How I Treat Metastatic Bladder Cancer

Master Lecture Series – Nashville

7/29/23

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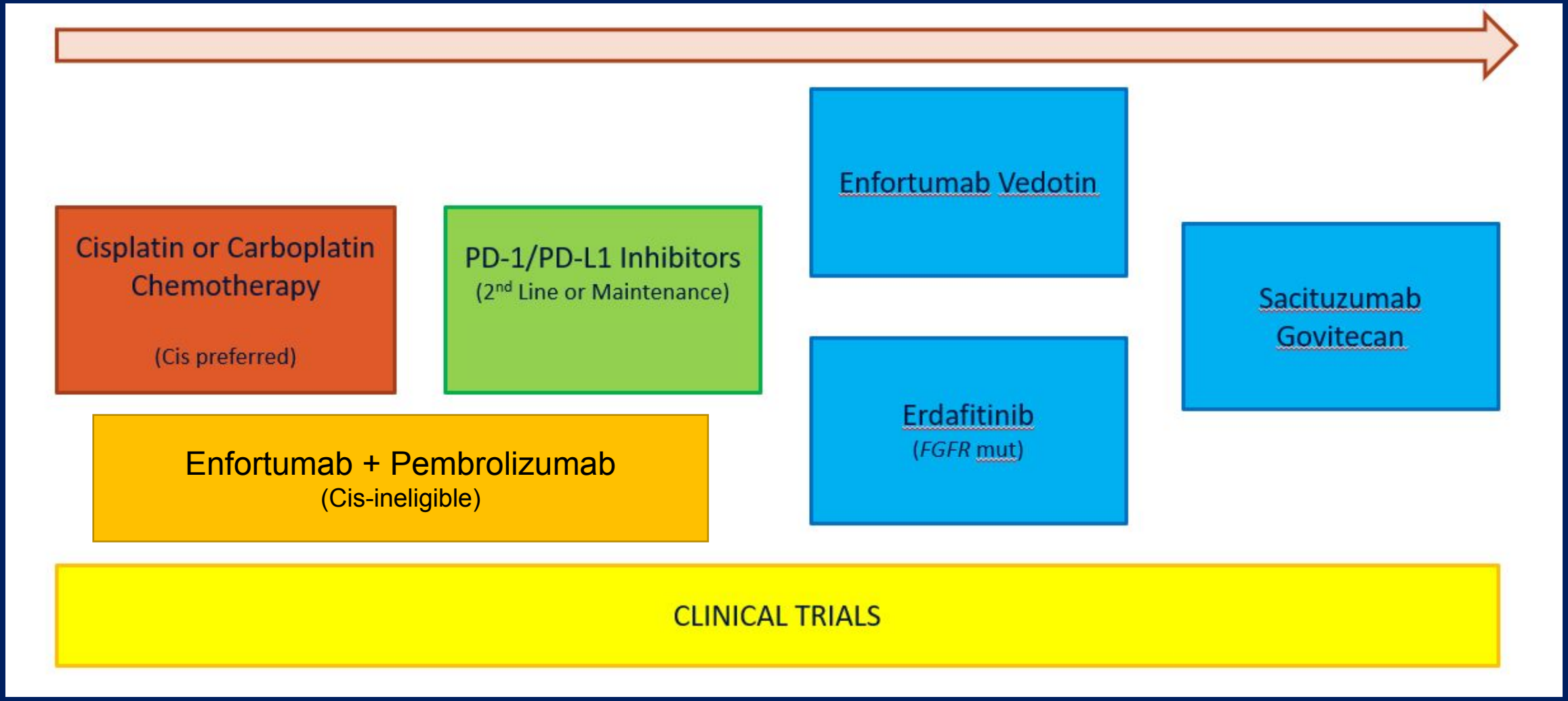
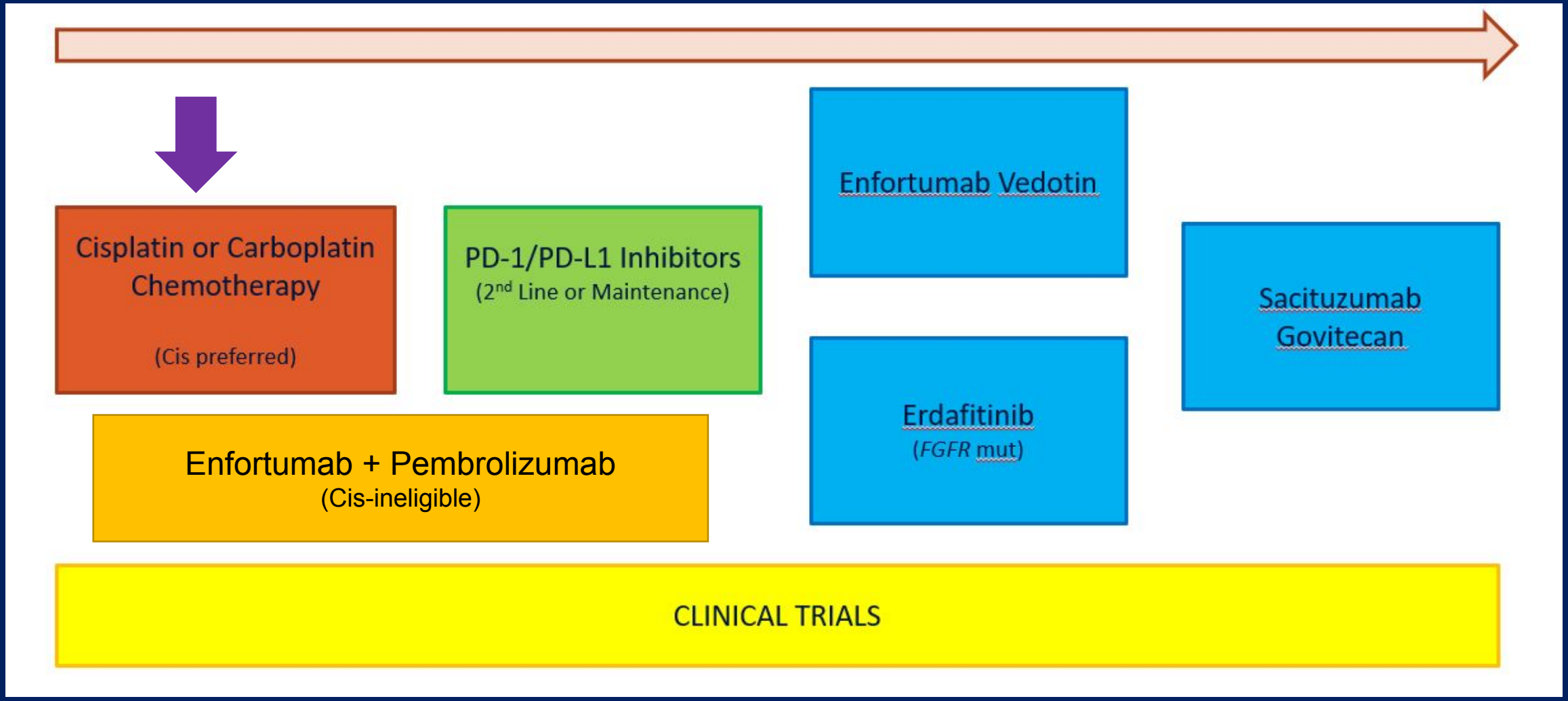
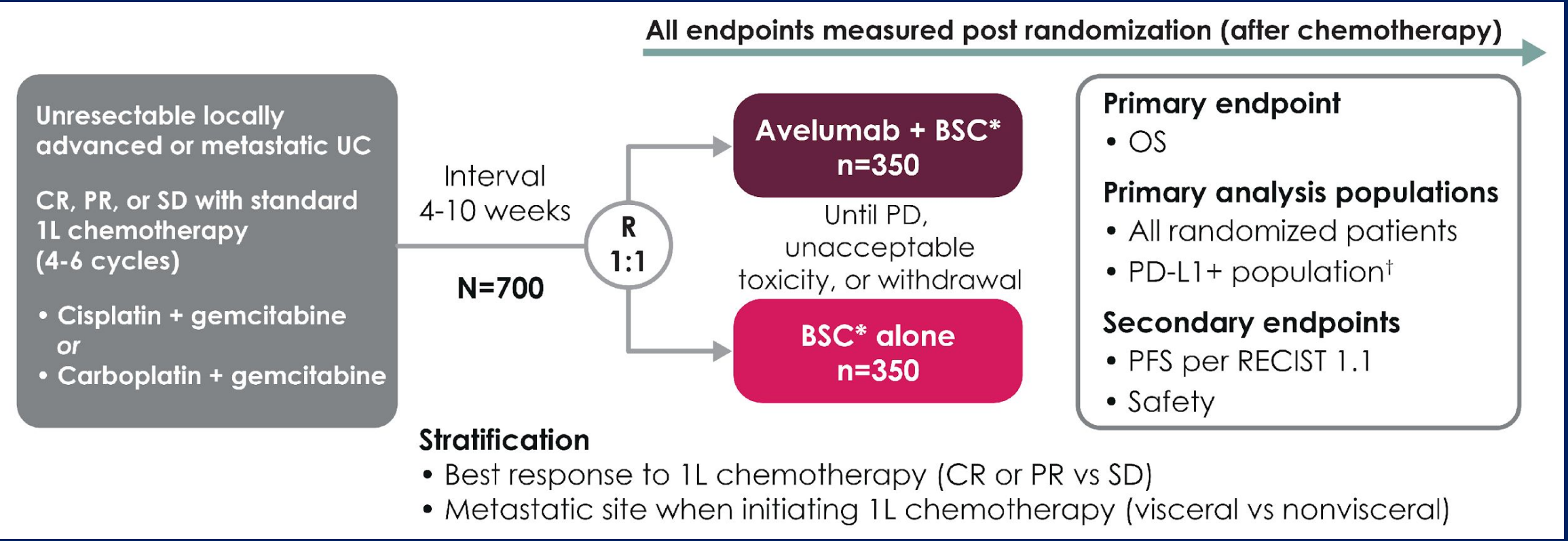
Metastatic Urothelial Carcinoma



