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INTERNATIONAL BLADDER CANCER GROUP

How I Treat Metastatic Bladder Cancer in 2023

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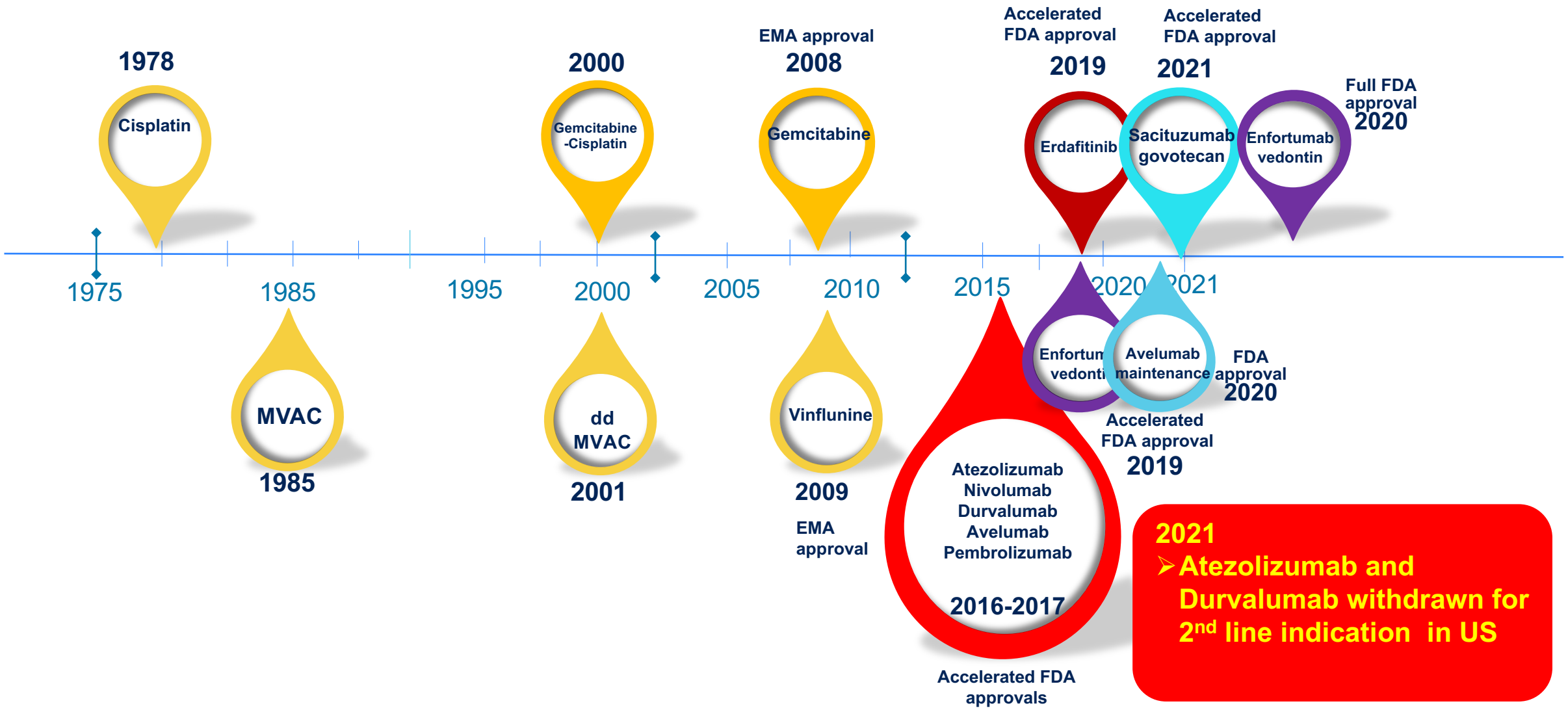
August 19, 2023

@shilpaonc

Therapy Advances in Advanced UC



2021

- **Atezolizumab and Durvalumab withdrawn for 2nd line indication in US**

First-line (IL) treatment of metastatic urothelial carcinoma (mUC)

Platinums are the backbone of 1L therapy in aUC

- Gemcitabine-Cisplatin (GC): Median OS ~ 14 months, ORR 49%
- ddMVAC: Median OS ~ 15 months, ORR 70%
- Gemcitabine-Carboplatin: Recent Trials show median OS~ 13 months ORR 43%
- Only a minority of patients receive 2nd-line therapy for mUC
- An unmet need to improve survival with 1st-line treatment

Von der Maase H et al. JCO 2005 Sternberg CN Eur J Cancer 2006, Galsky MD Lancet 2020, Flannery K et al. Future Oncol 2019, Powles T ASC) GU 2021

Is there a role for 1L Chemo-immunotherapy in mUC?

Keynote-361	IMvigor 130	NILE	Checkmate-901
Pembrolizumab + Chemo	Atezolizumab + Chemo	Durvalumab + Chemo	Nivolumab + Chemo
Pembrolizumab	Atezolizumab	Durvalumab Tremilimumab + Chemo	Nivolumab Ipilimumab Chemo
Chemo	Chemo	Chemo	Chemo
Negative for OS and PFS	Marginal PFS improvement	Ongoing	Results awaited

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Pembrolizumab alone or combined with chemotherapy vs chemotherapy alone as 1L therapy for la/mUC: KN-361

KEYNOTE-361 Study Design (NCT02853305)

Key Eligibility Criteria
- UC of renal pelvis, ureter, bladder or urethra
- Locally advanced unresectable or metastatic disease
- No prior systemic therapy for advanced disease
- ECOG PS 0, 1 or 2
- Tissue sample for PD-L1 assessment[a]

Stratification Factors
- PD-L1 expression[a] (CPS ≥10 vs <10)
- Choice of platinum

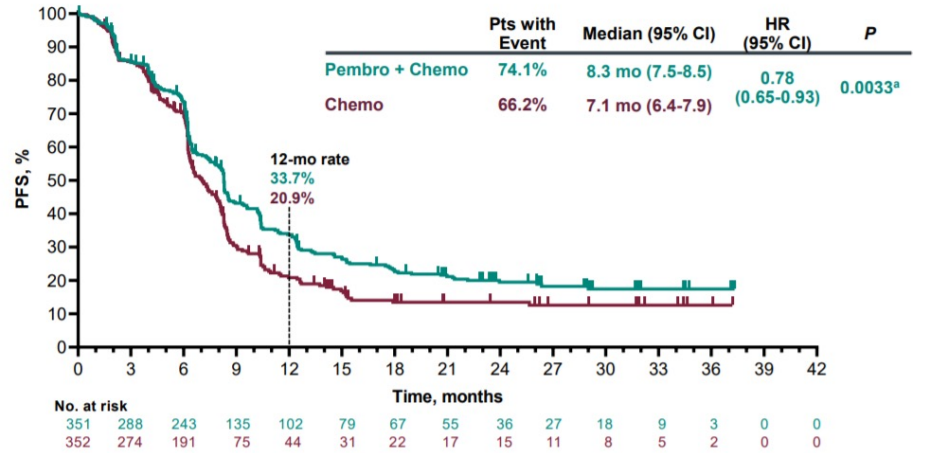
R (1:1:1)

- Pembrolizumab 200 mg Q3W + Gemcitabine 1000 mg/m² + Cisplatin 70 mg/m² *OR* Carboplatin AUC 5 for ≤6 cycles → Pembrolizumab 200 mg Q3W for ≤29 cycles
- Pembrolizumab 200 mg Q3W for ≤35 cycles
- Gemcitabine 1000 mg/m² on days 1 and 8 Q3W + Cisplatin 70 mg/m² *OR* Carboplatin AUC 5 on day 1 Q3W for ≤6 cycles

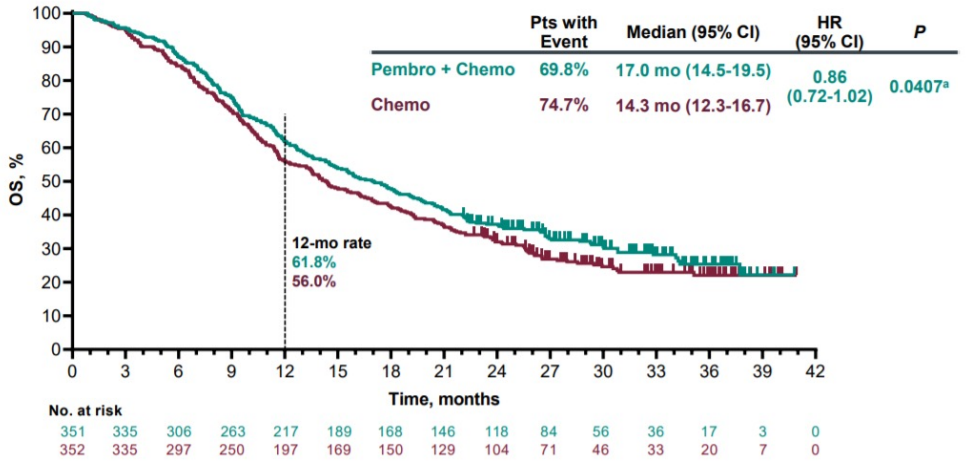
- Dual primary endpoints: PFS per RECIST v1.1 by BICR and OS
- Secondary endpoints: ORR, DCR, and DOR by BICR per RECIST v1.1, safety

N=1010

PFS by BICR: Pembro + Chemo vs Chemo, ITT Population (Primary Endpoint)



OS: Pembro + Chemo vs Chemo, ITT Population



Ajjai Alva ESMO 2020, Powles T et al. Lancet 2021

1L Atezolizumab with or without chemotherapy in IamUC (IMvigor130)

IMvigor130 study design

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

Arm A
Atezo + plt/gem

Arm B
Atezo monotherapy

Arm C
Placebo + plt/gem

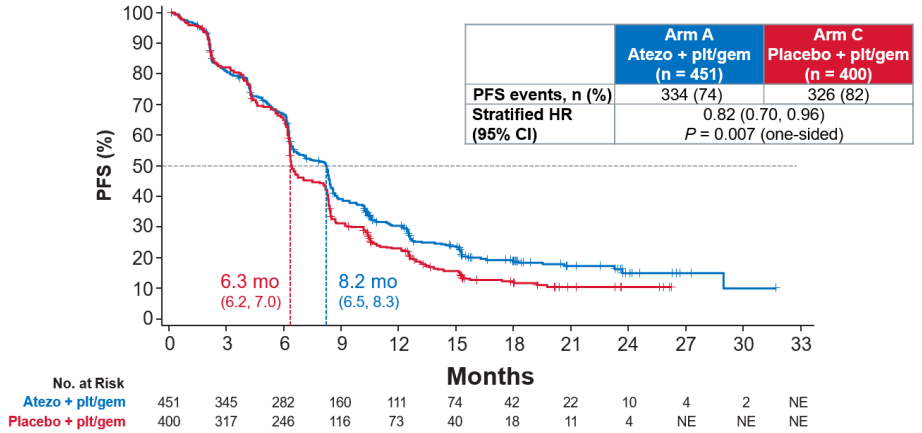
Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

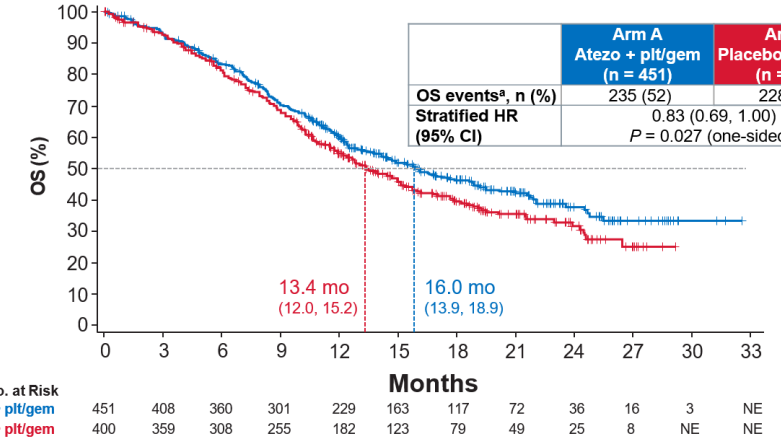
[a] per RECIST 1.1.

