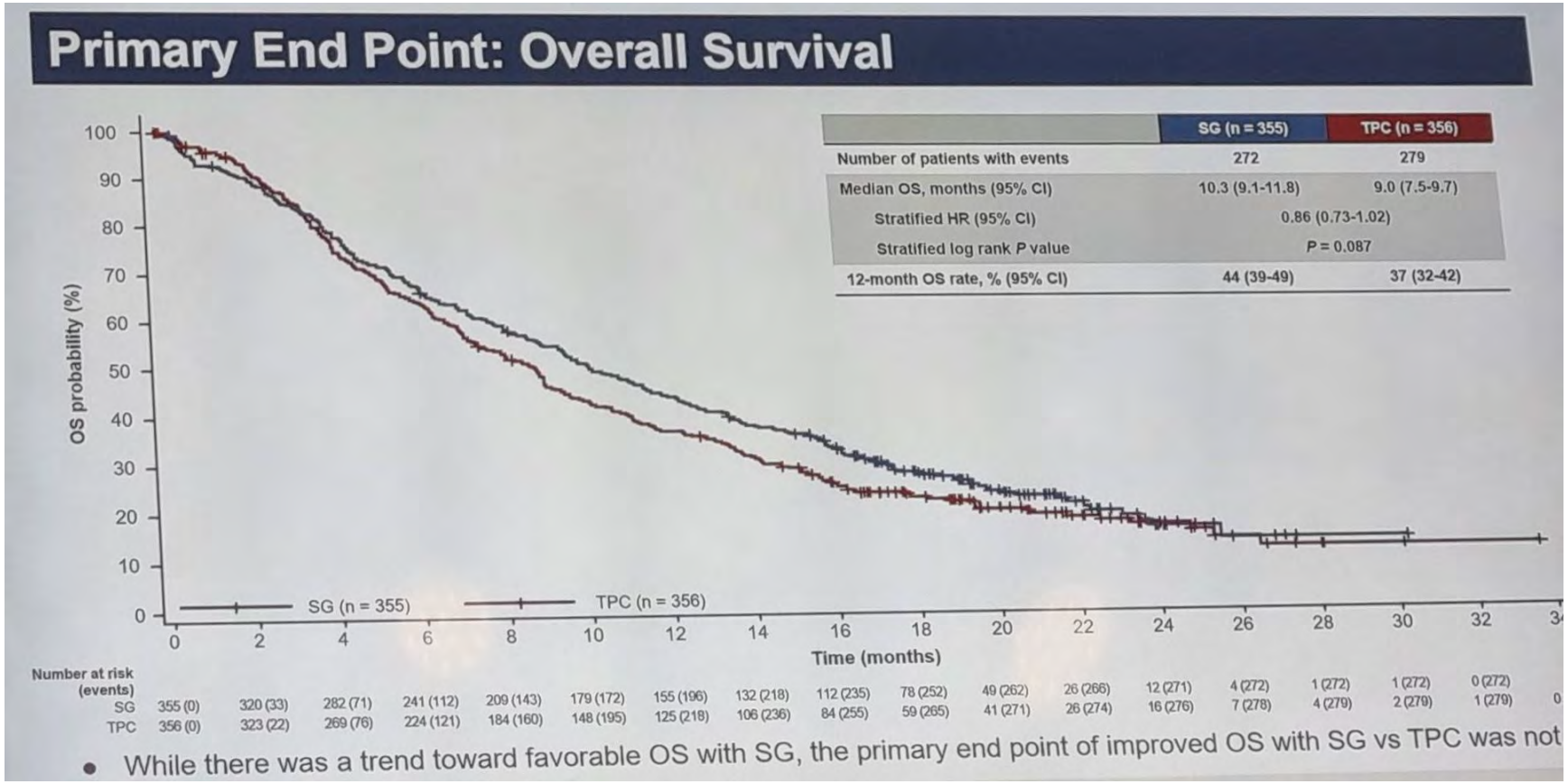
ORR (95% CI): 27% (19–37)[1]

*Median follow-up of 10.5 months; Data presented at ASCO GU 2023.[2]

1. Tagawa ST, et al. *J Clin Oncol* 2021;39(22):2474-2485; 2. Tagawa ST, et al. Presented at ASCO GU 2023 (abstract ID 526). 3. Sacituzumab govitecan, Prescribing information, Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761137s018.pdf Accessed September 2023

TROPICS04 (PHASE III) AFTER PLATIN AND IO-FAILURE

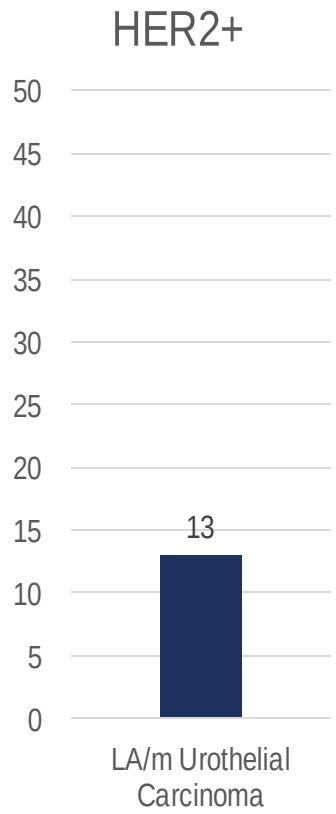
Sacituzumab govitecan is not superior to chemotherapy

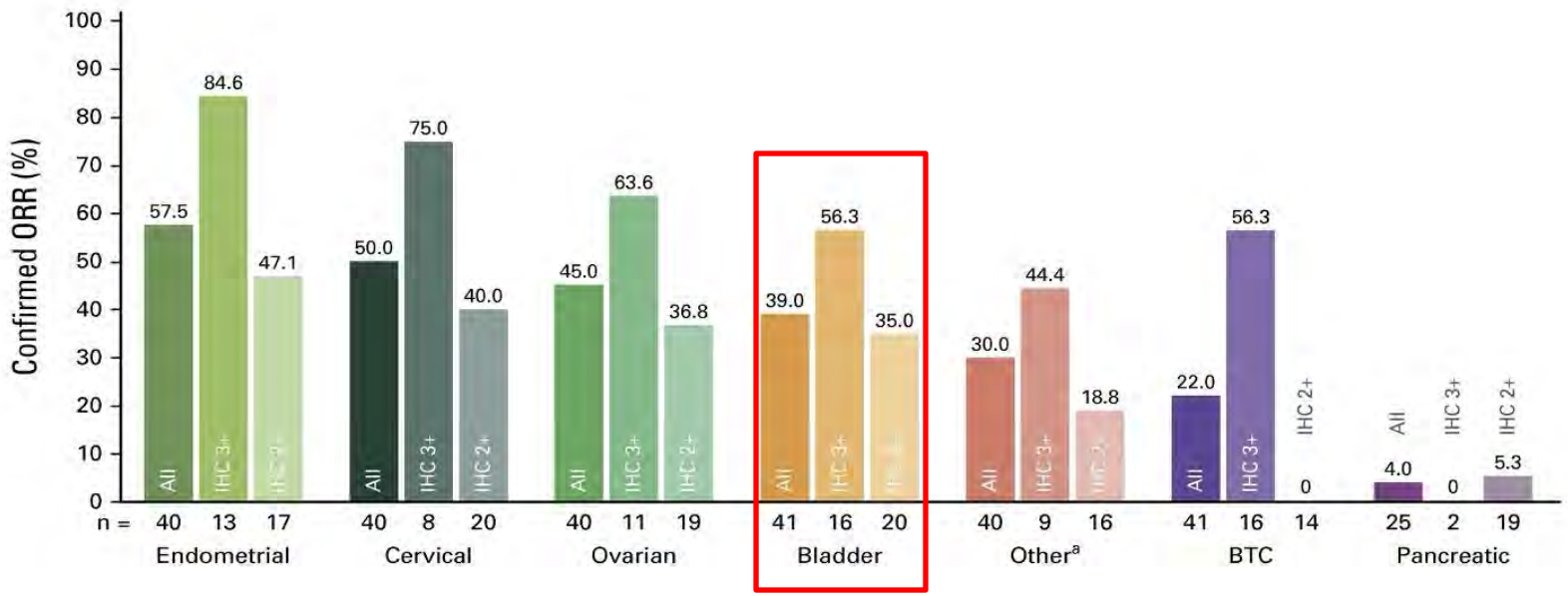


Grivas et al. ESMO Asia 2024: LBA9

HER2 EXPRESSION IS ASSOCIATED WITH RESPONSE TO TRASTUZUMAB DERUXTECAN

HER2 is a putative selector for ADC therapy





Scherrer et al. 2022 Oct 21:12:1011885.
doi: 10.3389/fonc.2022.1011885.