Metastatic Urothelial Carcinoma



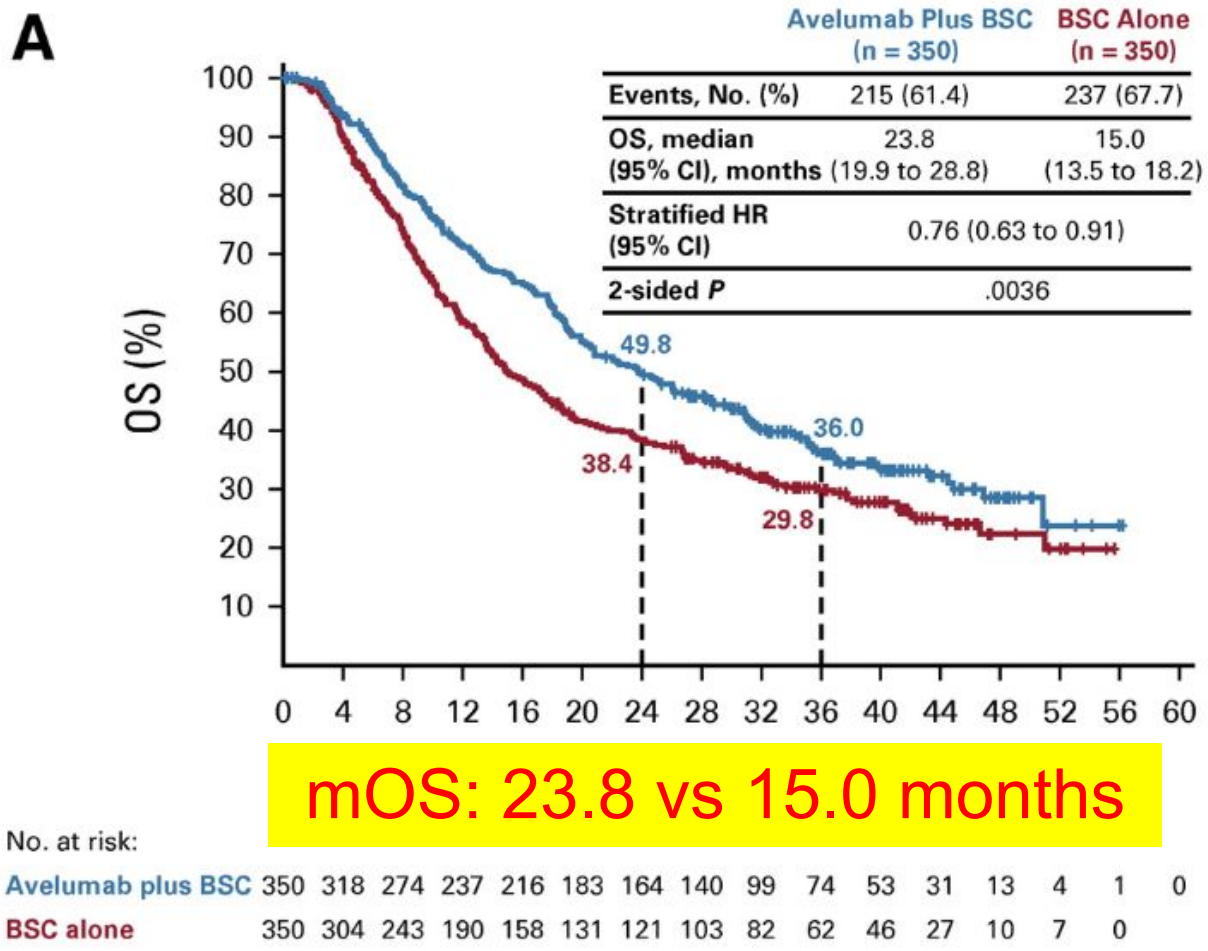
JAVELIN Bladder 100



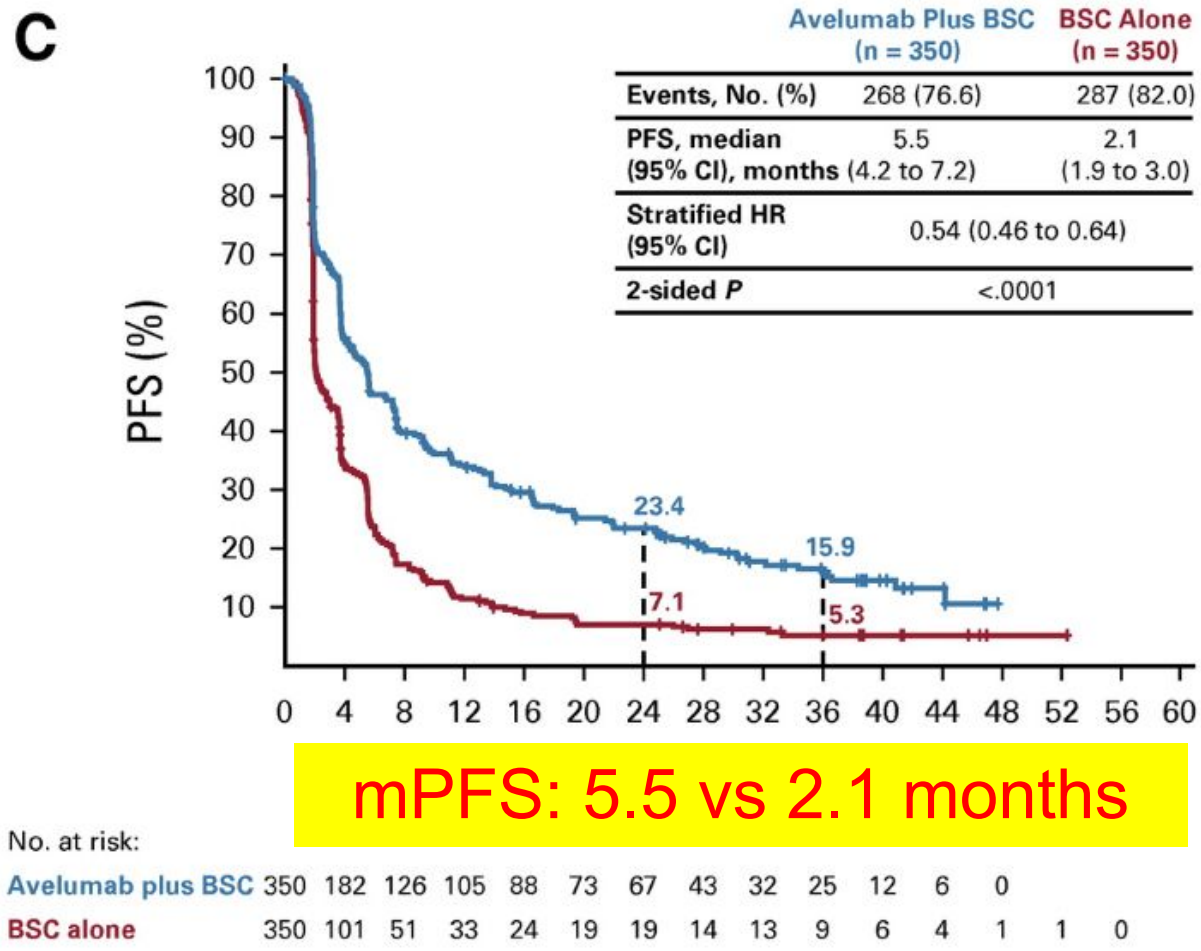
BSC, best supportive care; OS, overall survival; PFS, progression free survival

Powles et al. NEJM 2020.

JAVELIN Bladder 100: ≥2 years of Follow-Up



mOS: 23.8 vs 15.0 months



mPFS: 5.5 vs 2.1 months

Powles et al. JCO 2023.