Final PFS: ITT (Arm A vs Arm C)



	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)	

Interim OS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

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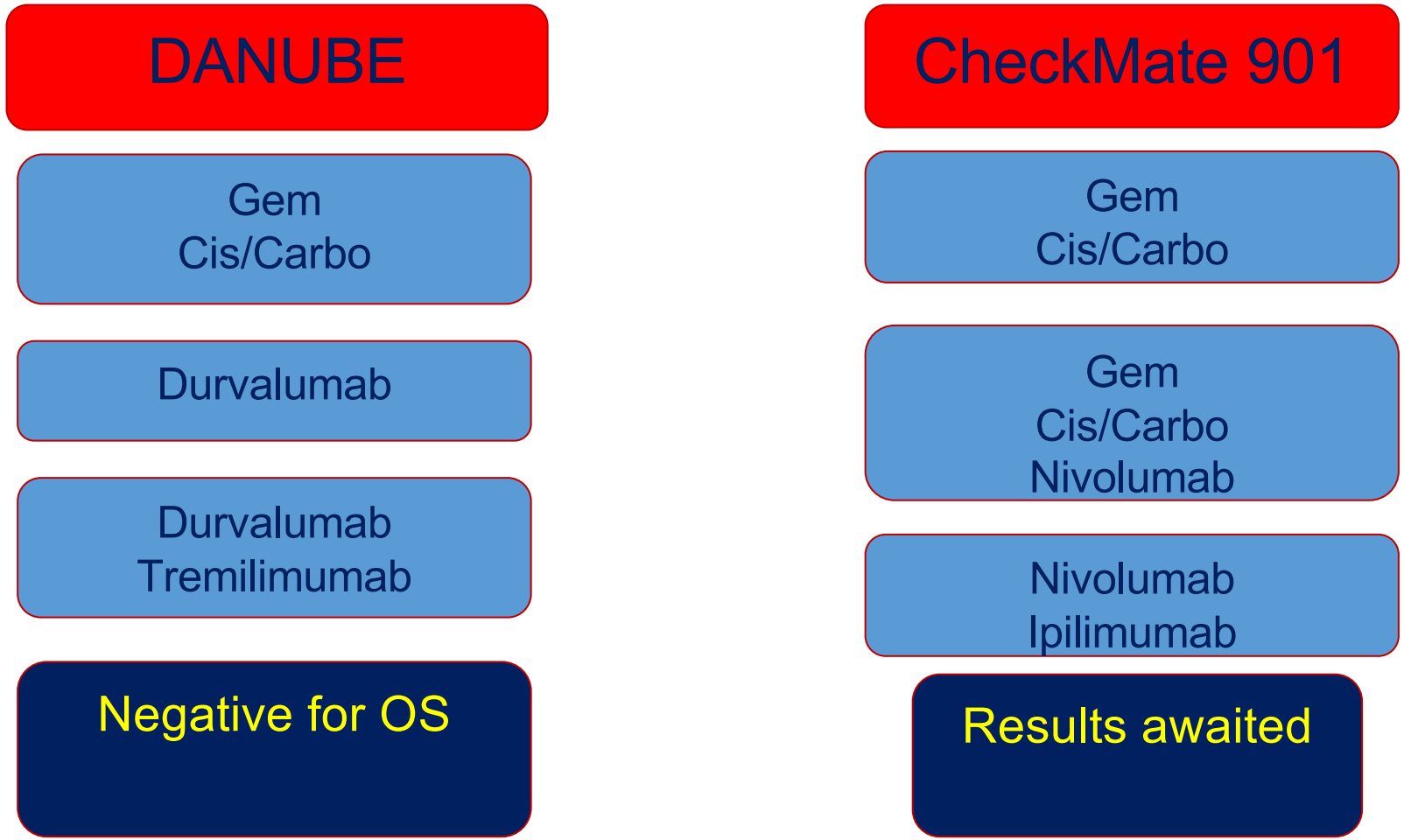
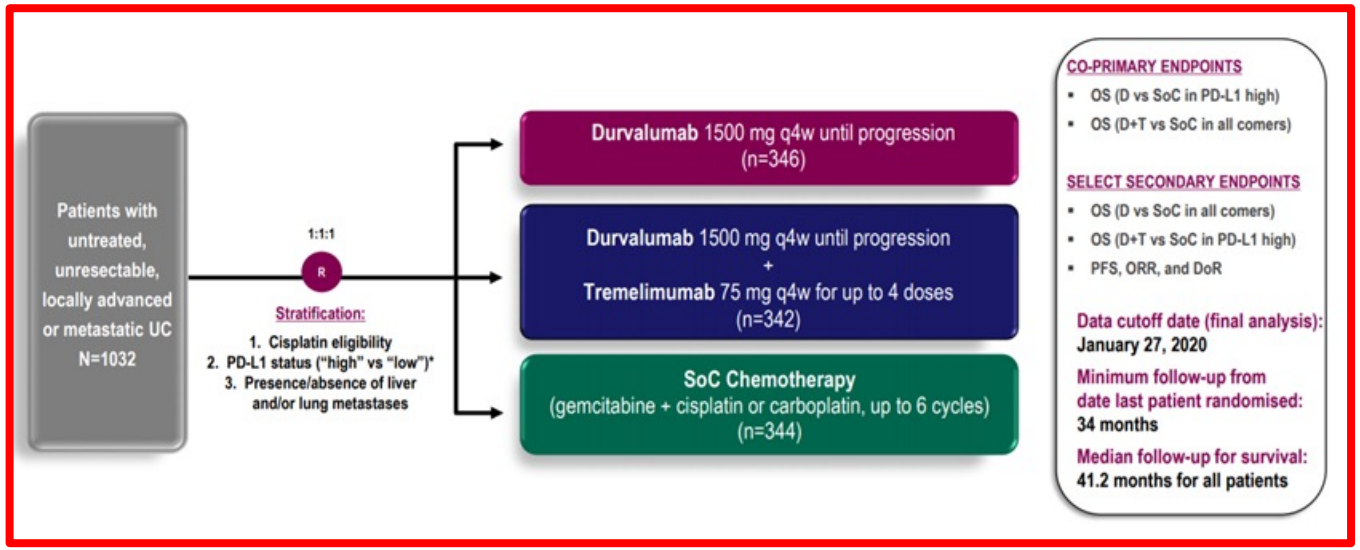
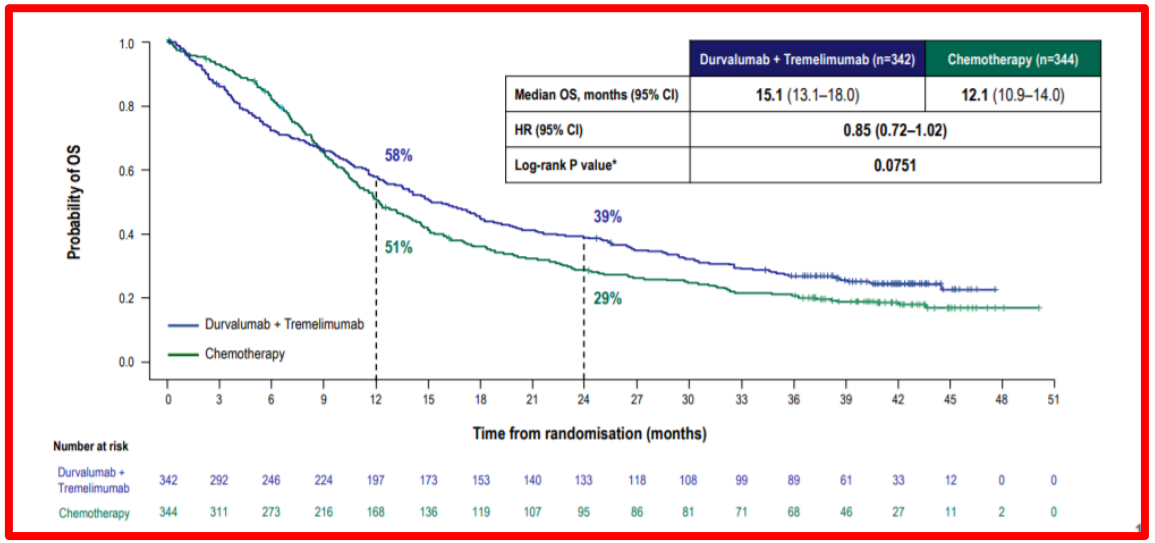
Galsky MD et et al. Lancet Oncology 2020

Is there a role for 1L Immunotherapy doublets in mUC?



1L durvalumab with or without tremelimumab vs SOC chemotherapy in patients with aUC (DANUBE)





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Powles T et al. *Lancet*. 2020

Evolution of First-Line Therapy in Cisplatin-Ineligible mUC

De Santis M et al. JCO 2021
.Balar AV Lancet 2017
Balar AV et al. Lancet 2017
Powles T et al. NEJM 2020

KEYNOTE-361: Pembro vs Choice of Carbo Patients

Response Rates and Disease Control Rates Lower with Pembro compared to Carbo-Gem

Total Patients

Confirmed Response	Pembro N = 170	Carbo + Gem N = 196
ORR (95% CI)	**27.6% (21.1–35.0)**	**41.8% (34.8–49.1)**
DCR (95% CI)	**45.3% (37.7–53.1)**	**73.5% (66.7–79.5)**
CR	10.0%	10.7%
PR	17.6%	31.1%
SD	17.6%	31.6%
PD	37.6%	11.7%
Non-CR/non-PD	2.9%	5.1%
Non-evaluable or no assessment	14.1%	9.7%

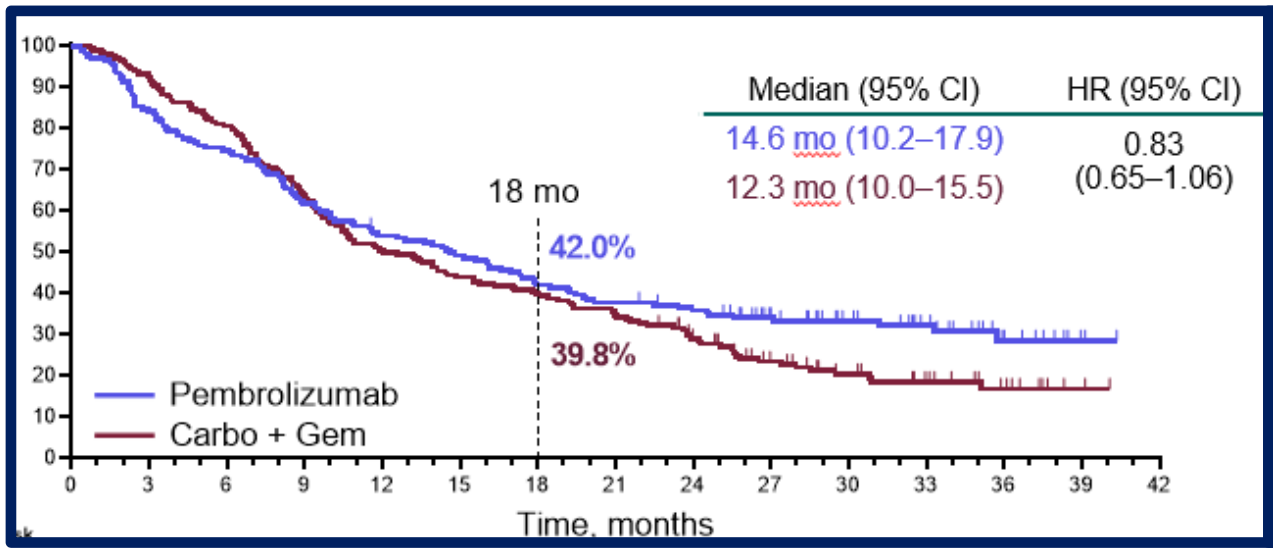
CPS ≥10

Confirmed Response	Pembro N = 84	Carbo + Gem N = 89
ORR (95% CI)	**29.8% (20.3–40.7)**	**46.1% (35.4–57.0)**
DCR (95% CI)	**48.8% (37.7–60.0)**	**73.0% (62.6–81.9)**
CR	11.9%	18.0%
PR	17.9%	28.1%
SD	19.0%	27.0%
PD	36.9%	7.9%
Non-CR/non-PD	1.2%	5.6%
Non-evaluable or no assessment	13.1%	13.5%

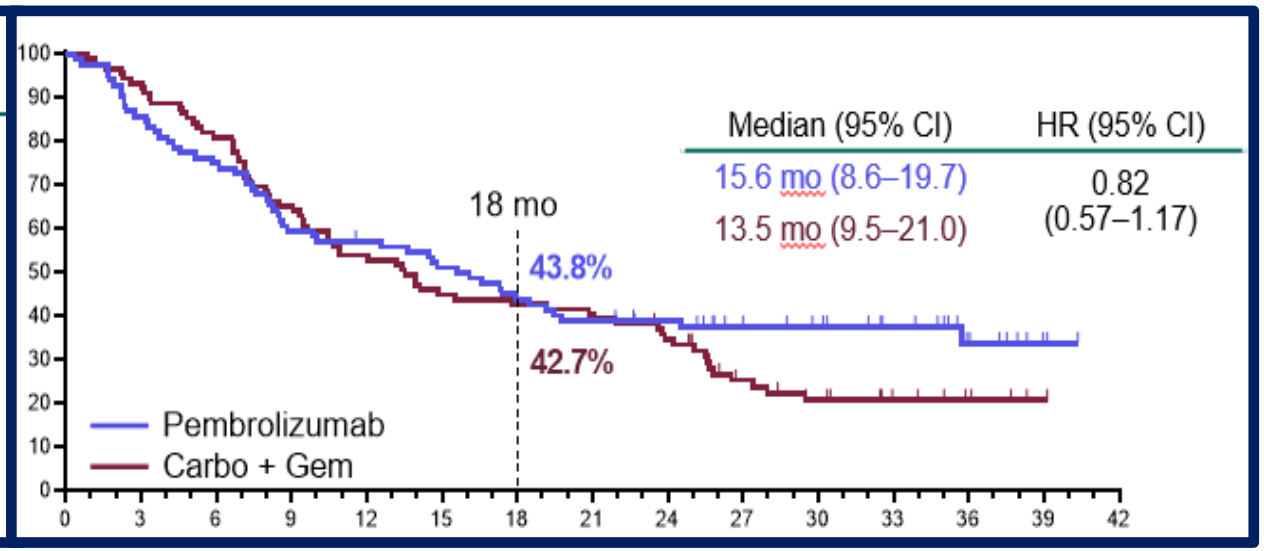
KEYNOTE-361: Pembro vs Choice of Carbo Patients

OS for Pembro cathes up but DOES NOT cross significantly enough for a positive trial