Meric-Bernstam et al, JCO, 2024

CONCLUSIONS

- ICI, chemo, ADC and FGFRi are standard options after platinum-failure
- Changes in treatment landscape led to a data gap in subsequent therapies
- In stage IV, approx. 17% of patients have FGFR alterations
- Molecular screening is mandatory to identify those patients early
- TROP2, NECTIN4 and HER2/3 are putative marker for future and biomarker-driven development of treatment strategies

ESMO WEBINARS

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Chair for interdisciplinary GU Oncology

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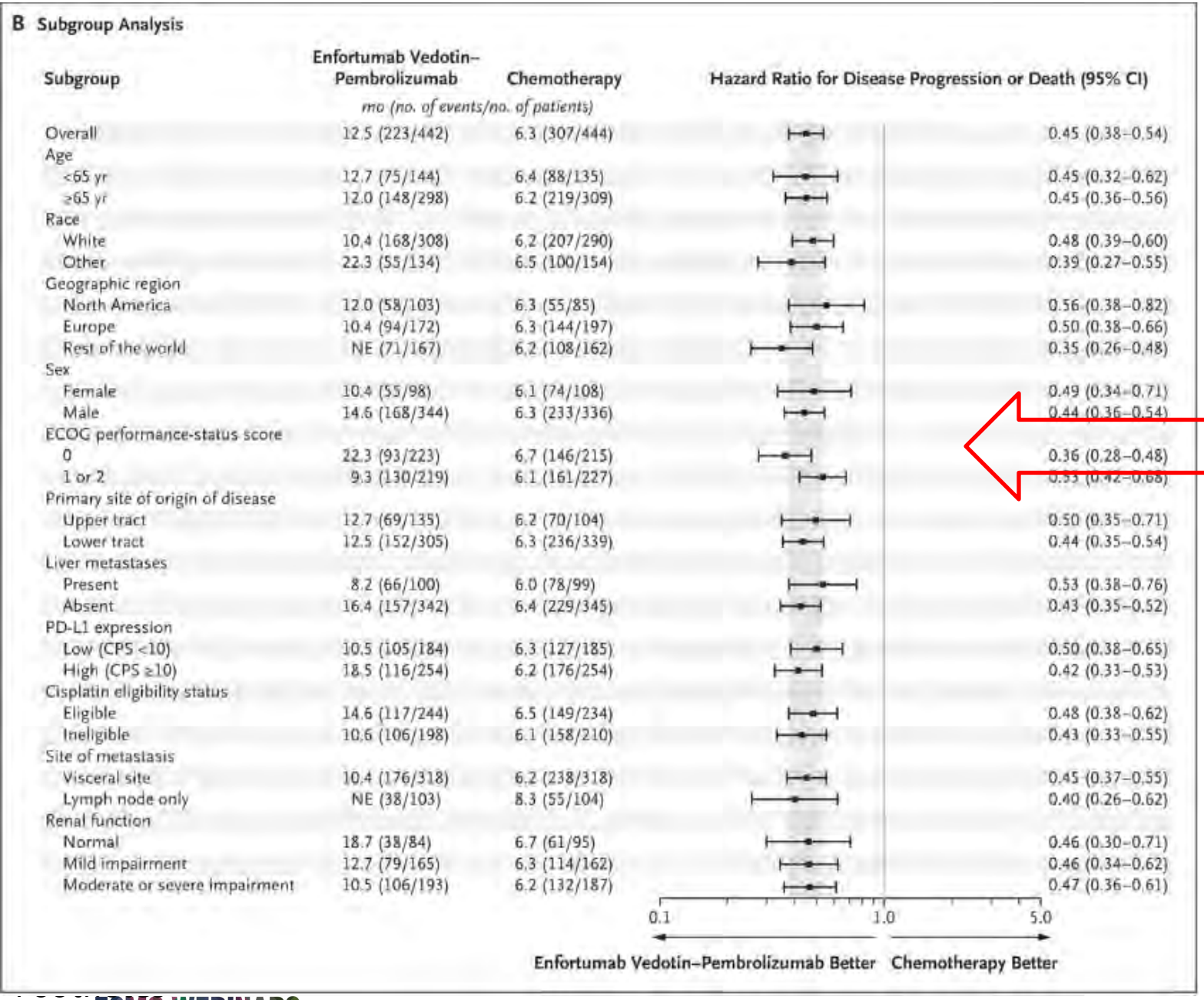
MANAGING TOXICITIES AND OPTIMISING TOLERABILITY OF NOVEL TREATMENT REGIMENS FOR PATIENTS WITH ADVANCED UROTHELIAL CANCER

Alison J Birtle FRCP FRCR MD, Rosemere Cancer Centre, Lancs Teaching Hospitals, UK

DISCLOSURES

- Alison Birtle has attended and received honoraria for advisory boards, travel expenses to medical meetings, or served as a consultant for:
  - Accord
  - Astellas
  - AstraZeneca
  - Bayer
  - Bristol Myers Squibb
  - Janssen
  - Merck
  - Novartis
  - Pfizer
  - Sanofi Aventis
  - Roche
  - Gilead
  - Alison Birtle is a member of the UTUC and NMIBC EAU Guidelines Group, Trustee Fight Bladder Cancer, Secretary British Uro Oncology Group

Goals Gains and Pains of treatment



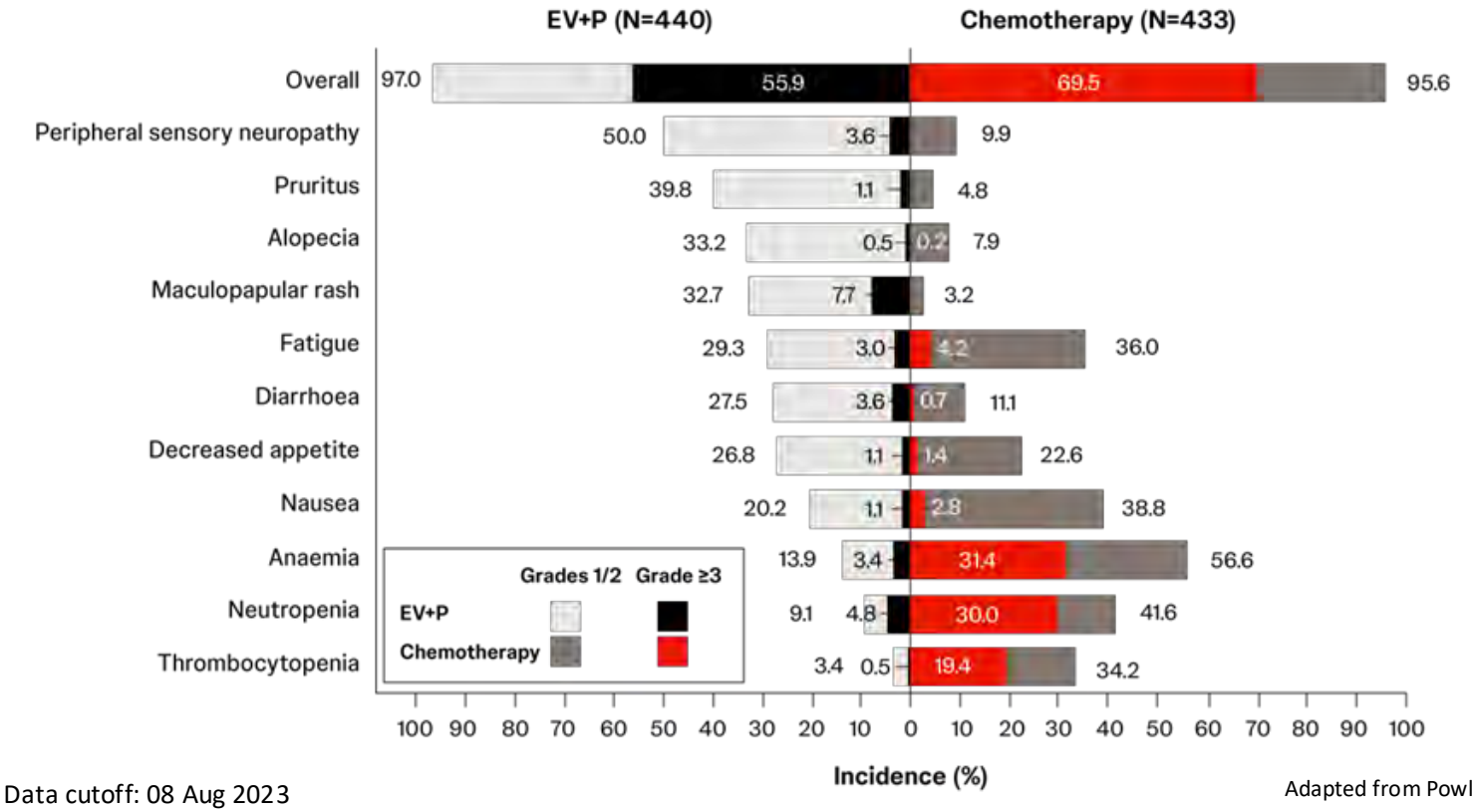
EV302 efficacy data

Nothing on this side…

Need to proactively manage side effects to avoid stopping life extending treatments.