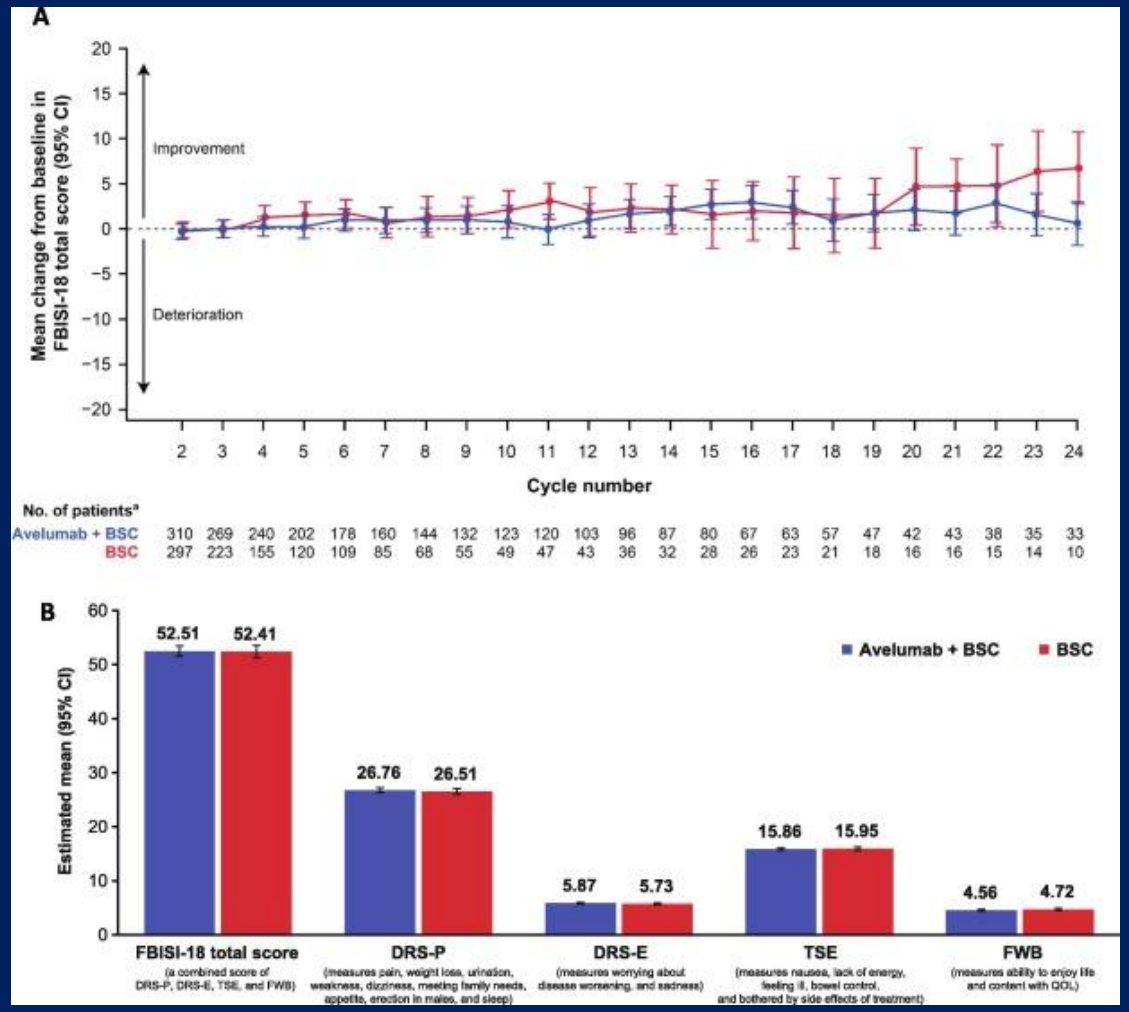
JAVELIN Bladder 100

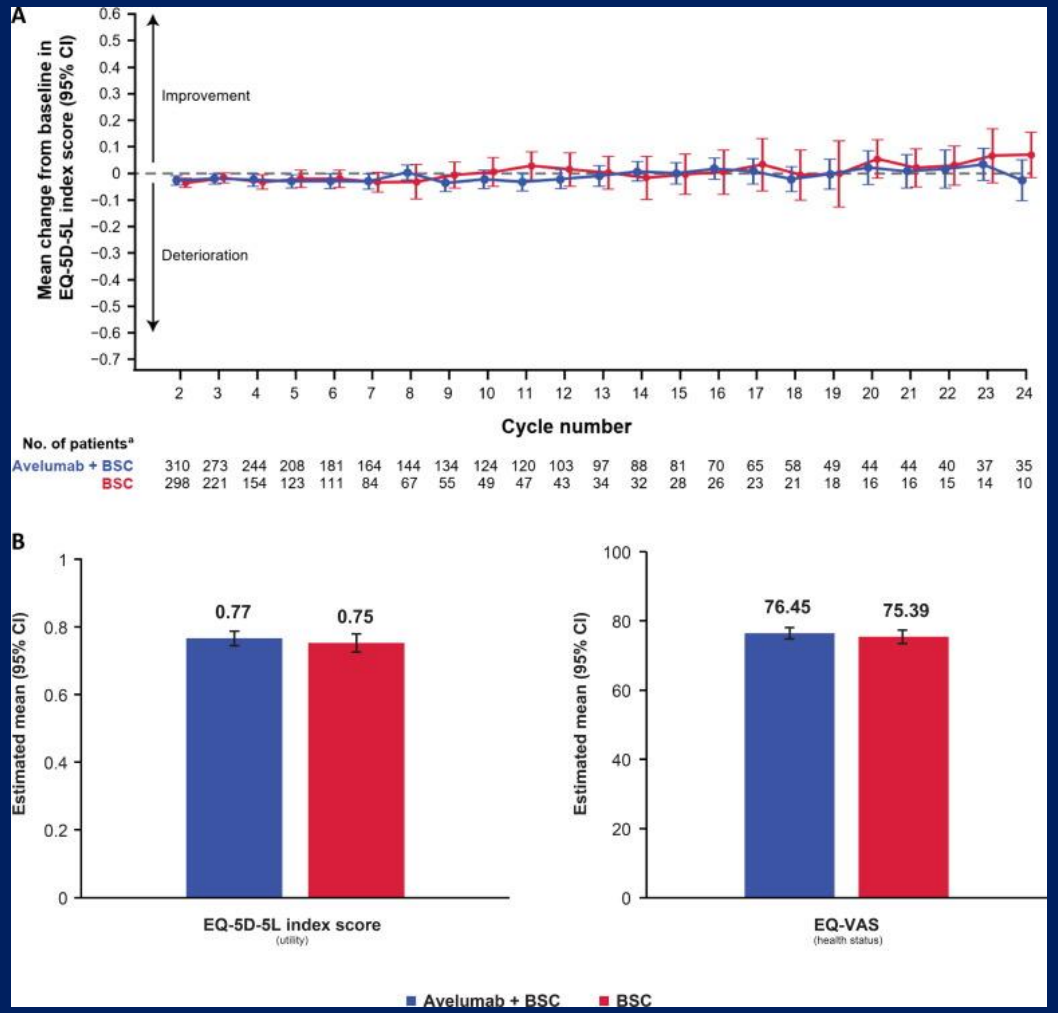
Table 3. Adverse Events (Safety Population).*

Event	Avelumab Group (N=344)		Control Group (N=345)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	337 (98.0)	163 (47.4)	268 (77.7)	87 (25.2)
Fatigue	61 (17.7)	6 (1.7)	24 (7.0)	2 (0.6)
Pruritus	59 (17.2)	1 (0.3)	6 (1.7)	0
Urinary tract infection	59 (17.2)	15 (4.4)	36 (10.4)	9 (2.6)
Diarrhea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0
Asthenia	56 (16.3)	0	19 (5.5)	4 (1.2)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	0
Back pain	55 (16.0)	4 (1.2)	34 (9.9)	8 (2.3)
Nausea	54 (15.7)	1 (0.3)	22 (6.4)	2 (0.6)
Pyrexia	51 (14.8)	1 (0.3)	12 (3.5)	0
Decreased appetite	47 (13.7)	1 (0.3)	23 (6.7)	2 (0.6)
Cough	44 (12.8)	1 (0.3)	16 (4.6)	0
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0
Rash	40 (11.6)	1 (0.3)	4 (1.2)	0
Anemia	39 (11.3)	13 (3.8)	23 (6.7)	10 (2.9)
Hematuria	36 (10.5)	6 (1.7)	37 (10.7)	5 (1.4)
Infusion-related reaction	35 (10.2)	3 (0.9)	0	0

Powles et al. NEJM 2020.