Total Patients



CPS ≥10



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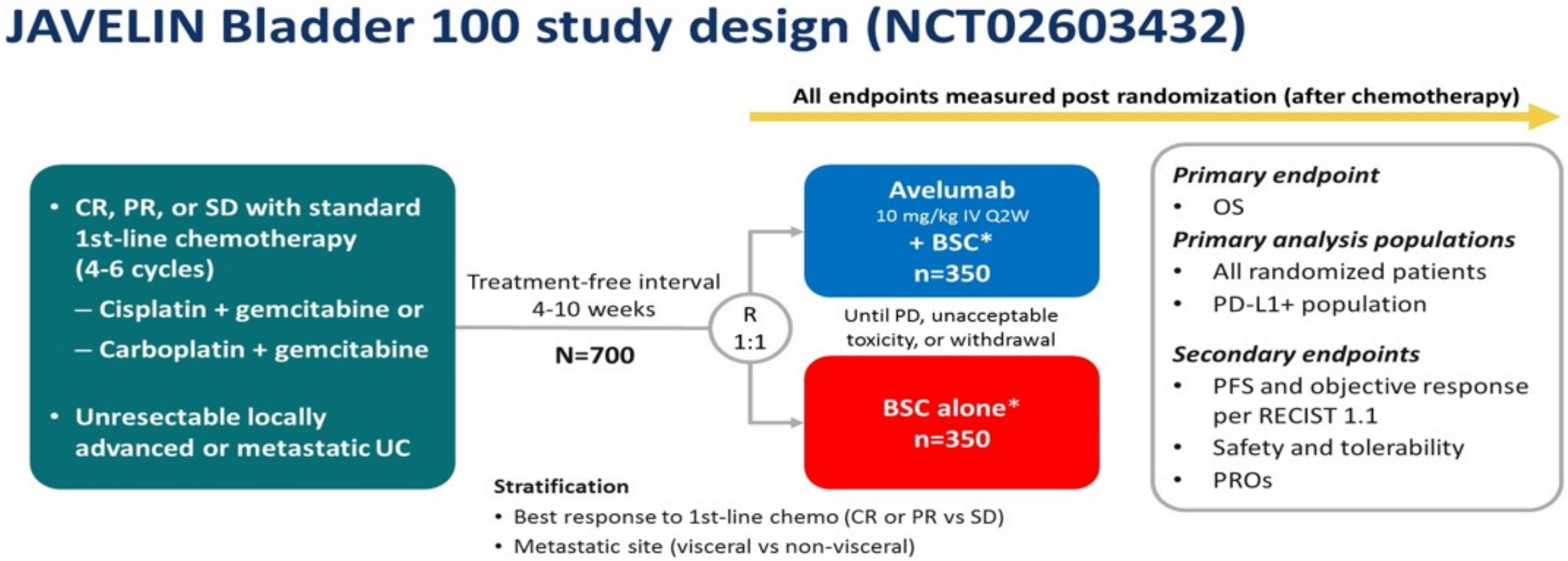
1L combination chemo-immunotherapy does **not** improve OS compared to chemotherapy alone in patients with aUC

1L immunotherapy is **not** better than gemcitabine-carboplatin in cisplatin-ineligible patients with aUC

But…..switch maintenance Immunotherapy after 1L platinum chemotherapy approach is effective in aUC

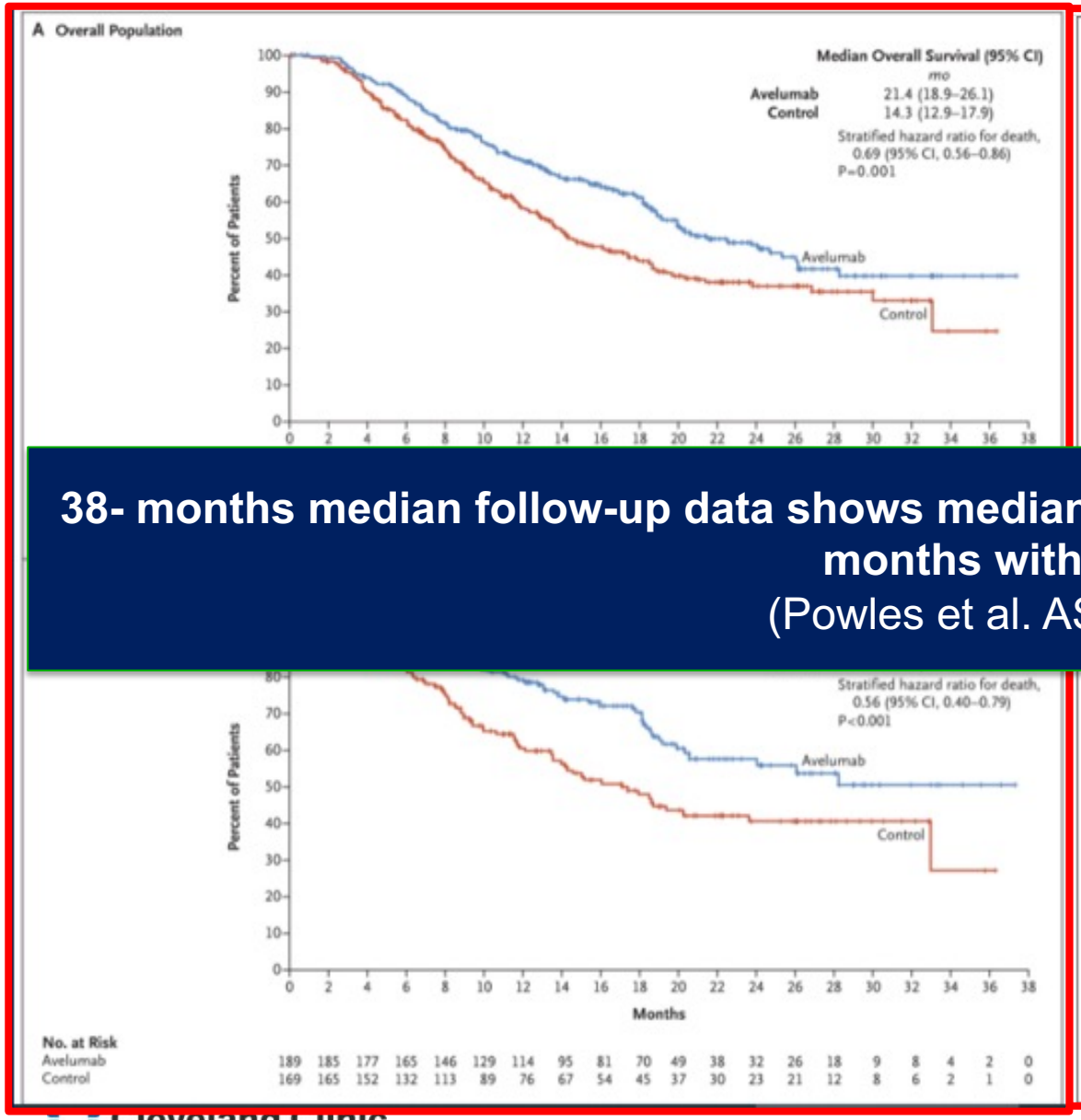
JAVELIN Bladder 100- “Switch Maintenance” Strategy After 1L platinum-based chemotherapy

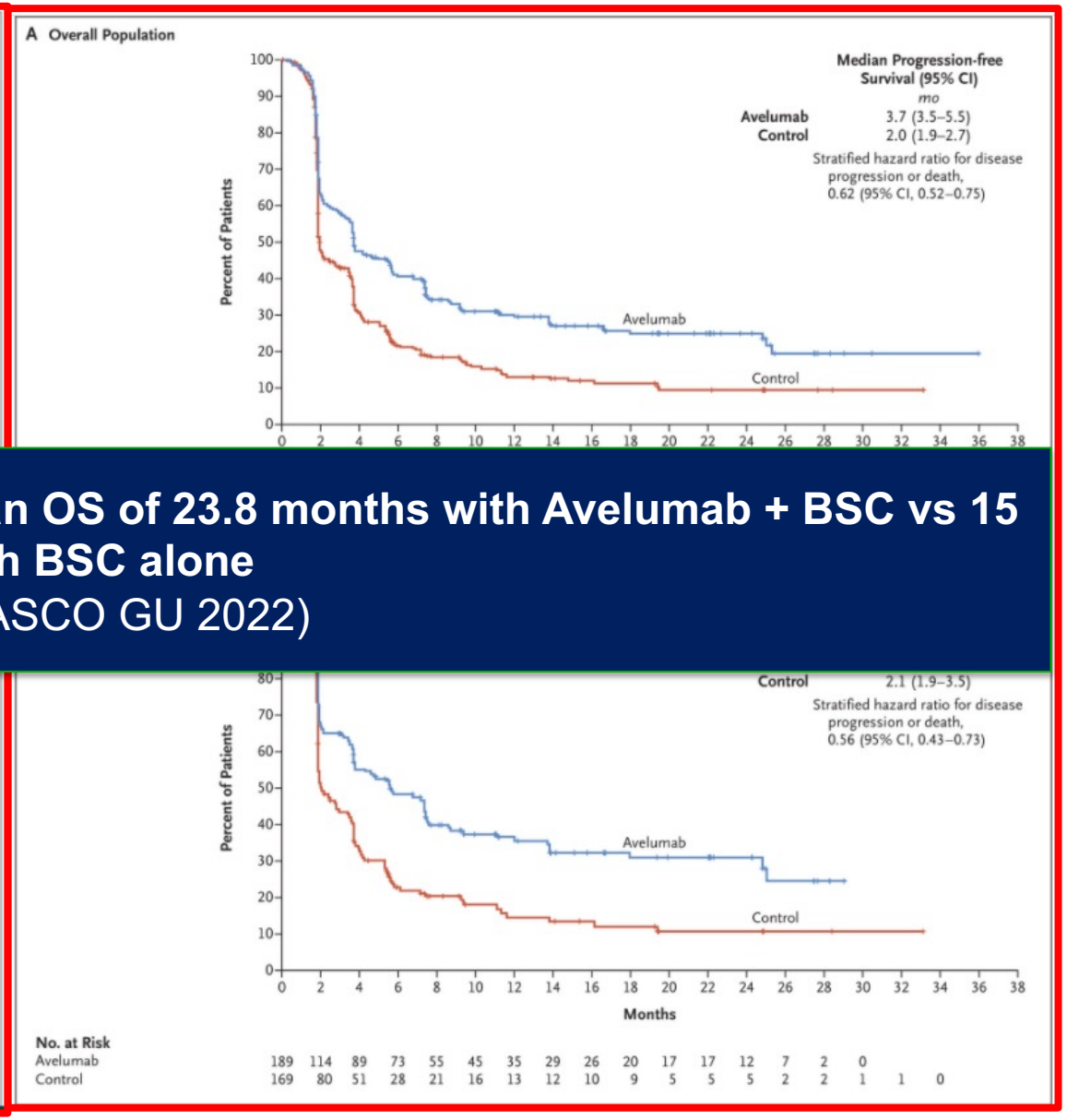


PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

Thomas Powles et al. NEJM 2020

Maintenance avelumab improves OS and PFS





38- months median follow-up data shows median OS of 23.8 months with Avelumab + BSC vs 15 months with BSC alone
(Powles et al. ASCO GU 2022)

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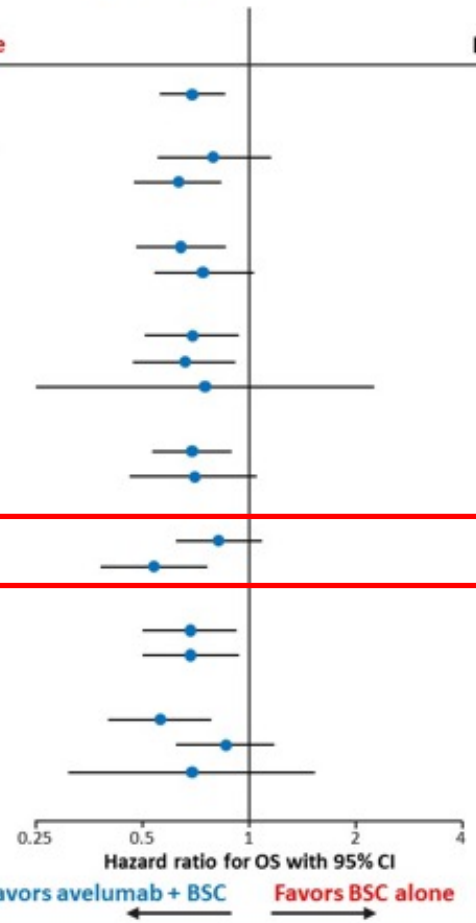
Thomas Powles et al. NEJM 2020

Subgroup analysis of OS in the overall population

Subgroup		Events/patients, n: Avelumab + BSC	Events/patients, n: BSC alone	Hazard ratio (95% CI)
All patients		145/350	179/350	**0.69** (0.56, 0.86)*
Age	<65 years	61/129	53/107	**0.79** (0.55, 1.15)
	≥65 years	84/221	126/243	**0.63** (0.47, 0.83)
ECOG PS score	0	77/213	101/211	**0.64** (0.48, 0.86)
	≥1	68/137	78/139	**0.74** (0.54, 1.03)
1st-line chemotherapy regimen	Gemcitabine + cisplatin	71/183	98/206	**0.69** (0.51, 0.94)
	Gemcitabine + carboplatin	68/147	73/122	**0.66** (0.47, 0.91)
	Gemcitabine + cisplatin/carboplatin	6/20	7/20	**0.75** (0.25, 2.25)
Best response to 1st-line chemotherapy	CR or PR	104/253	127/252	**0.69** (0.53, 0.89)
	SD	41/97	52/98	**0.70** (0.46, 1.05)
Site of baseline metastasis	Visceral	93/191	101/191	**0.82** (0.62, 1.09)
	Nonvisceral	52/159	78/159	**0.54** (0.38, 0.76)
Creatinine clearance	≥60 mL/min	74/181	97/196	**0.68** (0.50, 0.92)
	<60 mL/min	71/168	81/148	**0.68** (0.50, 0.94)
PD-L1 status	Positive	61/189	82/169	**0.56** (0.40, 0.78)
	Negative	76/139	72/132	**0.86** (0.62, 1.18)
	Unknown	8/22	25/49	**0.69** (0.31, 1.53)



Error bars show 95% CI
*Stratified (all other analyses are unstratified)

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Powles T et al. NEJM 2020

A032001: MAINCAV- Phase III randomized trial of maintenance cabozantinib and avelumab vs maintenance avelumab after 1L platinum-based chemotherapy in patients with mUC (NCT05092958)

Patients with locally advanced/mUC, N3 only disease allowed

CR/PR/SD with standard 1st-line platinum-based chemotherapy (4-6 cycles)

Stratification:

- **Best response to 1st-line chemo (CR vs PR vs SD)**
- **Sites of metastases: visceral vs non-visceral**

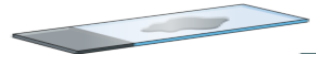
1:1

N = 654

Avelumab 800 mg IV q2 wk x 2 yrs

Cabozantinib 40 mg PO daily + Avelumab 800 mg IV q2 wk x2yrs

C1 D1 **C2 D1** **Progression/end of Tx**



RNAseq
WES
TCRseq
IHC multicolor
PBMC - Flow MDSC, etc

ctDNA
PBMC - Flow MDSC, etc
TCRseq
Cytokine/Chemokine assay

Primary endpoint: OS

Secondary endpoints: PFS, Safety, Tumor response, HRQOL

Study Chair: Shilpa Gupta

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Second-line therapy and beyond in aUC