Treatment-Related Adverse Events[1]

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Data cutoff: 08 Aug 2023

Adapted from Powles. 2023.[1]

Serious TRAEs:

- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

- Asthenia
- Diarrhoea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm.

EV, Enfortumab Vedotin; P, Pembrolizumab; TRAEs, treatment-related adverse events

1. Powles T. UroToday.ESMO 2023: Oral presentation. Available from: https://www.urotoday.com/conference-highlights/esmo-2023/esmo-2023-bladder-cancer/147538-esmo-2023-ev-302-keynote-a39-enfortumab-vedotin-in-combination-with-pembrolizumab-ev-p-vs-chemotherapy-in-previously-untreated-locally-advanced-metastatic-urothelial-carcinoma.html [Last Accessed: August 2024].

From AE we can give more thought ..

- Poorly controlled diabetes-latest HBA1c
- *NB HBa1c >/=8% excluded from EV302*. Symptomatic (thirst, urinary frequency)More common if high BMI (>30kg/m2)
- Peripheral neuropathy- some patients may have had neoadjuvant treatment > 12 months ago – pre-existing neuropathy due to cisplatin, Due to diabetes ?
- Skin conditions – how often do we look at whole of skin in clinic.
- Renal impairment *NB no dose reductions in SmPC for GFR 15ml/min or above*
- Hepatic impairment- no data on moderate /severe

- Interstitial lung disease- often asymptomatic finding on staging scan. Co-existent COPD, use of steroids over last year (may also affect diabetic control)

LETTER TO THE ED

Re: Thomas
Enfortumab
Urothelial C

Enrique Grande

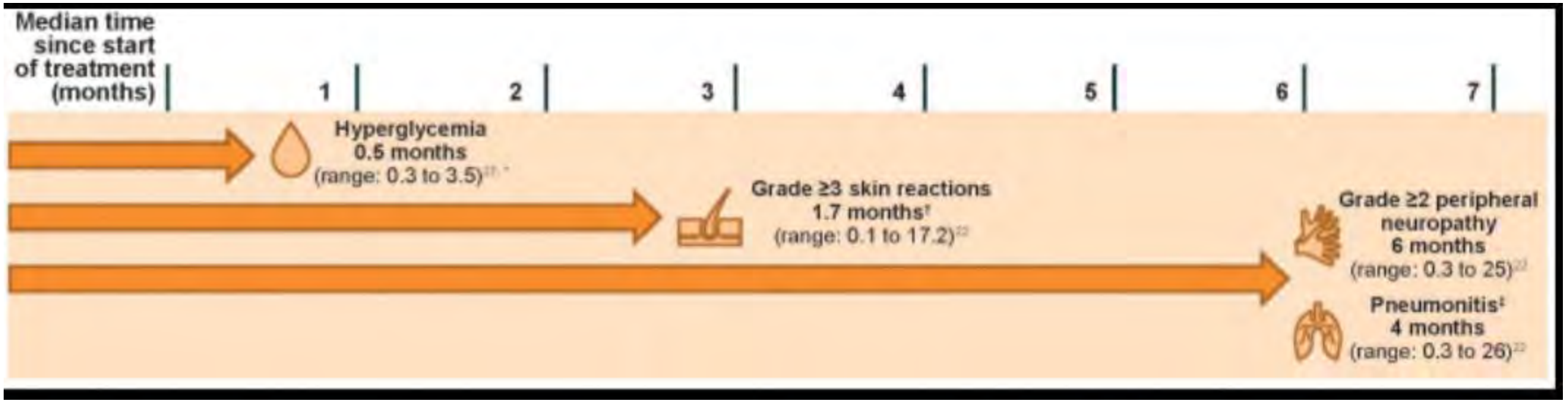
Published: July 09

Meet at least
out of 5

EV-302: safety outcomes – TRAEs of special interest*[1,2]

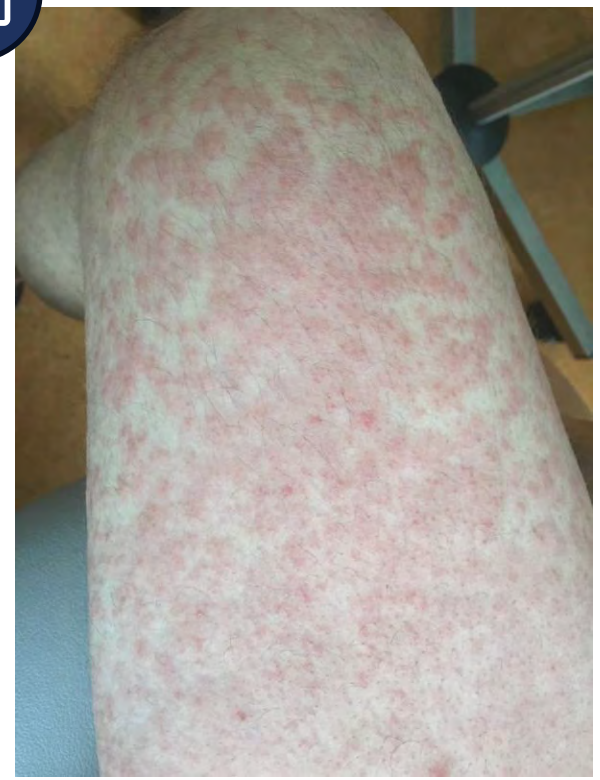
TRAEs of special interest for EV, n (%)	EV+pembro (n=440)		CT (n=433)	
	Any grade	**Grade ≥3**	Any grade	**Grade ≥3**
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0
Ocular disorders	94 (21.4)	0	12 (2.8)	0
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0
Infusion-related reactions	9 (2.0)	0	9 (2.1)	0

*There are differences in the rates of skin reactions reported for EV treatment-related AESIs and pembro TEAEs of special interest because these adverse events were reported via different methodologies developed for EV and pembro monotherapies, respectively. AESI, adverse events of special interest; CT, chemotherapy; EV, enfortumab vedotin; pembro, pembrolizumab; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event. 1. Powles T, et al. ESMO 2023 (Abstract No. LBA6 – presidential symposium); 2. Powles T, et al. N Engl J Med 2024;390:875–888.


Median time since start of treatment (months)
1
2
3
4
5
6
7
Hyperglycemia
0.5 months
(range: 0.3 to 3.5)
Grade ≥3 skin reactions
1.7 months†
(range: 0.1 to 17.2)
Grade ≥2 peripheral neuropathy
6 months
(range: 0.3 to 25)
Pneumonitis‡
4 months
(range: 0.3 to 26)

Patient case: Starting treatment with EV

- Administered on Days 1 and 8 at a dose of 1.25 mg/kg
  - Cycle 3: The patient called the helpline about a rash – itching, legs only
  - Patient was given corticosteroid cream and antihistamines
  - The patient was assessed 3 days later (at the next clinical visit) and advised to call the helpline again if symptoms worsened in the interim



EV, enfortumab vedotin.

Management of skin toxicities (1 of 2)

- Usually manifests as a maculopapular rash[1]
- Inspect all the skin on the body,[2] lymph nodes, and eyes, and check for mouth ulcers or any systemic symptoms[1,3]
- Check for a normal full blood count[3,4]
- Take a photo of the affected area[4]
- Check for bites, recent travel history[3], changes in detergent, etc[2] (i.e., do the basics!)
- Avoid using antibiotics if the AE is suspected to be drug related, as it will not be beneficial NB may have been started in primary care[3]
- Consider what may be in contact with the site of the rash (e.g., leg bag)[3]

Management of skin toxicities (2 of 2)

Should we involve a dermatologist early? YES if: >1/3 of the skin is affected, rash involves the mucosa (e.g. eyes/mouth)/bullous lesions/exfoliation, or the patient is not responding to treatment or dose modification for the AE[1,2]

Investigate which drug is the cause of the AE (if receiving 1L treatment with EV + P); a biopsy may be needed[4]

Most HCPs will know how to manage skin reactions and follow a treatment algorithm[2] (e.g., first-generation antihistamines, topical corticosteroids)[4]

Make sure patients look after their skin; use emollients, fragrance-free products, and sunscreen[1]

Complete an SAE report for Grade ≥2 AEs*. THIS PROCESS SHOULD BE AS EASY AS POSSIBLE FOR CLINICIANS[2]

AE management guidelines and SmPC guidance provide information on when to refer a patient to a dermatologist; if concerned, always consider referral[1,3]

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).

Skin toxicities: Red flags

- Skin pain[1]
- Erythroderma[2]
- Blisters[1]
- Earlobe swelling[2]
- Fever[1]

EV-related AE management guidelines and skin toxicity management algorithms can provide insights into other key red flags to be aware of[3,4]

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).

SmPC recommendations

Dose modification in patients with LA/mUC who are treated with EV	
Skin reaction severity*	**Dose modification***
• Suspected SJS/TEN or bullous lesions	• Immediately withhold and refer to specialised care
• Confirmed SJS/TEN • Grade 4 or recurrent Grade 3	• Permanently discontinue
• Grade 2 worsening • Grade 2 with fever • Grade 3	• Withhold until Grade ≤1 • Referral to specialised care should be considered • Resume at the same dose level or consider dose reduction by one dose level

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).

*Graded as per NCI CTCAE v5.0, where Grade 1 is mild, Grade 2 moderate, Grade 3 severe, and Grade 4 life threatening.`

SmPC-recommended dose modifications

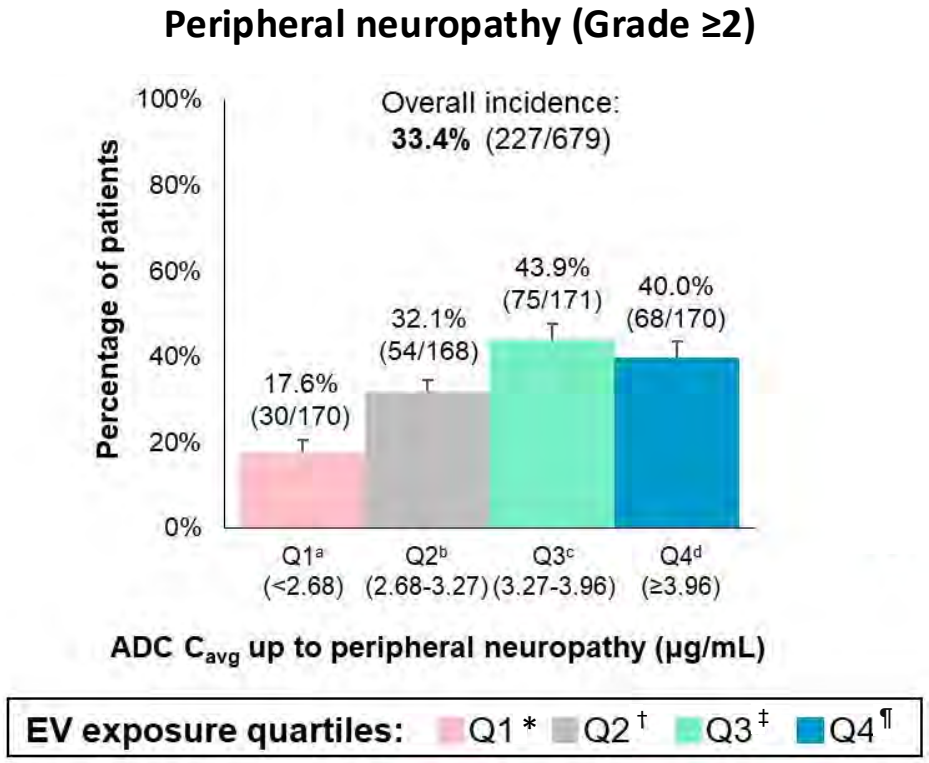
Recommended EV dose reductions for adverse reactions	
	Dose level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

Dose modification in patients with LA/mUC who are treated with EV	
Skin toxicity severity*	Dose modification*
• Suspected SJS/TEN or bullous lesions	• Immediately withhold and refer to specialised care
• Confirmed SJS/TEN • Grade 4 or recurrent Grade 3	• Permanently discontinue
• Grade 2 worsening • Grade 2 with fever • Grade 3	• Withhold until Grade ≤1 • Referral to specialised care should be considered • Resume at the same dose level or consider dose reduction by one dose level

‘I’m going to reduce the dose’

- Should we worry about whether EV will show continued efficacy if the dose is reduced?
- Should the patient worry?

Safety correlated with EV exposure, indicating that dose modifications are an effective way to manage AEs

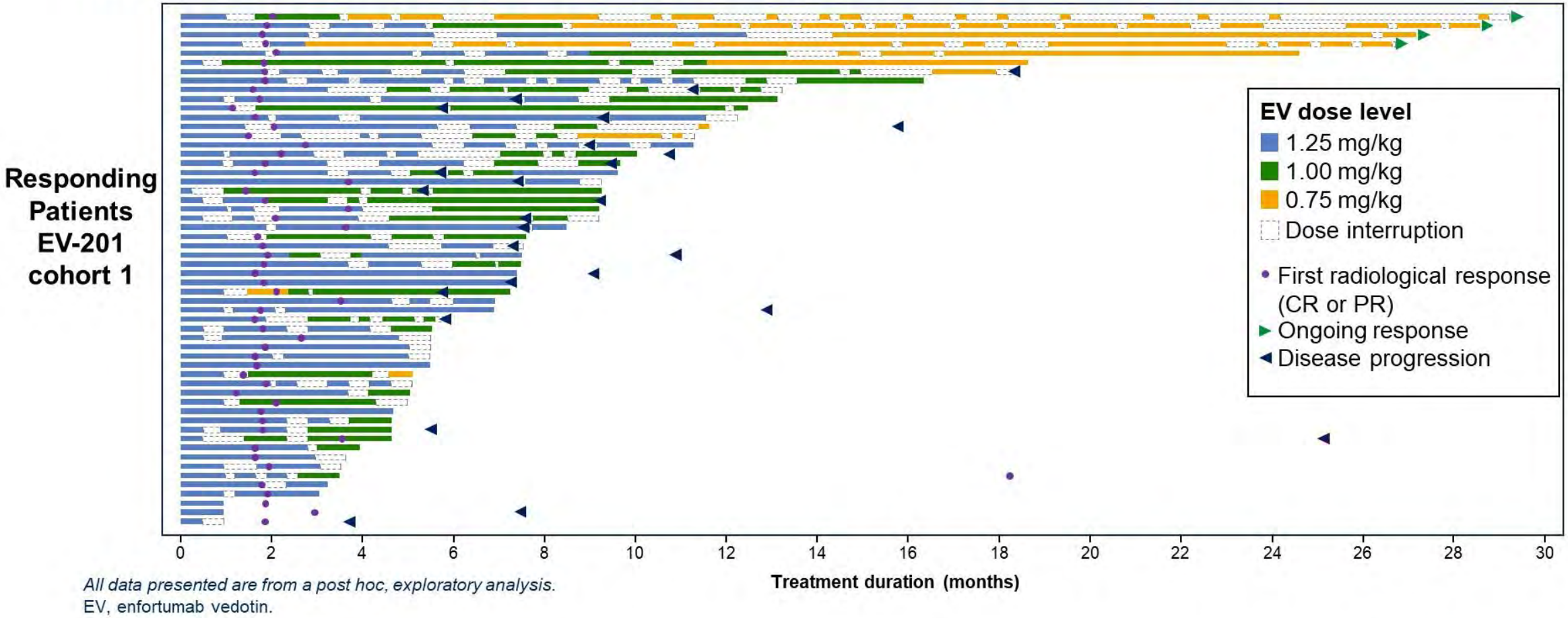


- Lower EV exposure was associated with lower risk ($p<0.0001$) of:
  - Skin reactions [§] (Grade ≥3: 12.5%); median time to onset: 0.6 months
  - Hyperglycaemia (Grade ≥3: 7.1%); median time to onset: 0.6 months
  - Peripheral neuropathy (Grade ≥2: 33.4%); median time to onset: 4.7 months
- Earlier time to onset of skin reactions and hyperglycaemia (median time to onset during Cycle 1) confounded the interpretation of exposure–safety results
- Unconjugated MMAE C_{avg} was not strongly correlated with the incidence of these AEs

Slide adapted from Petrylak D et al. Presented at ASCO 2024. Abstract 4503.
All data presented are from a *post hoc*, exploratory analysis.
Average EV exposures were divided into four quartiles: *Q1 represents EV exposures between 0–25%; †Q2: 25–50%; ‡Q3: 50–75%; ¶Q4: 75–100% (the highest EV exposure quartile); §Composite term.
ADC, antibody-drug conjugate; C_{avg}, time-averaged exposure up to an event of interest; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; Q, quartile.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Respon

Responding patients resume treatment and continue to benefit following dose interruptions and reductions



All data presented are from a post hoc, exploratory analysis.
EV, enfortumab vedotin.

Peripheral neuropathy NB if patient has symptoms, its GRADE 2. PAUSE REDUCE DOSE

Risk factors- older, diabetes, spinal disease. Other anti cancer treatment.

Usually sensory- direct questions, difficulty holding pen, drawing blinds etc.

Was this present but low grade before starting- check diabetic control (again!!), any subtle increase in urinary symptoms that could hint.

If second line, What chemo have they already had NB cisplatin and taxanes.

Could it be due to other causes - spinal problems.

Try amitriptyline or gabapentin.

Keep hands warm (NB pre –existing Reynaud's may worsen after chemotherapy).