Pembrolizumab is the preferred IO in patients with platinum-refractory la/mUC (KEYNOTE-045)

Initial efficacy was maintained at 2-, 3-, and 5-years follow-up

5-year follow-up	Pembrolizumab ITT n = 270	Chemotherapy ITT n = 272
ORR, % (95% CI)	21.9 (17.1-27.3)	11.0 (7.6-15.4)
Best response, n (%)		
CR	27 (10.0)	8 (2.9)
PR	32 (11.9)	22 (8.1)
SD	47 (17.4)	92 (33.8)
PD	129 (47.8)	90 (33.1)
NA[a]	31 (11.5)	51 (18.8)
NE[b]	4 (1.5)	9 (3.3)

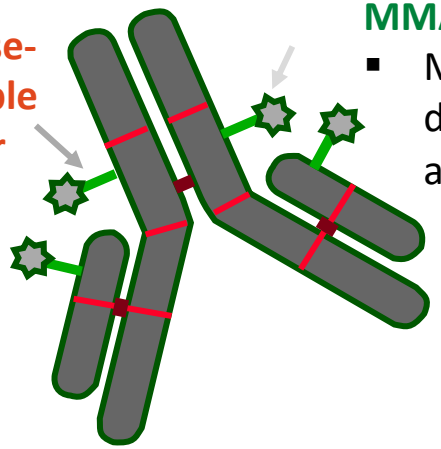
Pembrolizumab vs Investigator's choice chemotherapy
OS: 10.1 mo vs 7.2 mo
DOR: 29.7 mo vs 4.4 mo

Nivolumab and avelumab are also approved in this setting and are alternative options

Bellmunt J et al. N Engl Med. 2017;Fradet Y et al. Ann Oncol. 2019; Necchi A et al. Ann Oncol. 2019; Bellmunt J et al. ASCO 2021 Abstract 4532

Antibody–Drug Conjugates in Bladder Cancer

Enfortumab Vedotin



MMAE Payload

- Microtubule-disrupting agent

Fully Humanized Antibody

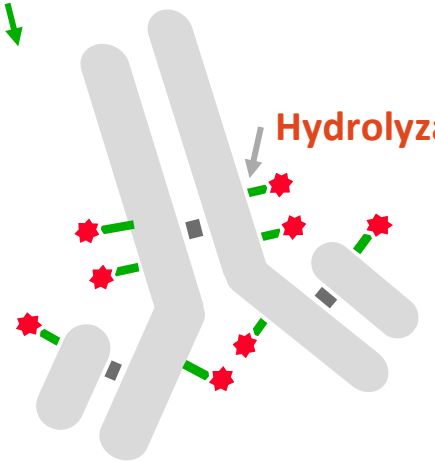
- Targets nectin-4, a transmembrane cell adhesion molecule highly expressed in mUC

- **FDA approval:** for adults with locally advanced or metastatic UC who have previously received a PD-1 or PD-L1 inhibitor and a platinum-containing CT or are ineligible for cisplatin-containing chemotherapy and have previously received 1 or more prior lines of therapy; **accelerated approval:** in combination with pembrolizumab for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy

Sacituzumab Govitecan

SN-38 Payload

- Active metabolite of irinotecan



Humanized RS7 Antibody

- Targets Trop-2, an epithelial cell surface antigen highly expressed in UC

- **Accelerated FDA approval:** for adults with locally advanced or metastatic UC who previously received a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor

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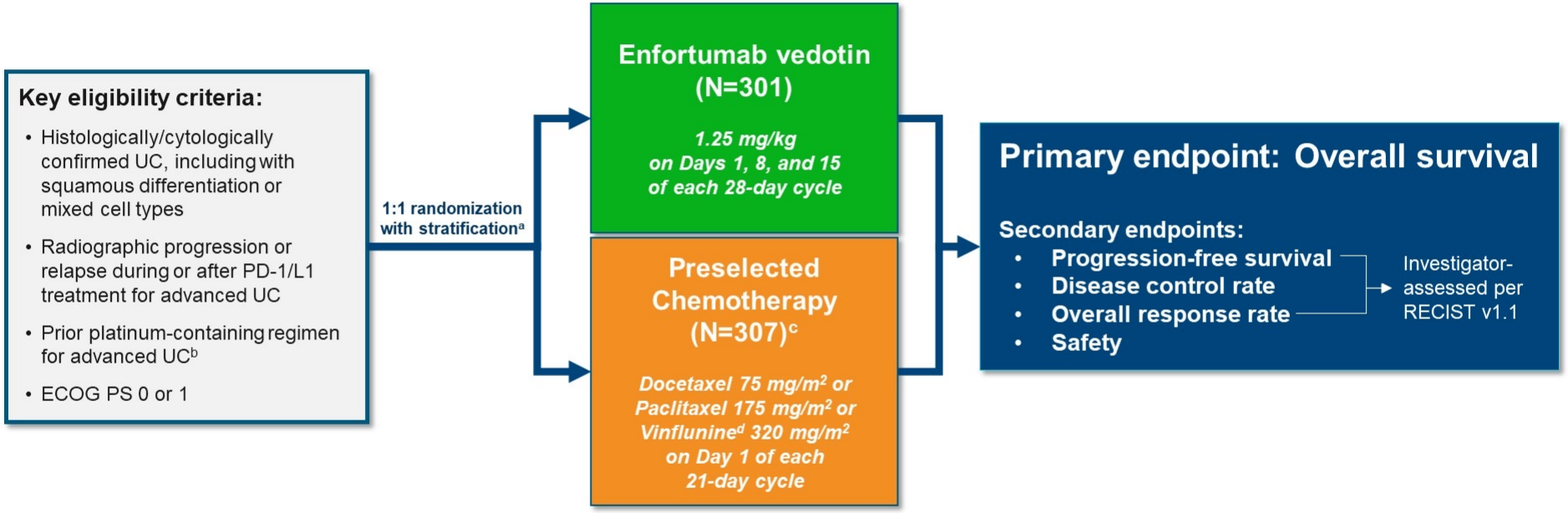
Samanta. Cell Mol Life Sci. 2015;72:645. Rosenberg. JCO. 2019;37:2592. Enfortumab vedotin PI. Sacituzumab govitecan PI. Avellini. Oncotarget. 2017;8:58642. Starodub. Clin Cancer Res. 2015;21:3870. Cardillo. Bioconjugate Chem. 2015;26:919.

Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

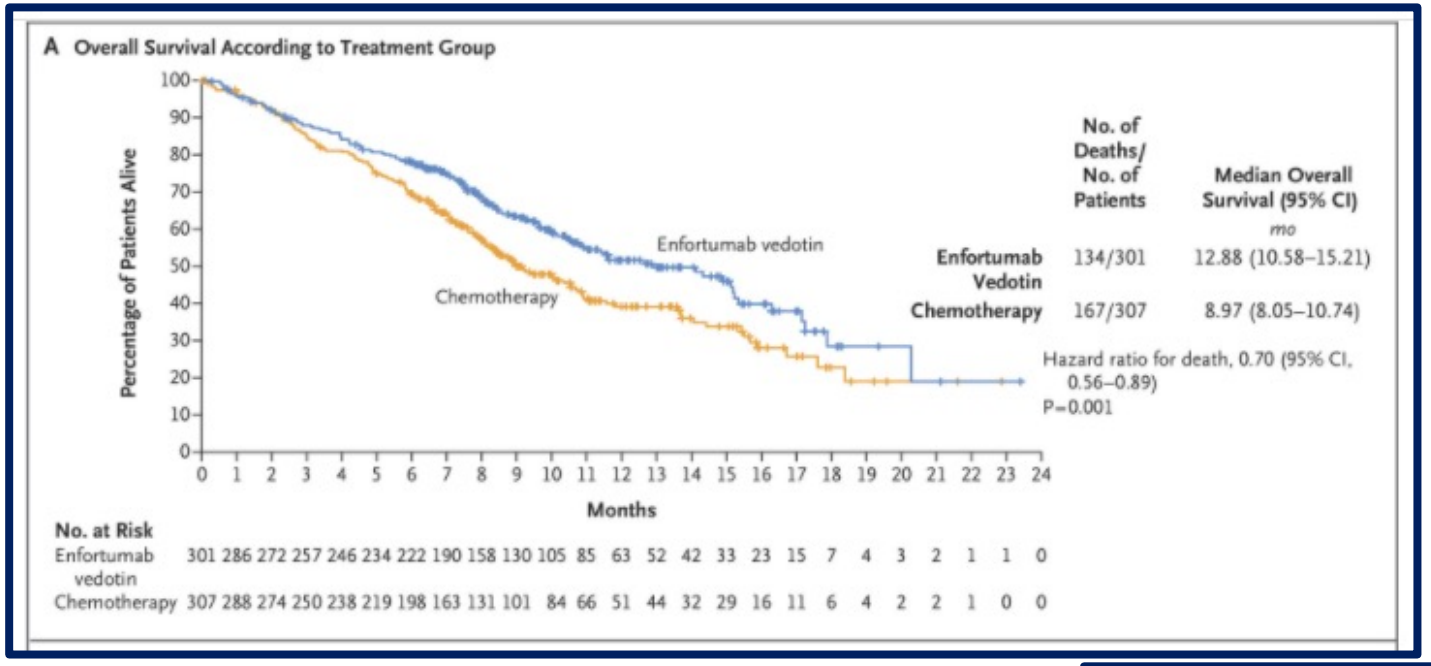
Thomas Powles, M.D., Jonathan E. Rosenberg, M.D., Guru P. Sonpavde, M.D., Yohann Loriot, M.D., Ph.D., Ignacio Durán, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Nobuaki Matsubara, M.D., Christof Vulsteke, M.D., Ph.D., Daniel Castellano, M.D., Chunzhang Wu, Ph.D., Mary Campbell, M.D., Maria Matsangou, M.B.,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

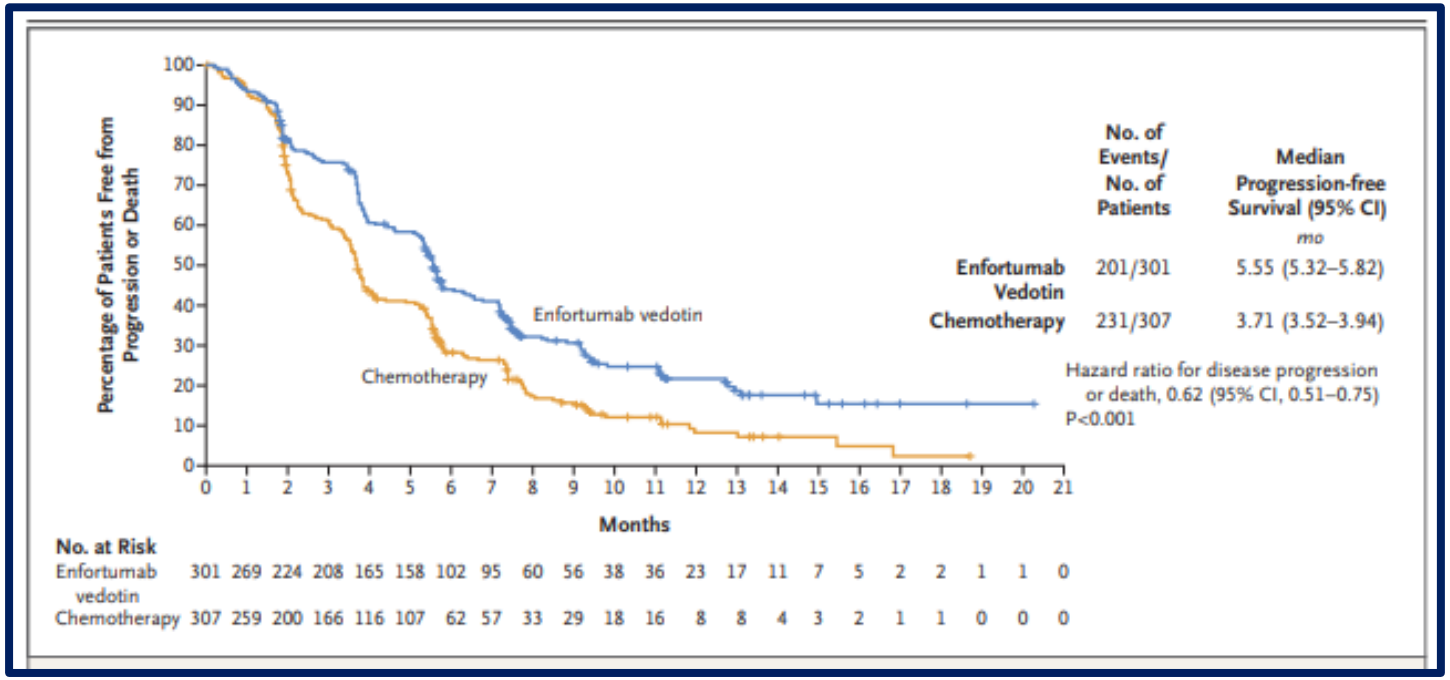
The NEW ENGLAND JOURNAL of MEDICINE

EV-301 Open-Label Phase 3 Trial Design



[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.