Menthol cream 1-2%.

Proactive dose reductions and pauses..

NB, nota bene.
Speaker's clinical experience.

Hyperglycaemia

Risk factors-Previous history, high BMI, use of steroids, concurrent infections, underlying fatty liver disease.

Education and close monitoring, ask about symptoms NB increased urinary frequency may NOT be infection.

Grade 1 continue treatment- do you need insulin

Grade 2 hold EV until blood glucose < 250 mg/ml and resume same disease. Continue Pembro. Insulin+/- oral anti hyperglycaemics

Grade 3 hold BOTH drugs. Resume Pembro when grade 1

Hold EV.

Manage DKA as per guidelines

..

NB, nota bene.
Speaker's clinical experience.

Pre-empt problems

Make sure you treat the right patient group

- Poorly controlled diabetics
- Preexisting peripheral neuropathy
- Poor performance status

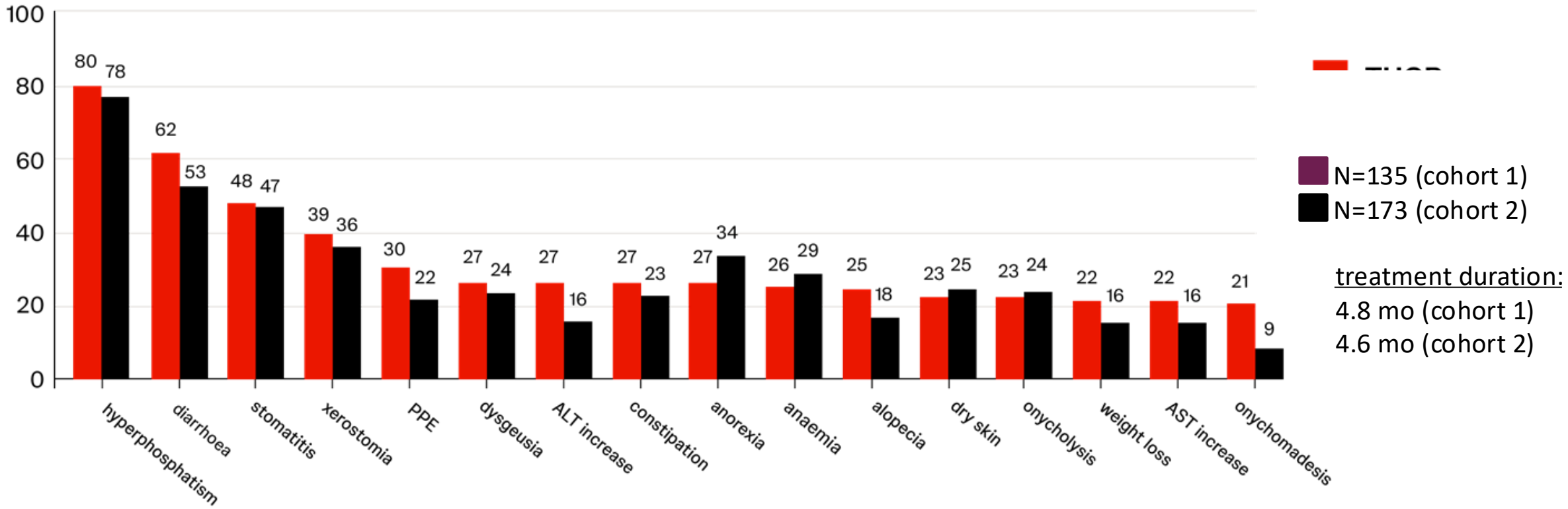
Training on the ground

- Anyone who might see the patient
- The patient
- If Grade 2 or above PAUSE

- Speaker's clinical experience.

ERDAFITINIB

THOR study with cohorts 1 (2nd–3rd line) and 2 (2nd line) treatment emergent adverse events (any grade, all causalities, >20% incidence)[1,2]

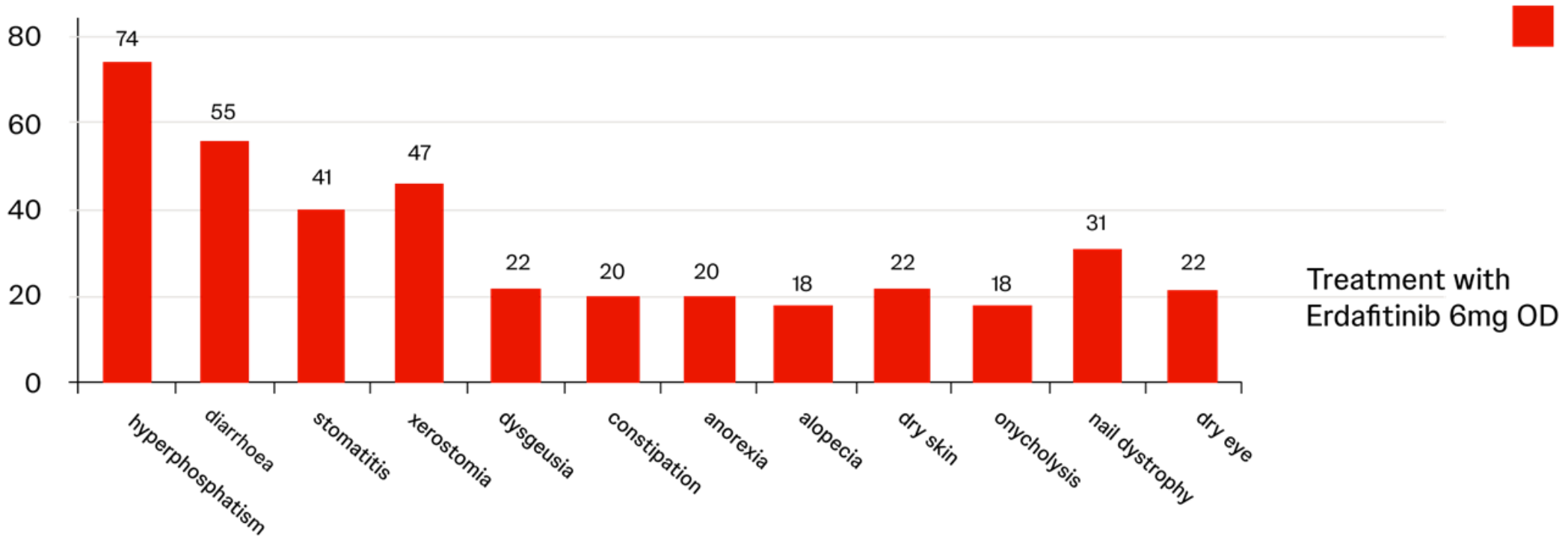


Adapted from Siefker-Radt et al. 2024[1] and Loriot et al. 2023.[2]

ALT, Alanine transaminase; AST, Aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia.

1. Siefker-Radtke AO, et al. Ann Oncol. 2024;35:107–117. 2. Loriot, Y et al. N Engl J Med. 2023;389:1961–1971.

THOR2: erdafitinib with a similar toxicity pattern in earlier stages (BCG unresponsive papillary UC)[1]



BCG, bacillus Calmette-Guérin; OD, once daily; UC, urothelial carcinoma.

Adapted from Catto et al. 2024.[1]

1. Catto JWF, et al. Ann Oncol. 2024;35(1):98–106.

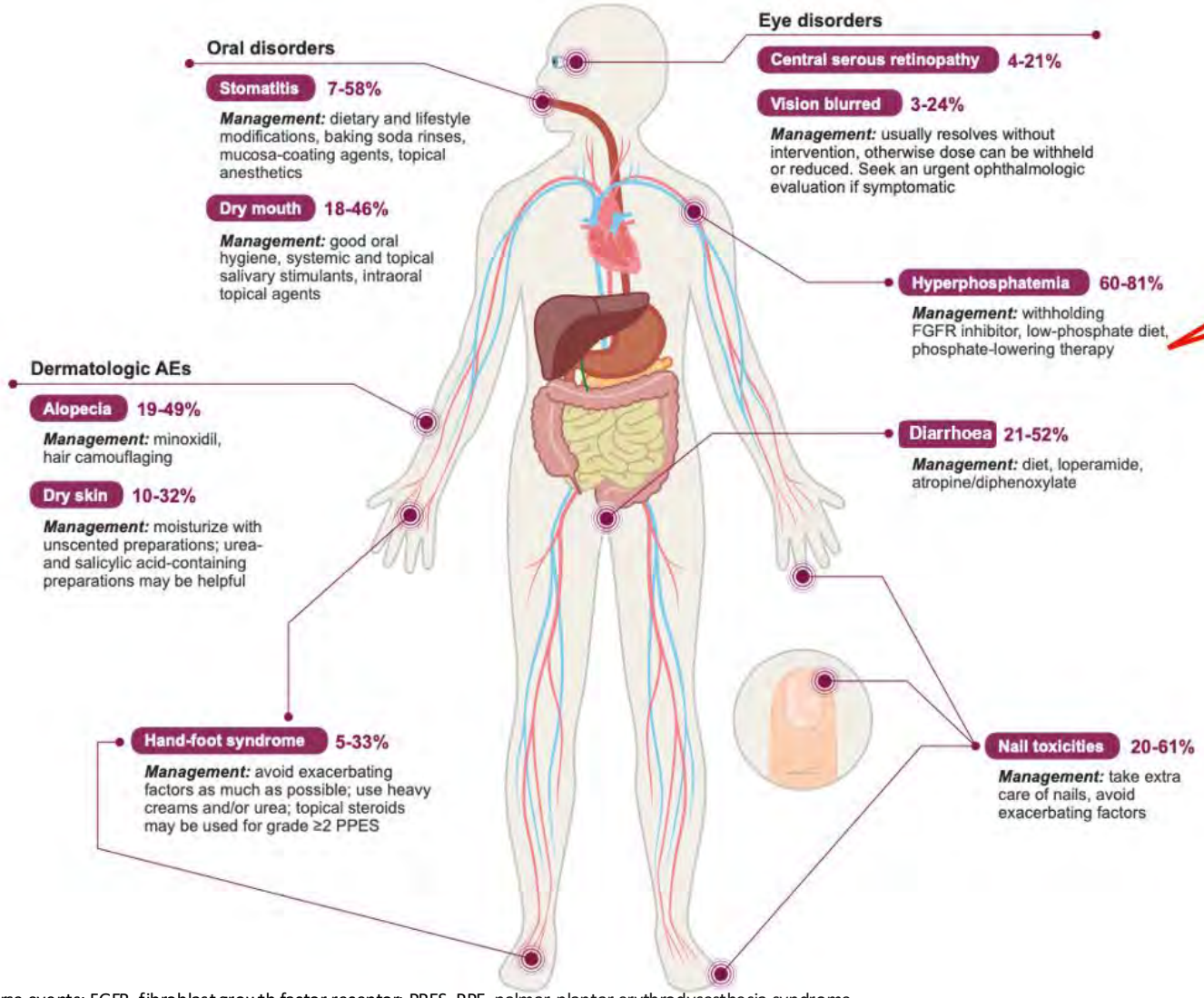
Key safety parameters

	THOR 2 (BCG failure)[1]	THOR (2nd line)[2]	THOR (post IO: 2nd or 3rd line)[3]
TRAE	100 %	97.7%	97.0%
Grade 3–4 TRAE	31 %	43.4%	45.9%
SAE (treatment related)	12 %	13.3%	13.3%
AE leading to death (treatment related)	0 %	0 %	0.7%
Discontinuation due to TRAE	27 %	15.0%	8.1%

AE, adverse event; BCG, bacillus Calmette-Guérin; IO, immuno-oncology; SAE, serious adverse event; TRAE, treatment-related adverse event.

1. Catto JWF, et al. Ann Oncol. 2024;35(1):98–106. 2. Siefker-Radtke, AO et al. Ann Oncol. 2024;35(1):107–117. 3. Loriot, Y et al. N Engl J Med. 2023;389(21):1961–1971.

Common AEs associated with *FGFR* inhibition[1]



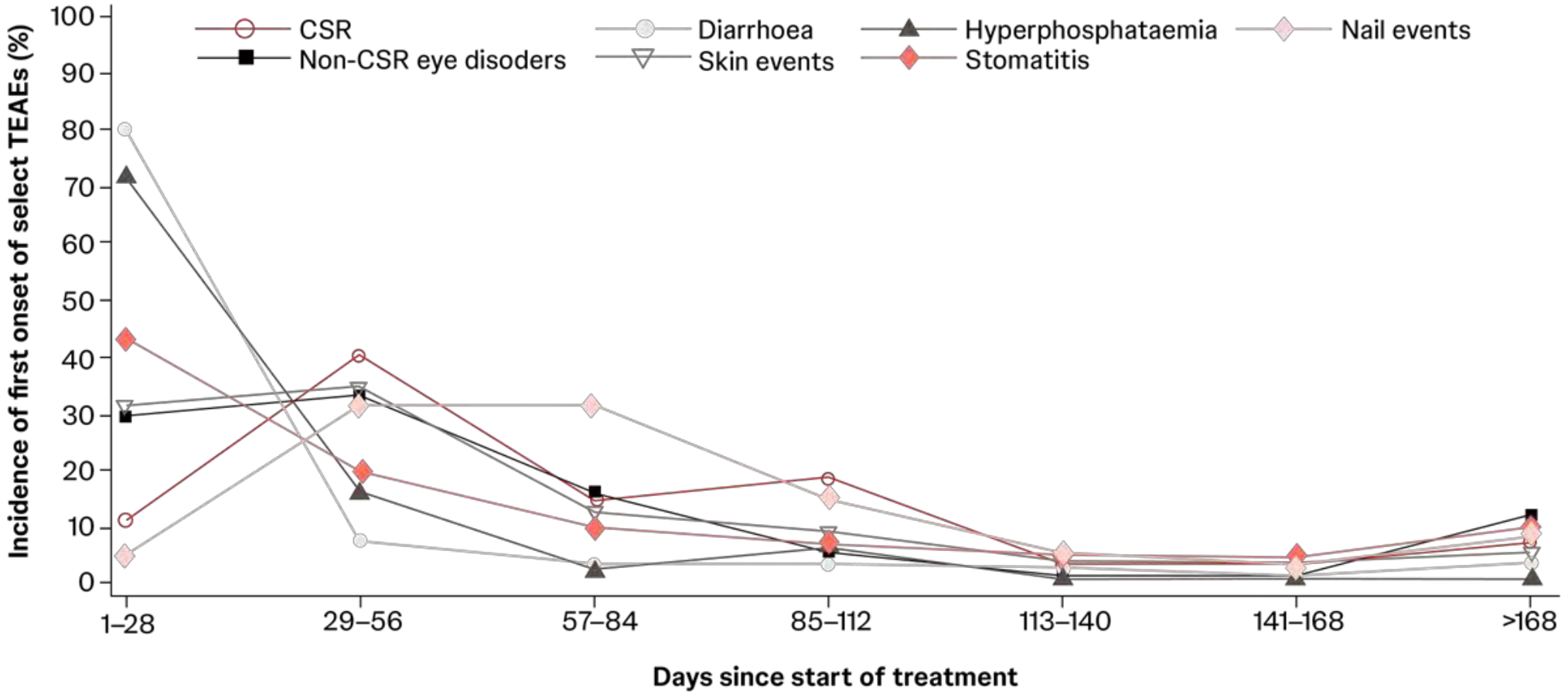
Pharmacodynamic marker for FGFR inhibition

From Subbiah V and Verstovsek S. 2023.[1]

AEs, adverse events; FGFR, fibroblast growth factor receptor; PPES, PPE, palmar-plantar erythrodysesthesia syndrome.

1. Subbiah V and Verstovsek S. Cell Rep Med. 2023;4:101204.

Time to onset of selected AE

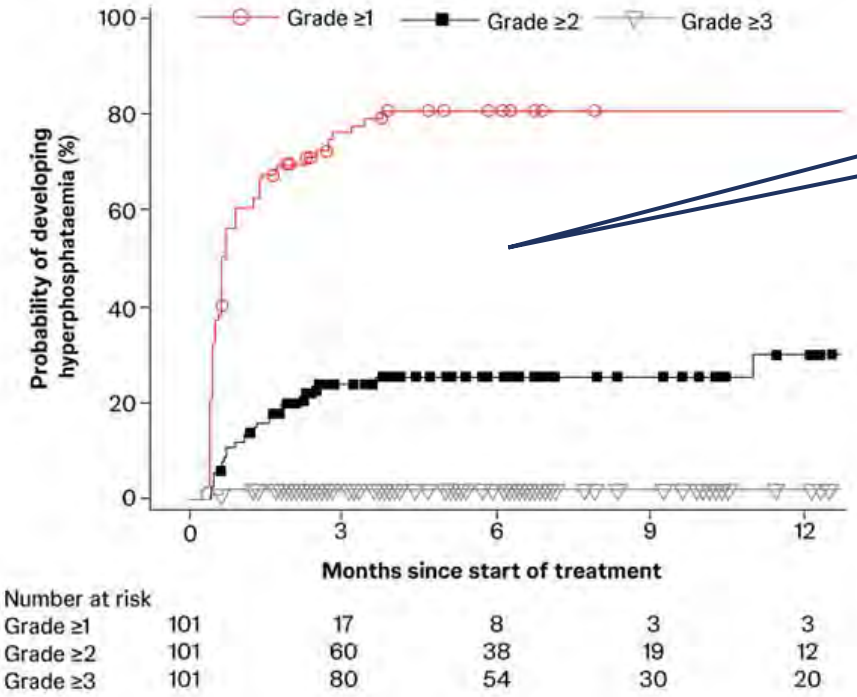


Adapted from Siefker-Radtke et al. 2023.[1]

AE, adverse event; CSR, Central serous retinopathy; TEAEs, treatment-emergent adverse events.