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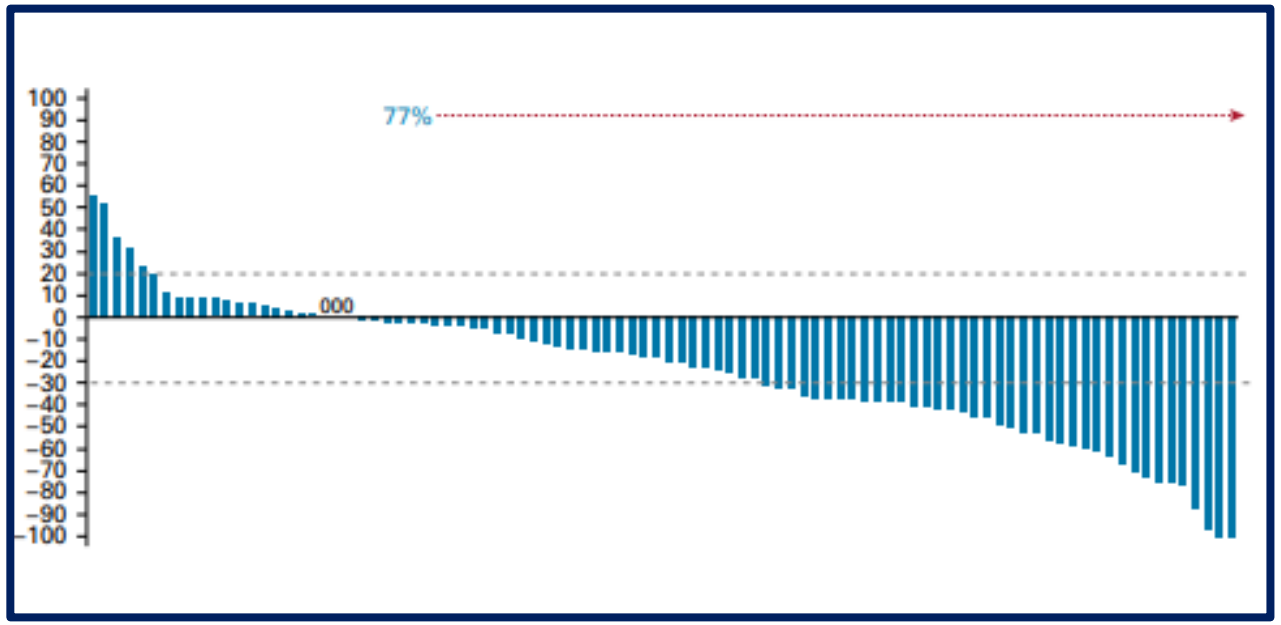
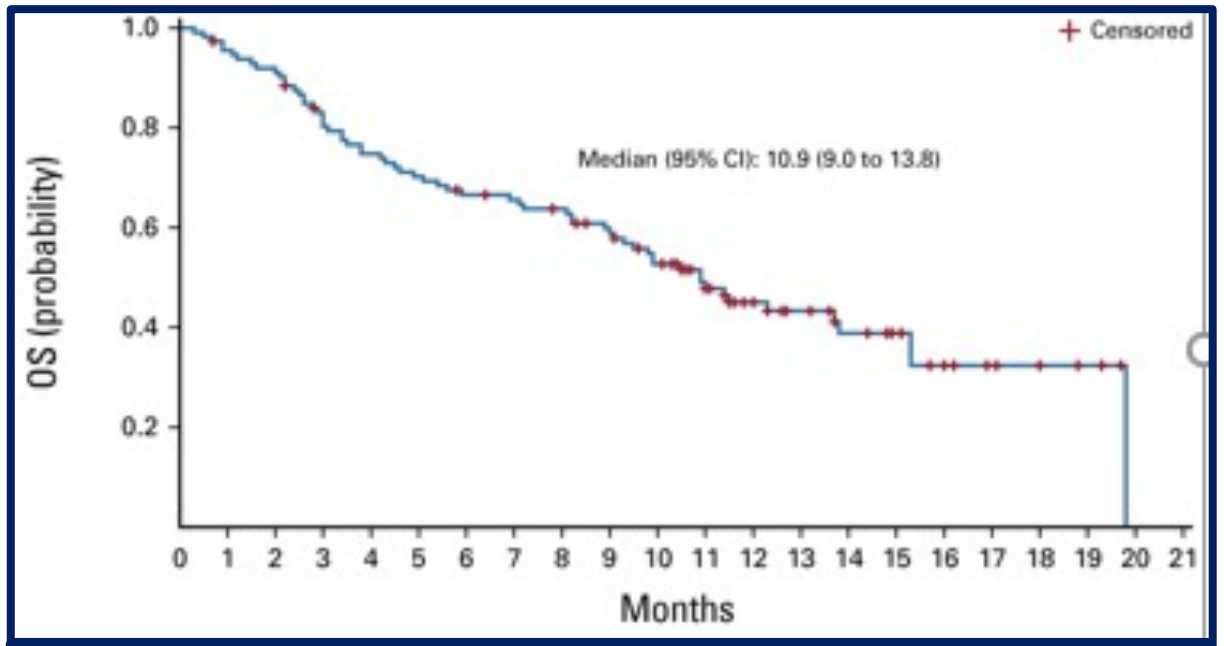
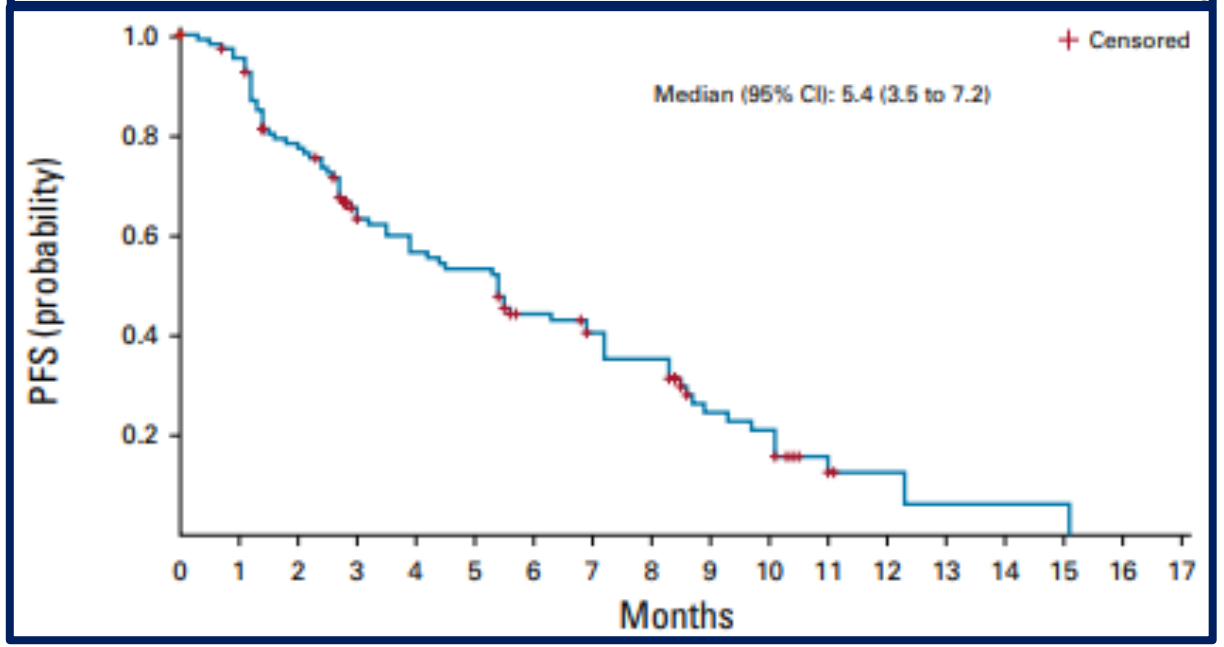
Powles T et al. NEJM 2021

TROPHY U-01: Phase II trial of SG in mUC after platinum-based regimen and/or IO







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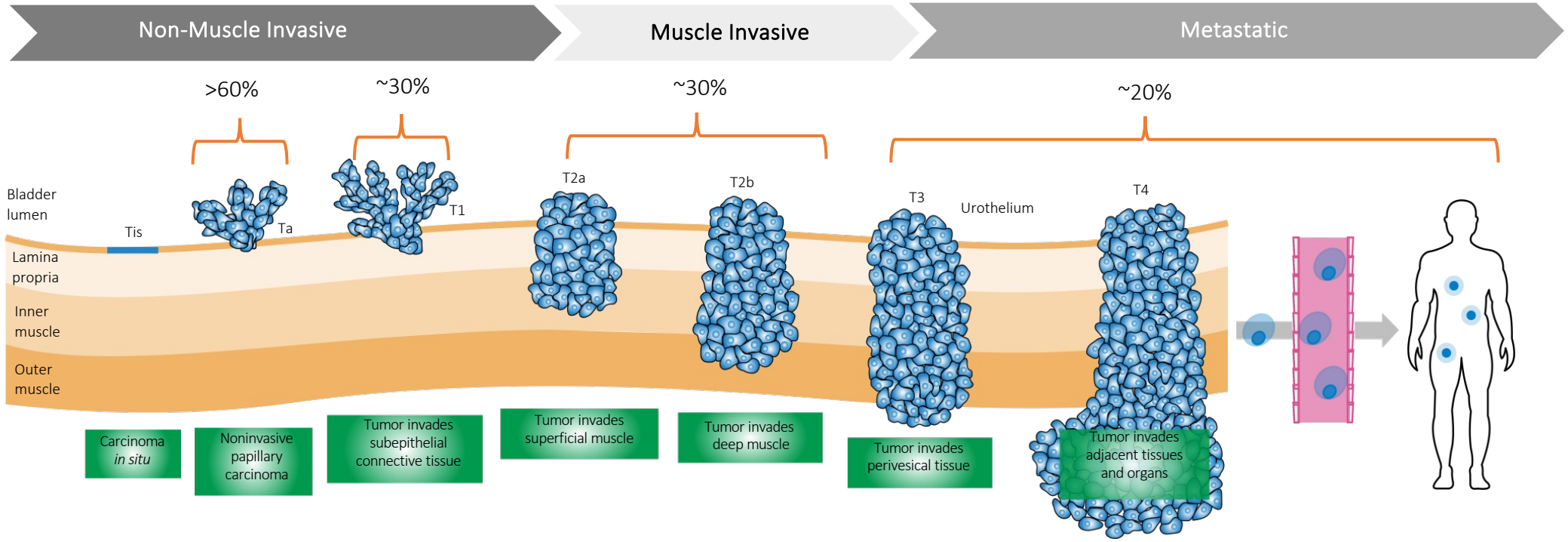
Tagawa S.T. et al. JCO 2021

Targeting FGFR in mUC



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Knowles MA et al. *Nat Rev Cancer*. 2015

Erdafitinib is a Pan-FGFR Inhibitor With Activity in Metastatic Urothelial Carcinoma

- ***FGFRalt*** are observed in **~20% of advanced or mUC** and may function as oncogenic drivers[1,2]

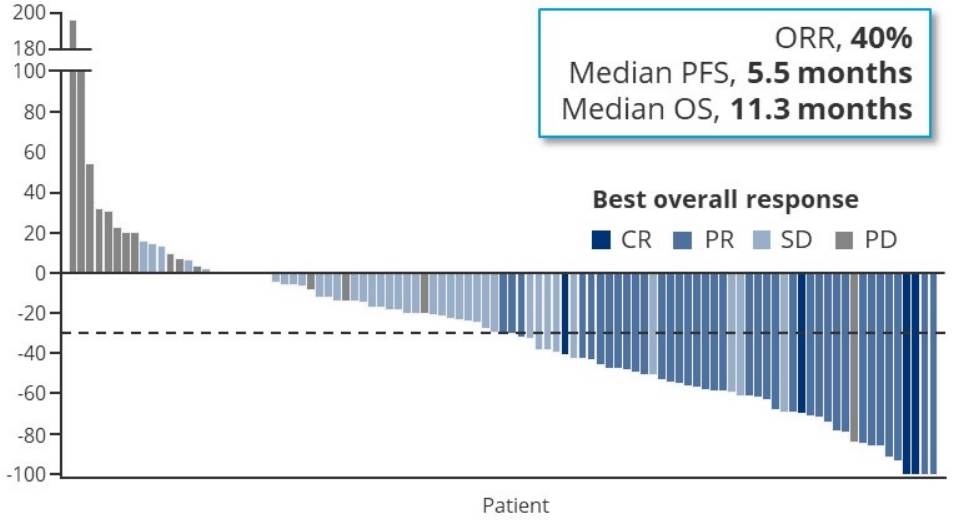
Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor[3]

  - Erdafitinib was granted accelerated approval in the United States and is approved in 17 other countries to treat locally advanced or mUC in adults with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemotherapy[4-6]

- **THOR** is a confirmatory, randomized phase 3 study:

  - Cohort 1 assessed whether erdafitinib improved survival over chemotherapy in patients with *FGFRalt* mUC who progressed on or after ≥1 prior treatment that included anti–PD-(L)1

In the single-arm phase 2 BLC2001 trial, erdafitinib showed a benefit in patients with *FGFR-altered* advanced urothelial cancer[4]



Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

FGFR, fibroblast growth factor receptor; *FGFRalt*, *FGFR* alterations; mUC, metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
[a]Patients received erdafitinib 8 mg/d with pharmacodynamically guided uptitration to 9 mg/d.

1. Necchi A, et al. *Eur Urol Focus*. 2019;5:853-586; 2. di Martino E, et al. *Future Oncol.* 2016;12:2243-2263; 3. Perera TPS, et al. *Mol Cancer Ther.* 2017;16:1010-1020; 4. Loriot Y, et al. *N Engl J Med.* 2019;381:338-348; 5. BALVERSA® (erdafitinib) [package insert]. Horsham, PA: Janssen Products, LP; 2023; 6. Siefker-Radtke AO, et al. *Lancet Oncol.* 2022;23:248-258.

Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Selected FGFR Aberrations

Cohort 1

Key eligibility criteria
- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed disease progression
- Prior tx with anti–PD-(L)1
- 1-2 lines of systemic tx
- Select *FGFR3/2alt* (mutation/fusion)[a]
- ECOG PS 0-2

1:1
N=266[b]
R

Erdafitinib
(n=136)
Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

Chemotherapy of Choice
(n=130)
docetaxel or vinflunine once every 3 weeks

Stratification factors: region (North America vs European Union vs rest of world), ECOG PS (0 or 1 vs 2), and disease distribution (presence vs absence of visceral [lung, liver, or bone] metastases)

Primary end point:
- OS

Key secondary end points:
- PFS
- ORR
- Safety

NCT03390504

[a]Molecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥1 of the following translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C.
[b]Number of patients randomized at the time of the interim analysis (data cutoff January 15, 2023).
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; *FGFR3/2alt*, *FGFR3/2* alterations; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.