1. Siefker-Radtke AO, et al. Eur Urol Open Sci. 2023;16:1–9.

Hyperphosphataemia is a class-effect of broad-spectrum *FGFRi* and a pharmacodynamic marker[1]



Median:
Time to onset 6 weeks
Time to resolution 17 days

Pts. with prolonged hyperphosphataemia have:

More anaemia (29% vs 20%)
More renal impairment (14% vs 6.3%)
Less hypotension (4.8% vs 7.5%)

Adapted from Siefker-Radtke et al. 2023.[1]

FGFRi, fibroblast growth factor receptor inhibitor.

1. Siefker-Radtke, AO et al. Eur Urol Open Sci. 2023;16:1–9.

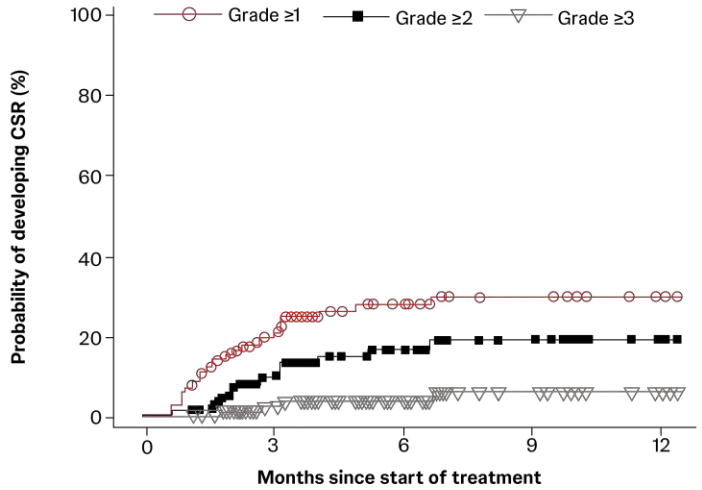
Therapy management of hyperphosphataemia

Adverse reaction	Dose modification
Erdafitinib	
Hyperphosphataemia	
Limit daily phosphate intake to 600–800 mg for all patients	
Serum phosphate 5.6–6.9 mg/dL	Maintain current dose of erdafitinib.
Serum phosphate 7.0–9.0 mg/dL	Withhold erdafitinib and assess serum phosphate concentration weekly. When the concentration is <5.5 mg/dL (or ≤ the patient's baseline concentration), restart the same dose of erdafitinib. If the hyperphosphatemia lasted > 1 week, then erdafitinib dose may be reduced.
Serum phosphate > 9.0 mg/dL	Withhold erdafitinib and assess serum phosphate concentration weekly. When the concentration is <5.5 mg/dL (or ≤ the patient's baseline concentration), restart erdafitinib 1 dose level lower than the previous dosage.
More than 10.0 mg/dL or significant alteration in baseline renal function or grade 3 hypercalcemia	Withhold erdafitinib and assess serum phosphate concentration weekly. When the concentration is <5.5 mg/dL (or ≤ the patient's baseline concentration), restart erdafitinib 2 dose levels below the previous dosage.

consider phosphate binder if phosphate ≥7 mg/dl:
- calcium carbonate
- sevelamer hydrochloride

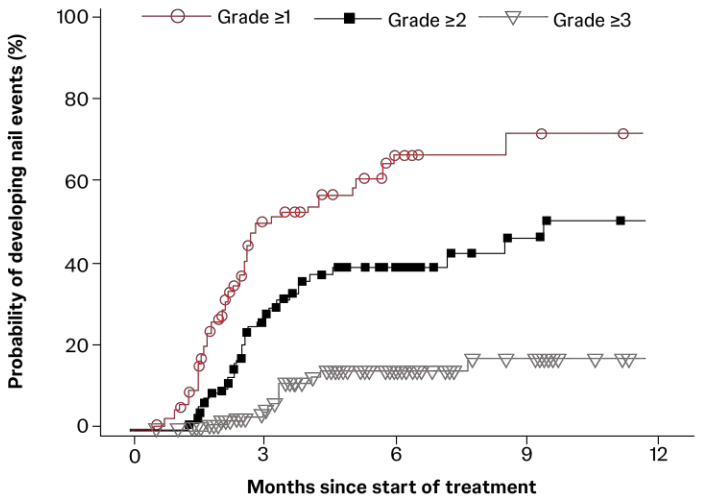
1. Subbiah V and Verstovsek S. Cell Rep Med. 2023;4:101204.

Most retinopathies, skin, and nail AEs occur early during erdafitinib treatment[1]



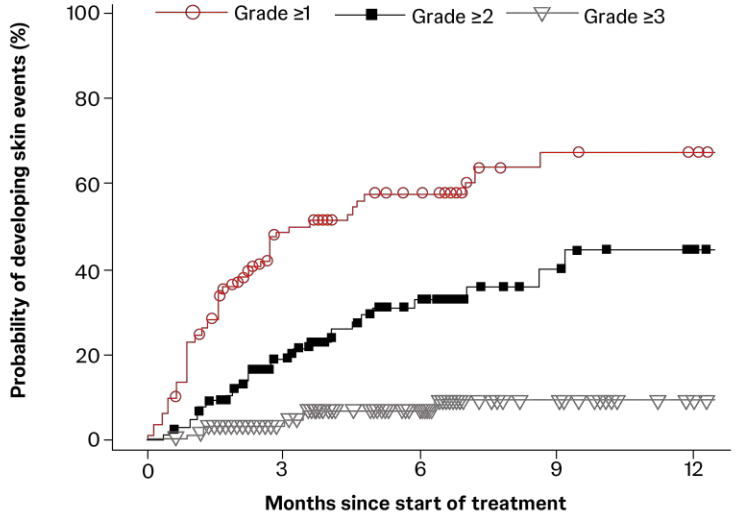
Number at risk

Grade ≥1	101	67	41	26	19
Grade ≥2	101	74	47	29	19
Grade ≥3	101	80	53	30	20



Number at risk

Grade ≥1	101	37	17	5	3
Grade ≥2	101	58	29	13	8
Grade ≥3	101	79	46	23	15



Number at risk

Grade ≥1	101	37	21	8	7
Grade ≥2	101	64	36	15	10
Grade ≥3	101	79	53	27	18

Figures adapted from Siefker-Radtke et al. 2023.[1]

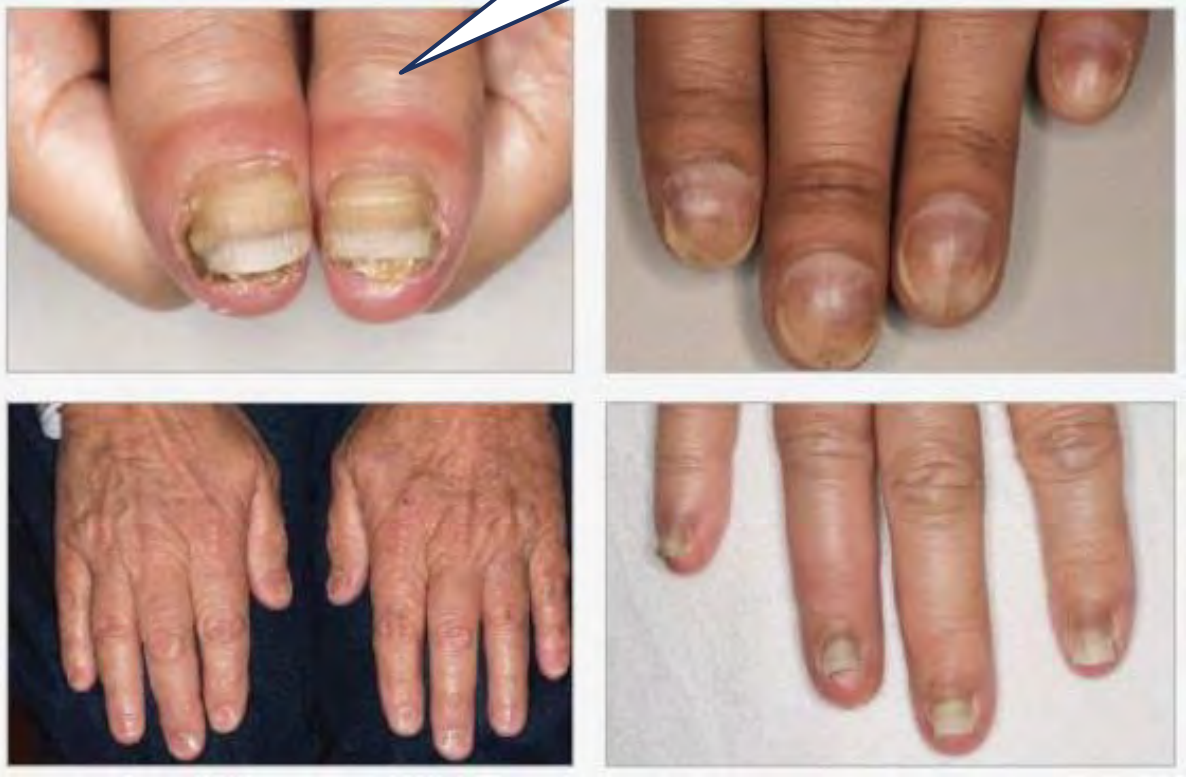
AEs, adverse events; CSR, central serous retinopathy.