Demographics and Disease Characteristics

Characteristic	Erdafitinib (n=136)	Chemotherapy (n=130)
Age, median (range), years	66 (32-85)	69 (35-86)
Men, n (%)	96 (70.6)	94 (72.3)
Race, n (%)		
White	81 (59.6)	63 (48.5)
Asian	37 (27.2)	40 (30.8)
Black or African American	0	1 (0.8)
Multiple	0	1 (0.8)
Not reported	18 (13.2)	25 (19.2)
Presence of visceral metastases, n (%)	101 (74.3)	97 (74.6)
Liver	31 (22.8)	38 (29.2)

Characteristic	Erdafitinib (n=136)	Chemotherapy (n=130)
ECOG PS 0-1, n (%)	124 (91.2)	117 (90)
Primary tumor upper tract, n (%)	41 (30.1)	48 (36.9)
PD-L1 low (CPS <10), n (%)	89 (92.7)[a]	68 (86.1)[a]
FGFRalt, n (%)[b]	(n=135)	(n=129)
Mutations	108 (79.4)	107 (82.3)
Fusions	25 (18.4)	19 (14.6)
Mutations and fusions	2 (1.5)	3 (2.3)
Prior lines of systemic therapy[c]		
1 line	45 (33.1)	33 (25.4)
2 lines	90 (66.2)	97 (74.6)

- Patient baseline characteristics were generally balanced between treatment arms

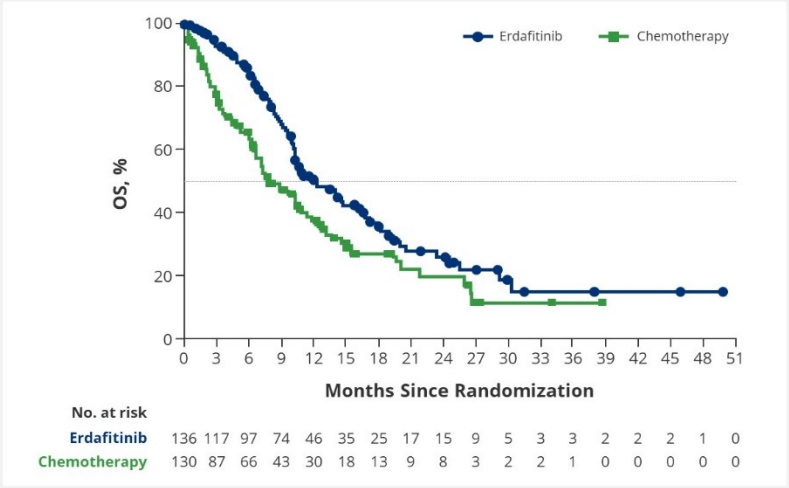
[a]For PD-L1 status, percentage is based on patients with available data (n=96 for erdafitinib and n=79 for chemotherapy).
[b]All patients enrolled had *FGFR3alt*. 2 patients were subsequently identified as false positives; they were included in the intent-to-treat population.
[c]1 patient in the erdafitinib group had 3 prior lines of systemic therapy.
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; *FGFRalt*, *FGFR* alterations; PD-L1, programmed death-ligand 1.

All Patients Enrolled in the Study Had Received Anti–PD-1 in the First- or Second-Line Setting

Patients receiving prior therapy, n (%)	Erdafitinib (n=136)[a]	Chemotherapy (n=130)
1 line of prior systemic therapy	**45 (33.1)**	**33 (25.4)**
Chemotherapy + anti–PD-(L)1[b]	33 (24.3)	15 (11.5)
Anti–PD-(L)1[c]	11 (8.1)	16 (12.3)
Chemotherapy	1 (0.7)	2 (1.5)
2 lines of prior systemic therapy	**90 (66.2)**	**97 (74.6)**
First line of therapy		
Chemotherapy	77 (56.6)	76 (58.5)
Chemotherapy + anti–PD-(L)1	6 (4.4)	10 (7.7)
Other	7 (5.1)	11 (8.5)
Second line of therapy		
Anti–PD-(L)1	76 (55.9)	76 (58.5)
Chemotherapy	10 (7.4)	14 (10.8)
Other	4 (2.9)	7 (5.4)

[a]1 patient in the erdafitinib group had 3 prior lines of systemic therapy.
[b]Includes patients who received other therapy in addition to chemotherapy + anti–PD-(L)1.
[c]Includes patients who received other therapy in addition to anti–PD-(L)1.
PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy



- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; *P* = 0.005)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; OS, overall survival.
[a]The significance level for stopping for efficacy was p=0.019, corresponding to a HR of 0.69.

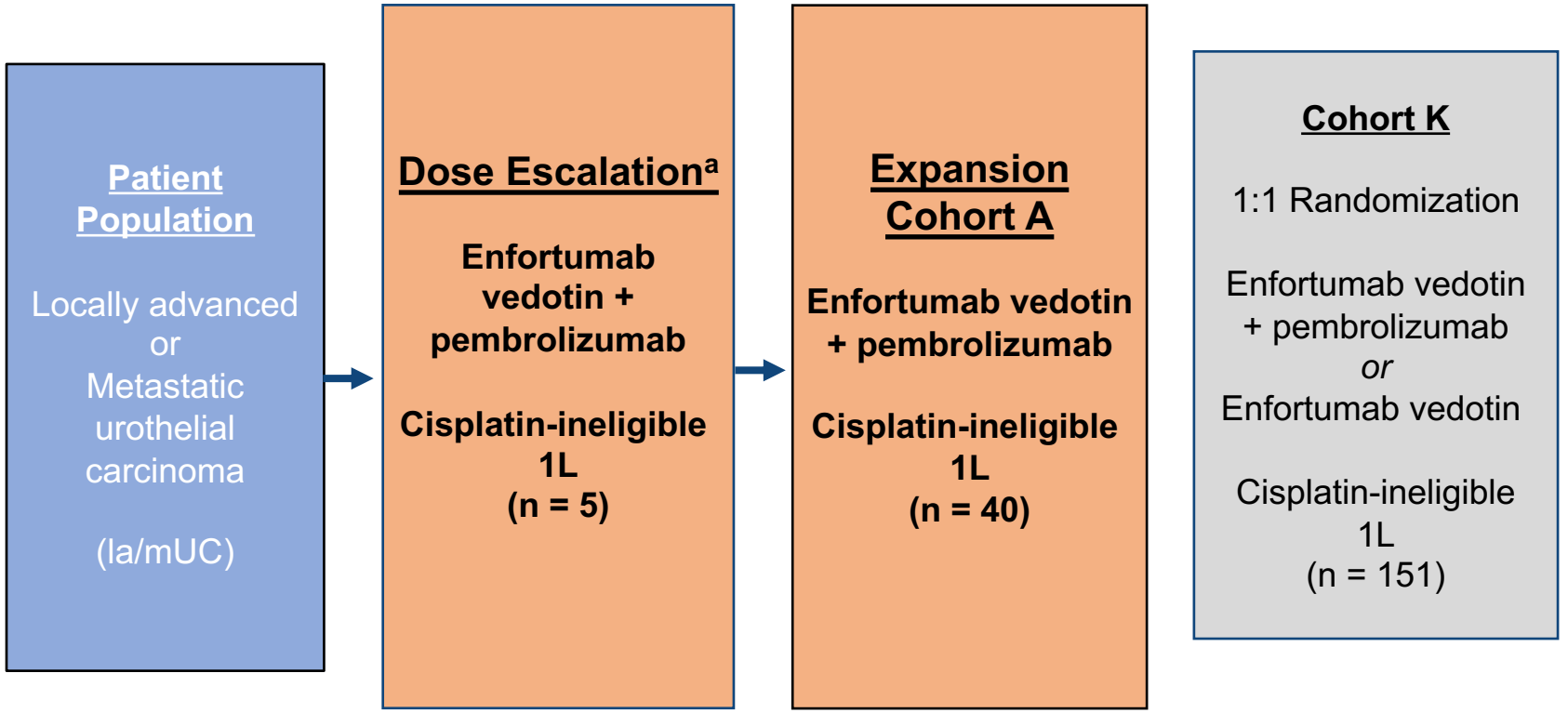
Overall Survival Benefit With Erdafitinib Versus Chemotherapy Was Consistently Observed Across Subgroups

	HR and 95% CI	Erdafitinib n/N[a]	Erdafitinib Median	Chemotherapy n/N[a]	Chemotherapy Median	HR and 95% CI
Overall		77/136	12.1	78/130	7.8	0.64 (0.47-0.88)
FGFR alteration type						
Translocation		13/25	16.4	15/19	8.0	0.49 (0.23-1.03)
Mutation		63/108	10.9	60/107	7.7	0.67 (0.47-0.95)
Baseline ECOG PS						
0-1		70/125	12.2	71/119	8.7	0.65 (0.46-0.90)
2		7/11	6.1	7/11	2.8	0.47 (0.16-1.35)
Lines of prior treatment						
1 line		27/45	14.0	21/33	7.8	0.61 (0.35-1.09)
2 lines		49/90	11.6	57/97	7.7	0.67 (0.45-0.98)
Visceral metastasis						
Presence		59/103	12.2	57/101	7.7	0.65 (0.45-0.93)
Absence		18/33	10.6	21/29	8.8	0.61 (0.32-1.14)
Primary tumor location						
Upper tract		16/41	23.3	27/48	7.2	0.34 (0.18-0.64)
Lower tract		61/95	10.5	51/82	9.6	0.82 (0.56-1.18)
Chemotherapy						
Docetaxel		77/136	12.1	40/69	10.6	0.76 (0.52-1.11)
Vinflunine		77/136	12.1	30/43	7.7	0.60 (0.39-0.92)

[a]n=number of events; N=number of patients in subgroup. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

Study Design – EV+P Cohorts

EV-103 is an open-label, multiple cohort, phase 1b/2 study



- **Dosing:** EV 1.25 mg/kg IV on Days 1 and 8, and P 200 mg IV on day 1 of every 3-week cycle
- **Primary endpoints:** AEs, lab abnormalities
- **Key secondary endpoints:** confirmed ORR, DOR, DCR, and PFS per RECIST v1.1 by BICR[b] and investigator; OS, plasma/serum PK of EV

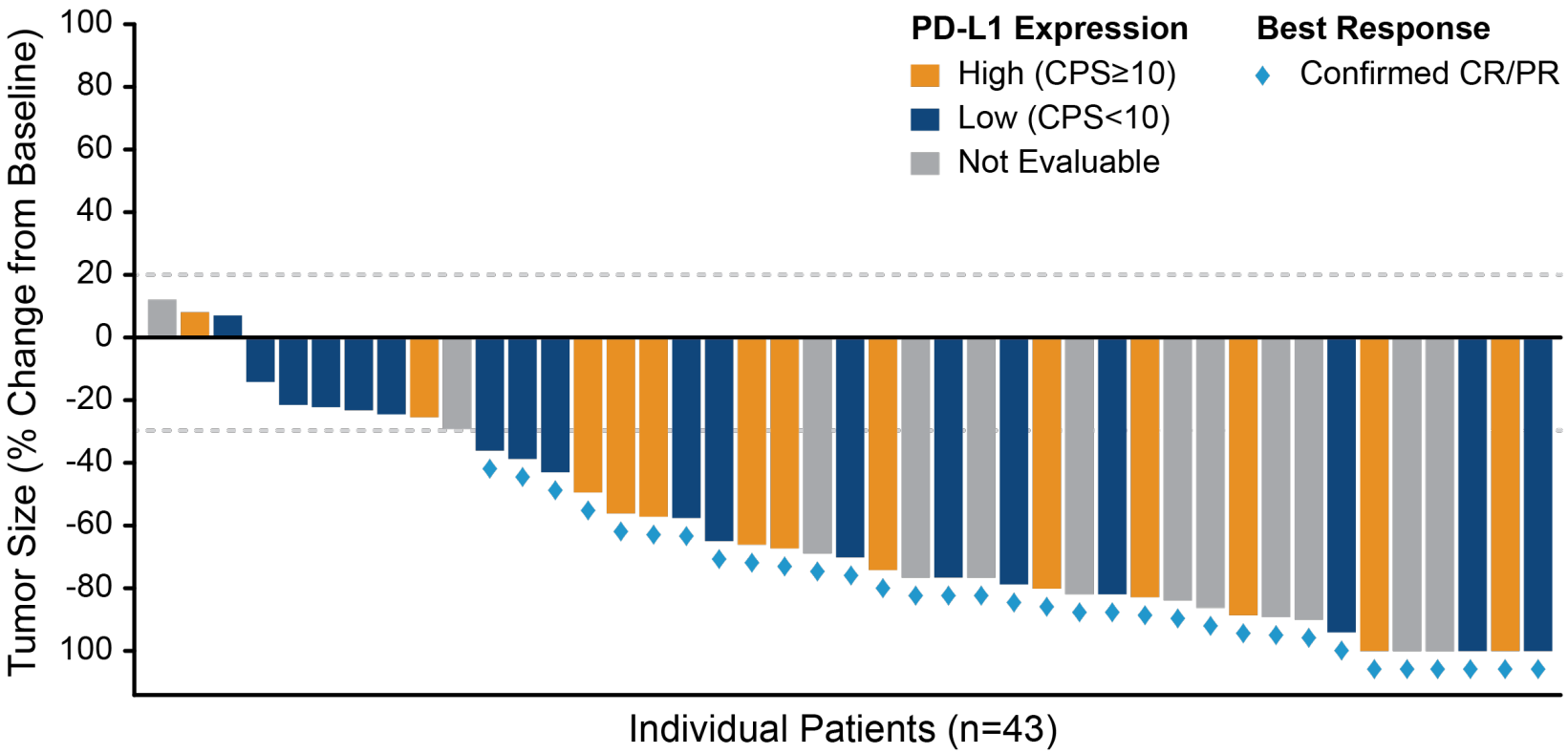
AE = adverse events; BICR = blinded independent central review; DCR = disease control rate; DOR = duration of response; EV = enfortumab vedotin; ORR = objective response rate; OS = overall survival; P = pembro; PFS = progression-free survival; PK = pharmacokinetics; 1L = first-line

Exploratory endpoints: biomarkers of activity including baseline PD-L1 status and Nectin-4 expression; **Dose Escalation/Cohort A** completed enrollment in Jan 2019; **Data cutoff** was 16 Sep 2022

[a]Patients assigned to EV 1.25 mg/kg + pembro and for whom study treatment was administered as 1L therapy

[b]The efficacy endpoints per RECIST v1.1 by BICR are presented for the first time herein. Results by investigator assessment have been previously published (Hoimes CJ, et al. JCO 2022).