1. Siefker-Radtke, AO et al. Eur Urol Open Sci. 2023;16:1–9.

Frequent AEs on *FGFRi* treatment[1]

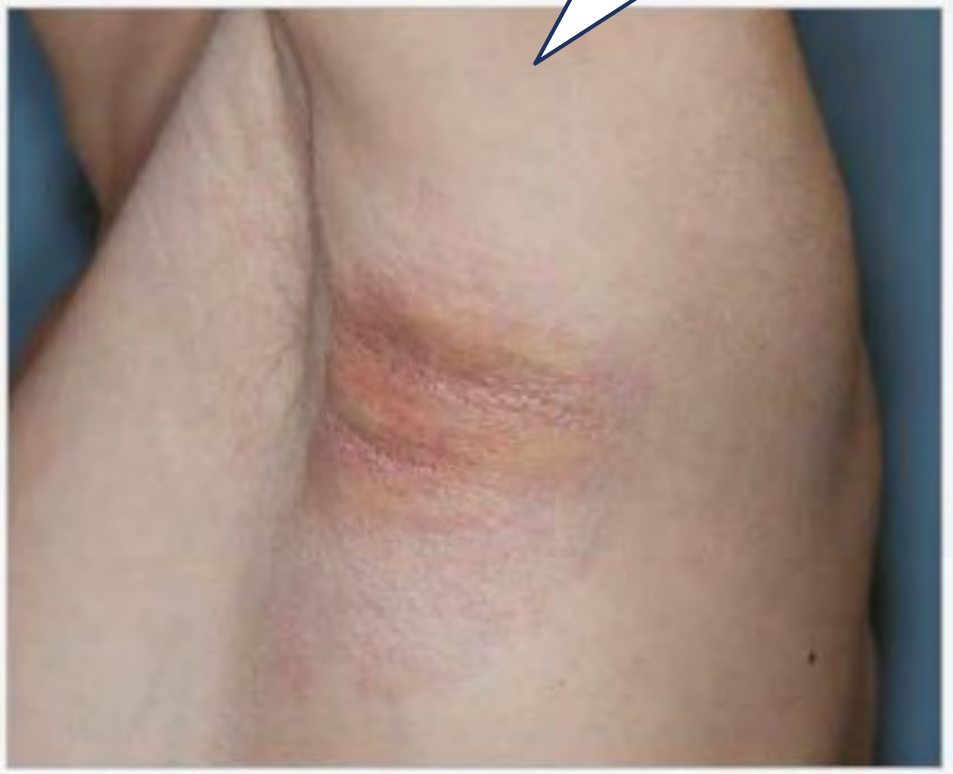
Inform, intensify nail care, avoid exacerbating factors

Nail changes

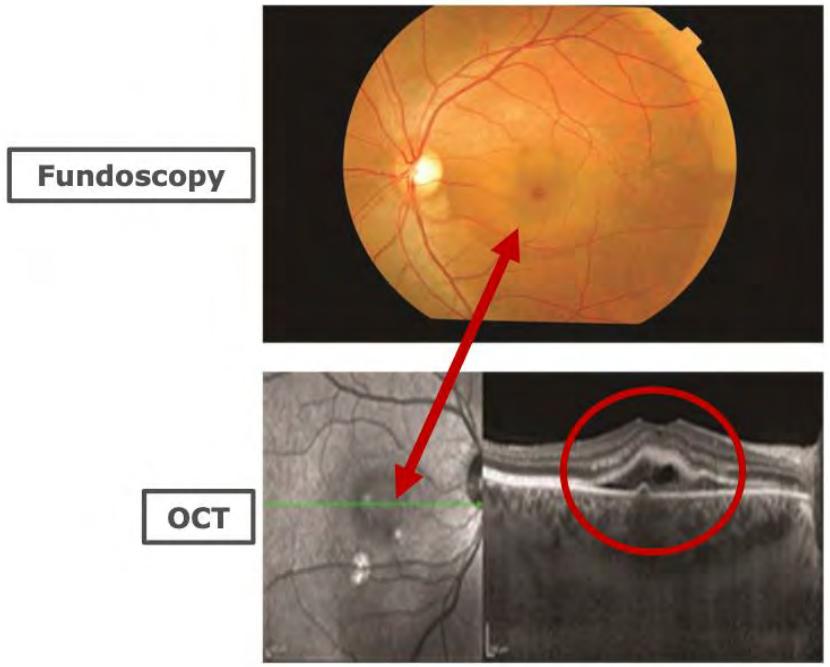


Optimise phosphate metabolism

Axillary calcification



Central serous retinopathy (CSR)[1]



- Acute CSR
  - Typically self-limiting process
- Recovery
  - Recovery of visual acuity typically occurs within 1–4 months
  - Coincides with reattachment of the neurosensory retina
- Management
  - Observation is the standard initial management to induce reattachment of the neurosensory retina
  - Active management may be warranted if the duration is more than 4–6 months or a second episode follows a complete resolution of the first one
  - Surgical interventions includes photodynamic therapy or subthreshold micropulse laser treatment

CSR, central serous retinopathy; OCT, optical coherence tomography.

1. BALVERSA™ (erdafitinib) –Ocular Toxicities: Overview, Screening and Management. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File. 2020.

CSR management[1,2]

Incidence	Onset	Dosing Modifications	Treatment Discontinuation
CSR, n (%): Any Grade: 21 (21) **Grade ≥3:** 3 (3)	CSR, n (%): Any Grade: 53 days **Grade ≥3:** 87 days	CSR, n (%): Dose reduction: 13 (13) Dose interruption: 8 (8)	CSR, n (%): Discontinuation: 3 (3)
Non-CSR Ocular Events, n (%): Any Grade: 51 (52) **Grade ≥3:** 5 (5)	Other Eye Disorders, median onset: Any Grade: 50 days **Grade ≥3:** 162 days	Other Eye Disorders†, n (%): Dose reduction: 12 (12) Dose interruption: 8 (8)	Other Eye Disorders†, n (%): Discontinuation: 3 (3)

*Safety population include 87 patients previously treated with chemotherapy and an additional 12 chemotherapy-naïve patients who were ineligible for cisplatin-based therapy.[2]

†Other eye disorders occurring in ≥10% of patients included dry eye, blurred vision, conjunctivitis and increased lacrimation. [2]

CSR, central serous retinopathy.

1. Loriot, Y et al. N Engl J Med. 2019;381(4):338–348. 2. BALVERSA™ (erdafitinib) –Ocular Toxicities: Overview, Screening and Management. Clinical Study Report, Janssen Research and Development. Protocol 42756493BLC2001; Phase 2: Study on File. 2020.

CSR management on Erdafitinib[1]

Adverse reaction	Dose modification
Central serous retinopathy (CSR)/retinal pigment epithelial detachment (RPED)	
Grade 1: asymptomatic; clinical, or diagnostic observations only	Withhold erdafitinib until resolution. Resume at 1 dose lower if CSR/RPED resolves within 4 weeks. Consider re-escalating dose if no CSR/RPED recurrence for a month. If CSR/RPED remains stable for 2 consecutive eye exams but has not resolved, then resume erdafitinib at the next lower dose level.
Grade 2: visual acuity 20/40 or better or ≤3 lines of decreased vision from baseline	Withhold erdafitinib until resolution. May resume at 1 dose lower if CSR/RPED resolves within 4 weeks.
Grade 3: visual acuity worse than 20/40 or >3 lines of decreased vision from baseline	Withhold erdafitinib until resolution. May resume at 2 dose lower if CSR/RPED resolves within 4 weeks. Consider permanent discontinuation if CSR/RPED recurs.
Grade 4: visual acuity 20/200 or worse in the affected eye	Permanently discontinue erdafitinib.
Other adverse reactions	
Grade 3	Withhold erdafitinib until resolution to grade 1 or baseline. Then, erdafitinib, may be resumed at 1 dose level lower.
Grade 4	Permanently discontinue erdafitinib.

CSR, central serous retinopathy; RPED, retinal pigment epithelial detachment.

1. Subbiah V and Verstovsek S. Cell Rep Med. 2023;4(10):101204.

Take-home messages[1,2]

- Education
- Early intervention
- MDT involvement
- Dose modifications

ESMO WEBINARS

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