EV 103: Pembrolizumab and EV in 1L cisplatin-ineligible mUC



Confirmed ORR 95% CI	**73.3% (33/45)** (58.1, 85.4)
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

Best Overall Response Per RECIST v 1.1 by investigator (N=45)

Responses observed regardless of PD-L1 expression level

Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment. These patients are included in the full analysis set used to calculate ORR, but are not included in the figure above.

Horizontal lines at positive 20% and negative 30% denote thresholds for target lesions for disease progression and response, respectively.

Hoimes C et al. JCO 2022

2023 ASCO® ANNUAL MEETING

Study EV-103 Dose Escalation/Cohort A: Long-term Outcome of Enfortumab Vedotin + Pembrolizumab in First-line (1L) Cisplatin-ineligible Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC) with Nearly 4 Years of Follow-up

Shilpa Gupta, MD[1]; Jonathan E. Rosenberg, MD[2]; Rana R. McKay, MD[3]; Thomas W. Flaig, MD[4]; Daniel Peter Petrylak, MD[5]; Christopher J. Hoimes, DO[6]; Terence W. Friedlander, MD[7]; Mehmet Asim Bilen, MD[8]; Sandy Srinivas, MD[9]; Earle Burgess, MD[10]; Jaime R. Merchan, MD[11]; Scott Tagawa, MD[12]; Jason Brown, MD[13]; Yao Yu, PhD[14]; Anne-Sophie Carret, MD[14]; Heidi S. Wirtz, PharmD, PhD[14]; Maria Guseva, MD, PharmD[15]; Blanca Homet Moreno, MD, PhD[16]; Matthew I. Milowsky, MD[17]

[1]Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [3]University of California San Diego, San Diego, CA, USA; [4]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [5]Yale Cancer Center, New Haven, CT, USA; [6]Duke Cancer Institute, Duke University, Durham, NC, USA; [7]University of California San Francisco Medical Center, San Francisco, CA, USA; [8]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [9]Stanford University Medical Center, Stanford, CA, USA; [10]Atrium Health Levine Cancer Institute, Charlotte, NC, USA; [11]University of Miami, Miami, FL, USA; [12]Weill Cornell Medical Center, New York, NY, USA; [13]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [14]Seagen Inc, Bothell, WA, USA; [15]Astellas Pharma, Northbrook, IL, USA; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

Key Demographic and Baseline Disease Characteristics

Patient characteristics are representative of the cisplatin-ineligible population with la/mUC

	Dose Escalation + Cohort A (N = 45)
Male sex, n (%)	36 (80.0)
Age (yrs), median (range)	69.0 (51-90)
White race, n (%)	42 (93.3)
ECOG PS, n (%)	
0	15 (33.3)
1	22 (48.9)
2	8 (17.8)
Primary tumor location, n (%)	
Lower tract	30 (66.7)
Upper tract	15 (33.3)

	Dose Escalation + Cohort A (N=45)
Metastasis disease sites, n (%)	
Lymph nodes	34 (75.6)
Lung	19 (42.2)
Intra-thoracic/abdominal soft tissue	17 (37.8)
Liver	14 (31.1)
Metastasis category, n (%)	
Visceral disease	38 (84.4)
Lymph node only disease	7 (15.6)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; la/mUC = locally advanced or metastatic urothelial carcinoma

Overall Objective Response Rates by BICR

High confirmed ORR (73.3%) with high concordance rate between BICR and INV assessments

	Dose Escalation + Cohort A (N = 45)
Objective Response Rate, n (%)	33 (73.3)
95% CI[a] for ORR	58.1-85.4
Best Overall Response, n (%)	
Complete response	7 (15.6)
Partial response	26 (57.8)
Stable disease	5 (11.1)
Progressive disease	5 (11.1)
No assessment[b]	2 (4.4)
Disease Control Rate, n (%)	38 (84.4)
95% CI[a] for DCR	70.5-93.5
Concordance rate of BOR between BICR and INV[c] assessment	95.3%

BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; DCR = disease control rate; INV = investigator; ORR = objective response rate
[a]CI was computed using the Clopper-Pearson method (Clopper 1934)
[b]Patients had no response assessment post-baseline
[c]ORR per INV assessment was 33/45 (73.3%)

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Dr. Shilpa Gupta, MD

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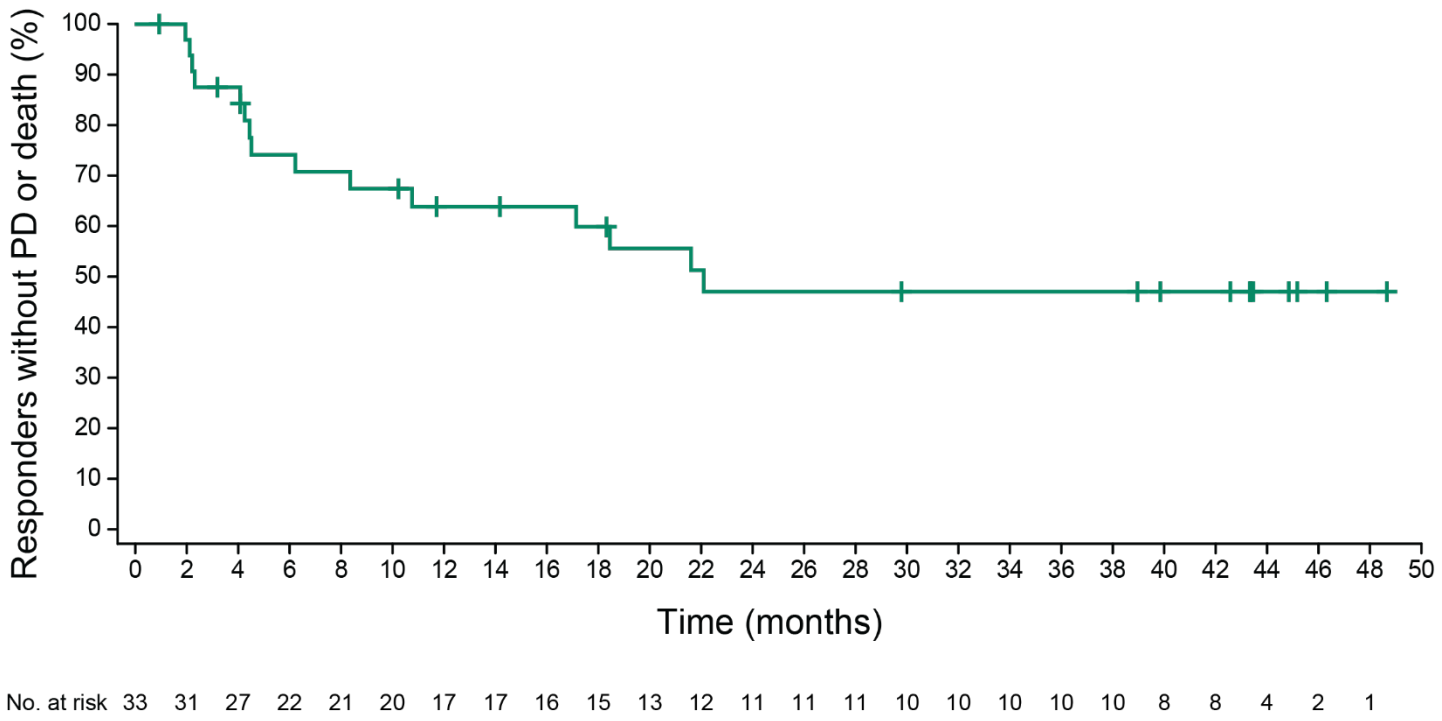
Duration of Response by BICR

1L EV+P is associated with durable responses

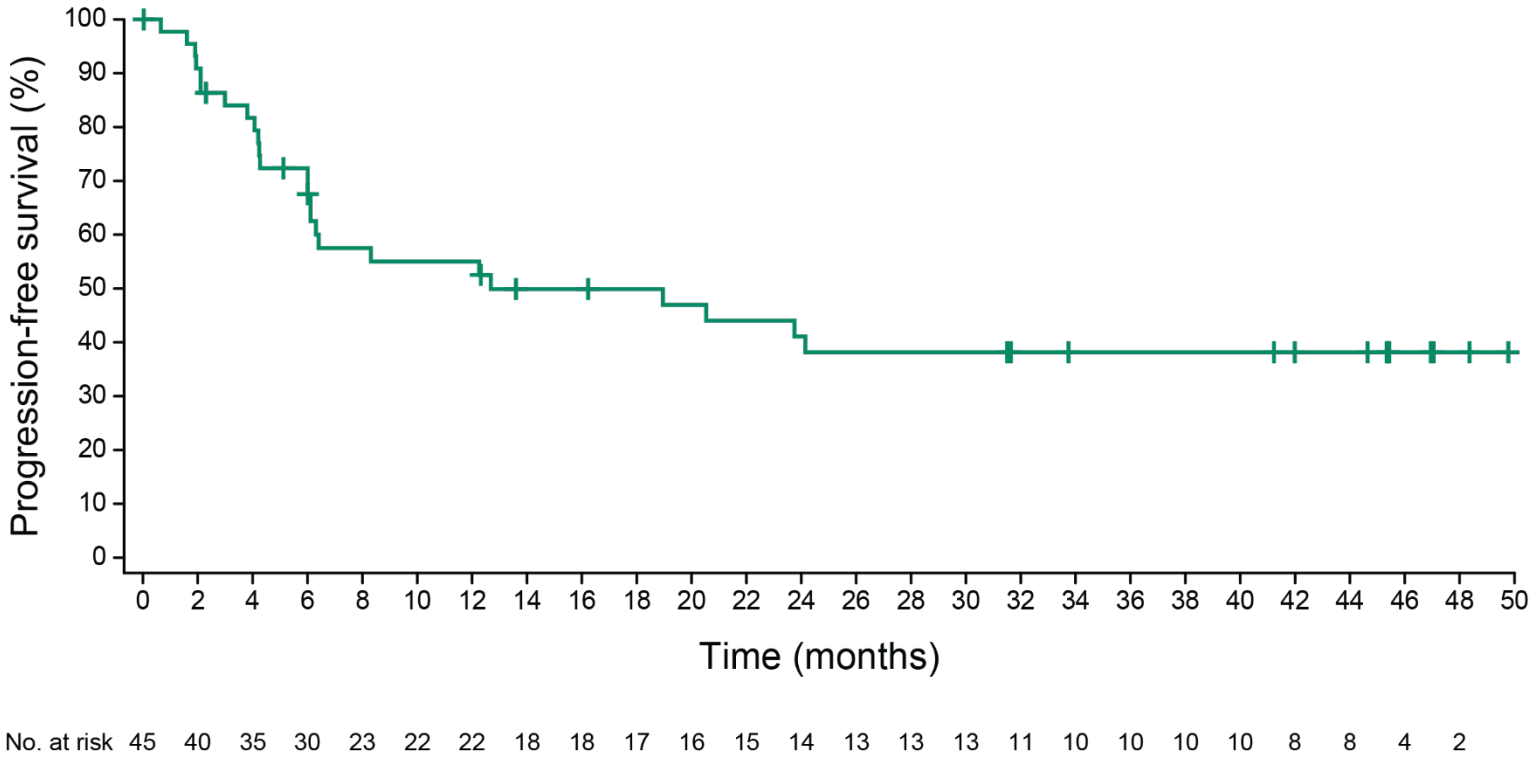


	Dose Escalation + Cohort A (N = 45)
DOR events, n	15
Median DOR (95% CI[a])	22.1 months (8.38-NE)
Patients without PD or death at:	
6 months, % (95% CI[a])	74.1 (54.82-86.17)
12 months, % (95% CI[a])	63.9 (44.19-78.17)
24 months, % (95% CI[a])	47.0 (27.57-64.31)

BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; EV = enfortumab vedotin; NE = not estimable; P = pembrolizumab, PD = progressive disease; 1L = first-line
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)

Progression-Free Survival by BICR

41.1% of patients were progression-free at 24 months



	Dose Escalation + Cohort A (N = 45)
PFS events, n	25
Median PFS (95% CI[a])	12.7 months (6.11-NE)
PFS rate[b] at:	
6 months, % (95% CI[a])	72.4 (56.47-83.26)
12 months, % (95% CI[a])	55.0 (38.84-68.58)
24 months, % (95% CI[a])	41.1 (25.69-55.88)

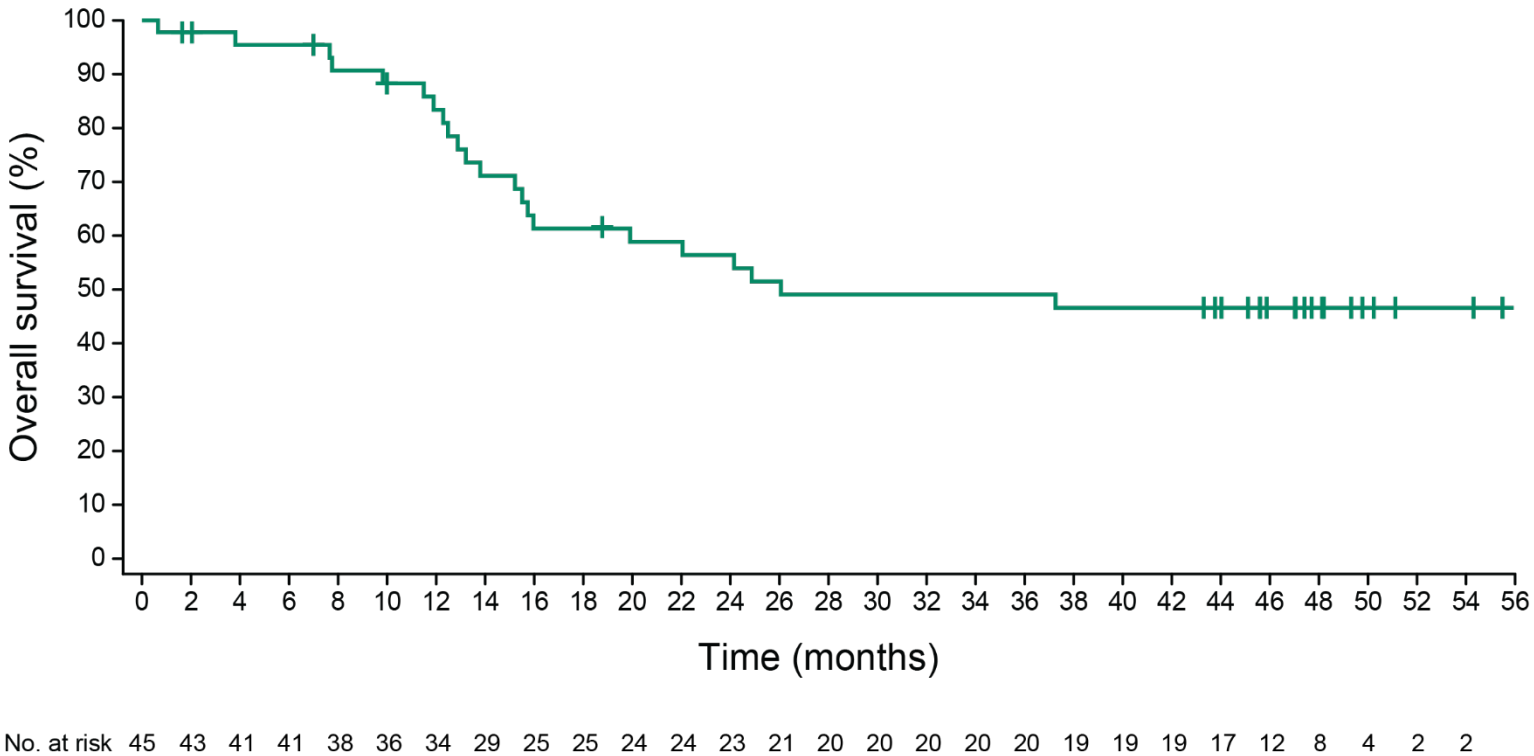
BICR = blinded independent central review; CI = confidence interval; NE = not estimable; PFS = progression-free survival

[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)

[b]As estimated using Kaplan-Meier method

Overall Survival

Median survival exceeds 2 years



	Dose Escalation + Cohort A (N = 45)
OS events, n	22
Median OS (95% CI[a])	26.1 months (15.51-NE)
OS rate[b] at:	
6 months, % (95% CI[a])	95.4 (83.00-98.84)
12 months, % (95% CI[a])	83.4 (68.25-91.72)
24 months, % (95% CI[a])	56.4 (40.03-69.91)
Median follow-up time	47.0 months

CI = confidence interval; NE = not estimable; OS = overall survival
[a]CI was calculated using the complementary log-log transformation method (Collett, 1994)
[b]As estimated using Kaplan-Meier method

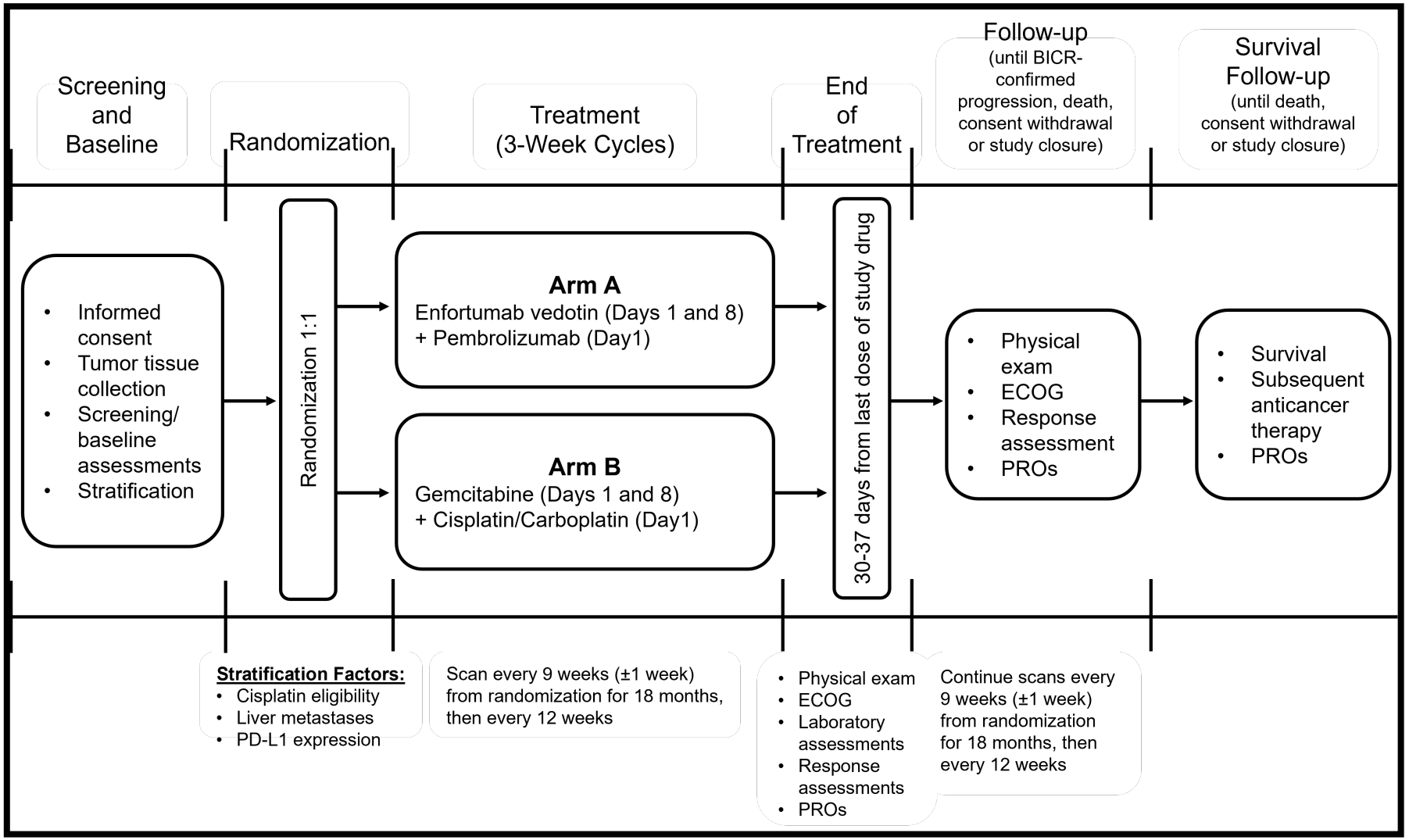
EV 103: Pembro and EV vs EV monotherapy in 1L cisplatin-ineligible advanced UC (Cohort K)

	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

Data cutoff: 10Jun2022
BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

Rosenberg J et al. ESMO 2022

EV 302: Completed accrual



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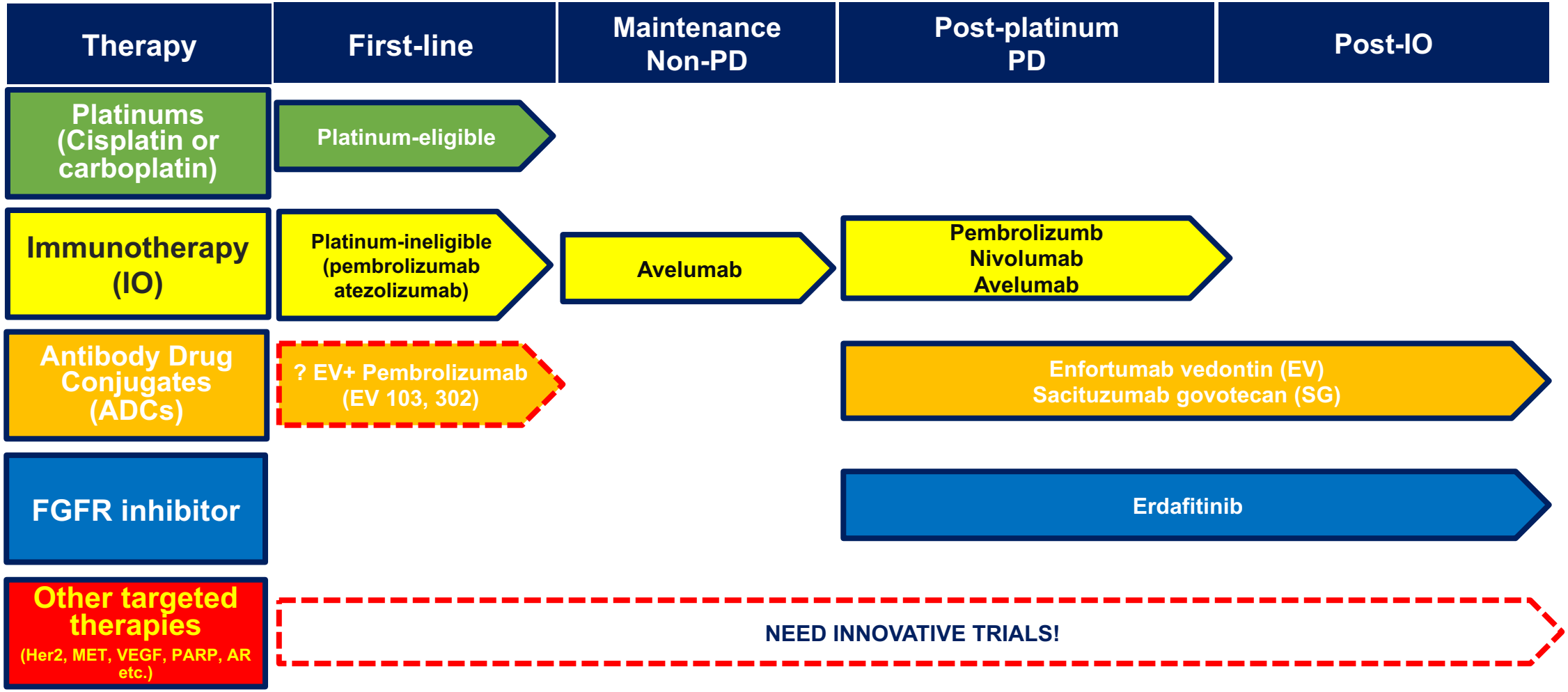
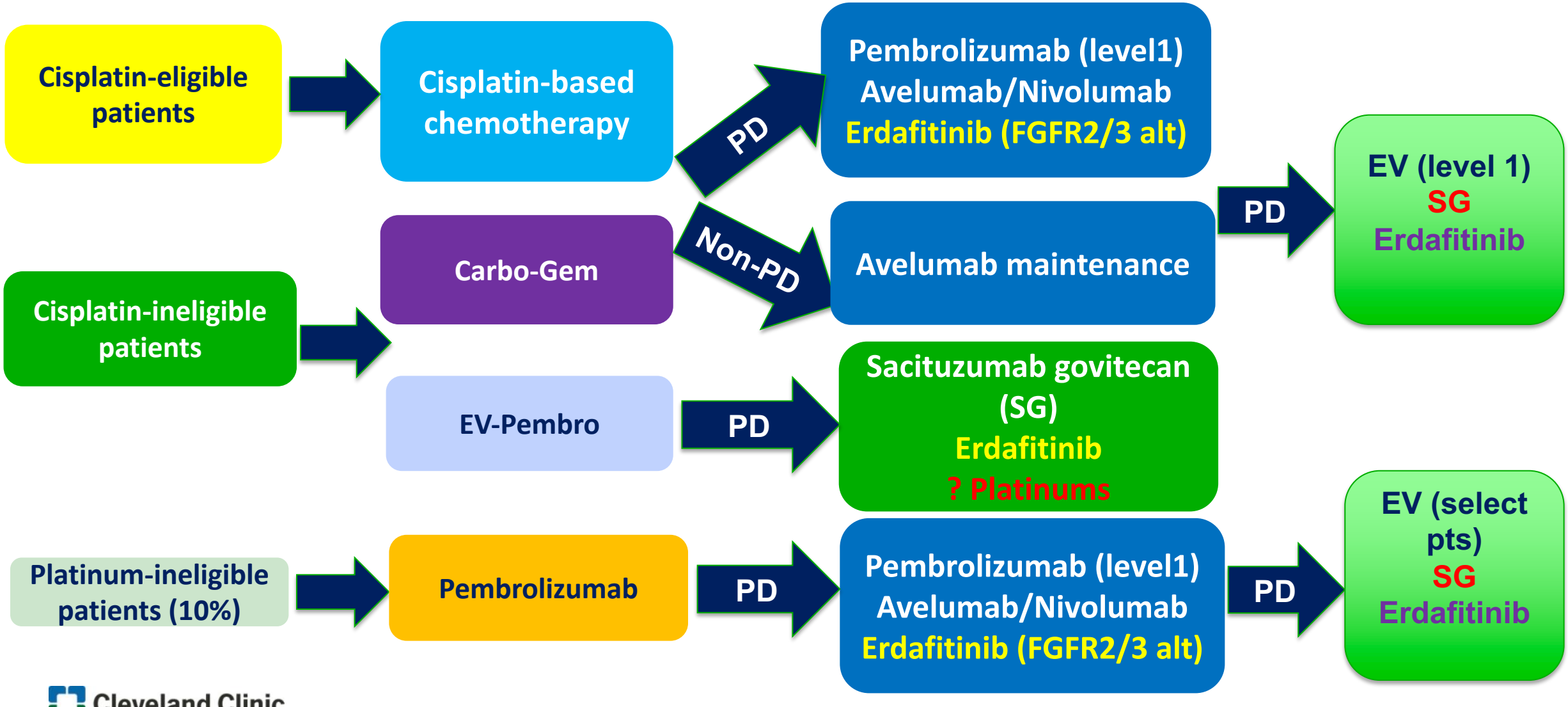
Conclusions

- Platinum-based chemotherapy followed by switch maintenance avelumab is the current standard
- Single-agent immunotherapy only recommended in platinum-ineligible mUC patients
- Enfortumab + pembrolizumab combination is a promising 1L regimen in cisplatin-ineligible mUC patients



My Treatment Paradigm for mUC in 2023



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