JAVELIN Bladder 100 PROs: Similar QOL with Avelumab vs BSC

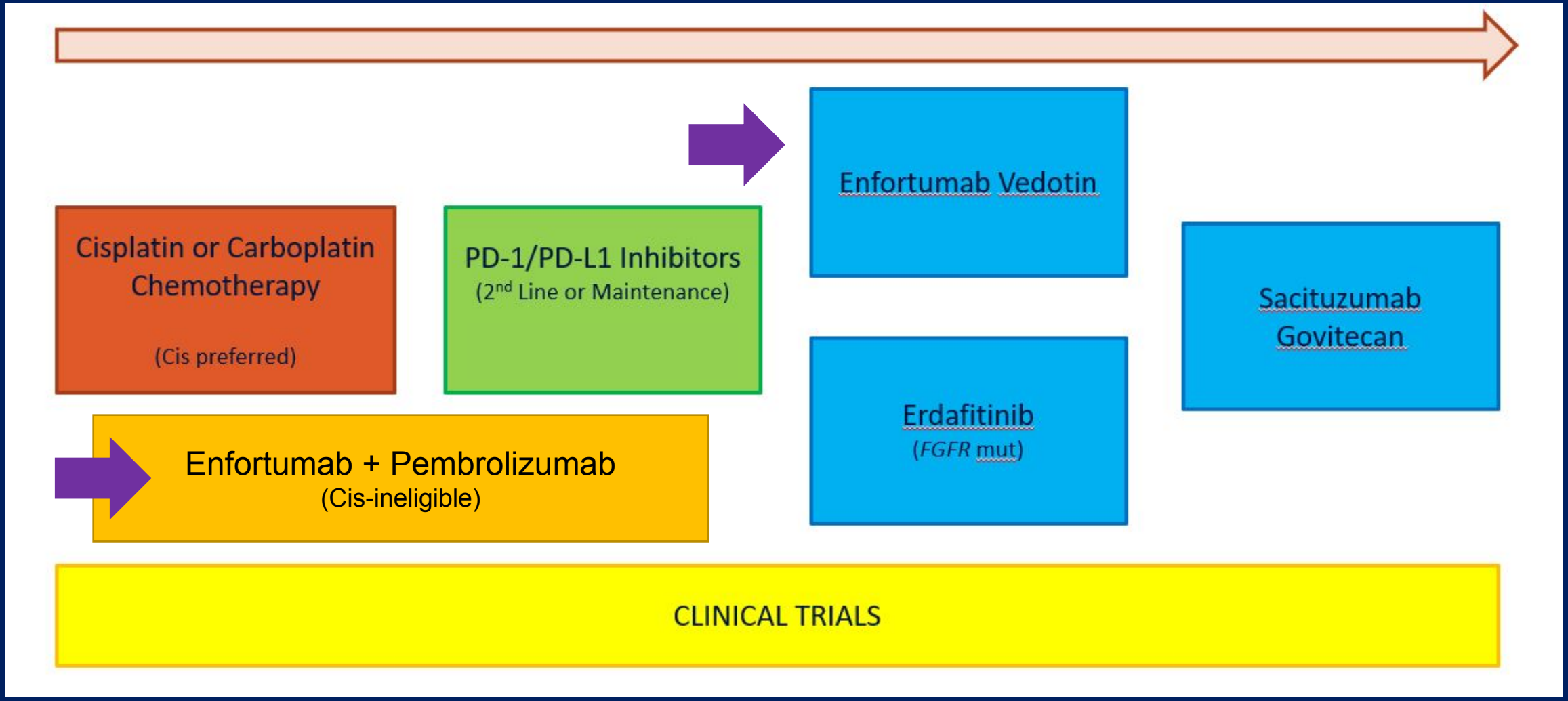


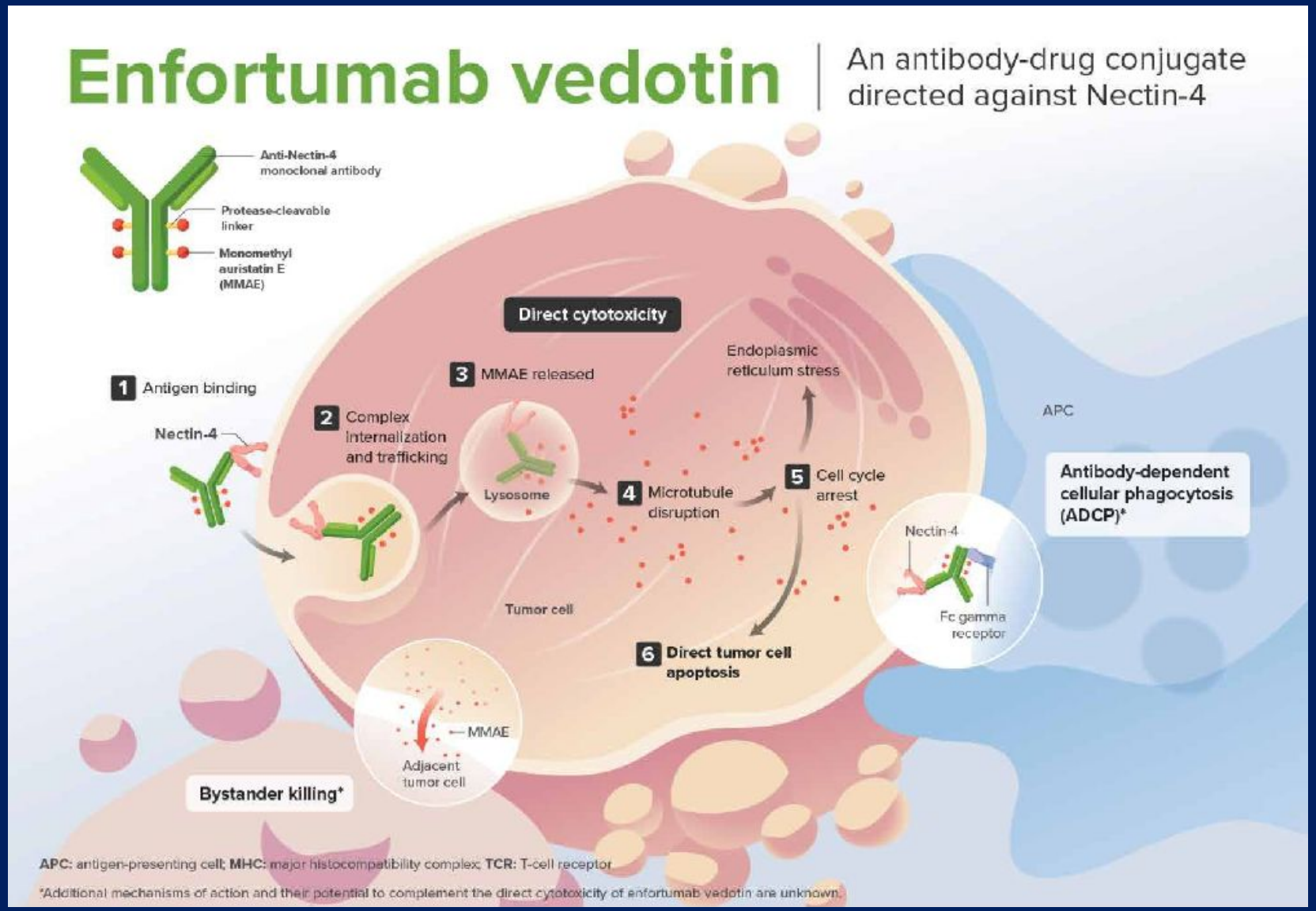


PRO, patient reported outcome; QOL, quality of life; BSC, best supportive care

Grivas et al. Eur Urol 2023.

Metastatic Urothelial Carcinoma




Enfortumab vedotin
An antibody-drug conjugate directed against Nectin-4
Anti-Nectin-4 monoclonal antibody
Protease-cleavable linker
Monomethyl auristatin E (MMAE)
Direct cytotoxicity
1 Antigen binding
Nectin-4
2 Complex internalization and trafficking
3 MMAE released
Lysosome
4 Microtubule disruption
5 Cell cycle arrest
Endoplasmic reticulum stress
Tumor cell
6 Direct tumor cell apoptosis
APC
Antibody-dependent cellular phagocytosis (ADCP)*
Nectin-4
Fc gamma receptor
MMAE
Adjacent tumor cell
Bystander killing*
APC: antigen-presenting cell; MHC: major histocompatibility complex; TCR: T-cell receptor
*Additional mechanisms of action and their potential to complement the direct cytotoxicity of enfortumab vedotin are unknown.

Seagen, 2022.

EV-301: Enfotumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Key eligibility criteria:
- Histologically/Cytologically confirmed UC
- Radiographic progression/ relapse during or after PD-1/L1 treatment for advanced UC
- Prior platinum-containing regimen for advanced UC
- ECOG PS 0–1

1:1 randomization with stratification

Enfortumab vedotin (N=301)
1.25 mg/kg on days 1, 8, and 15 of each 28-d cycle

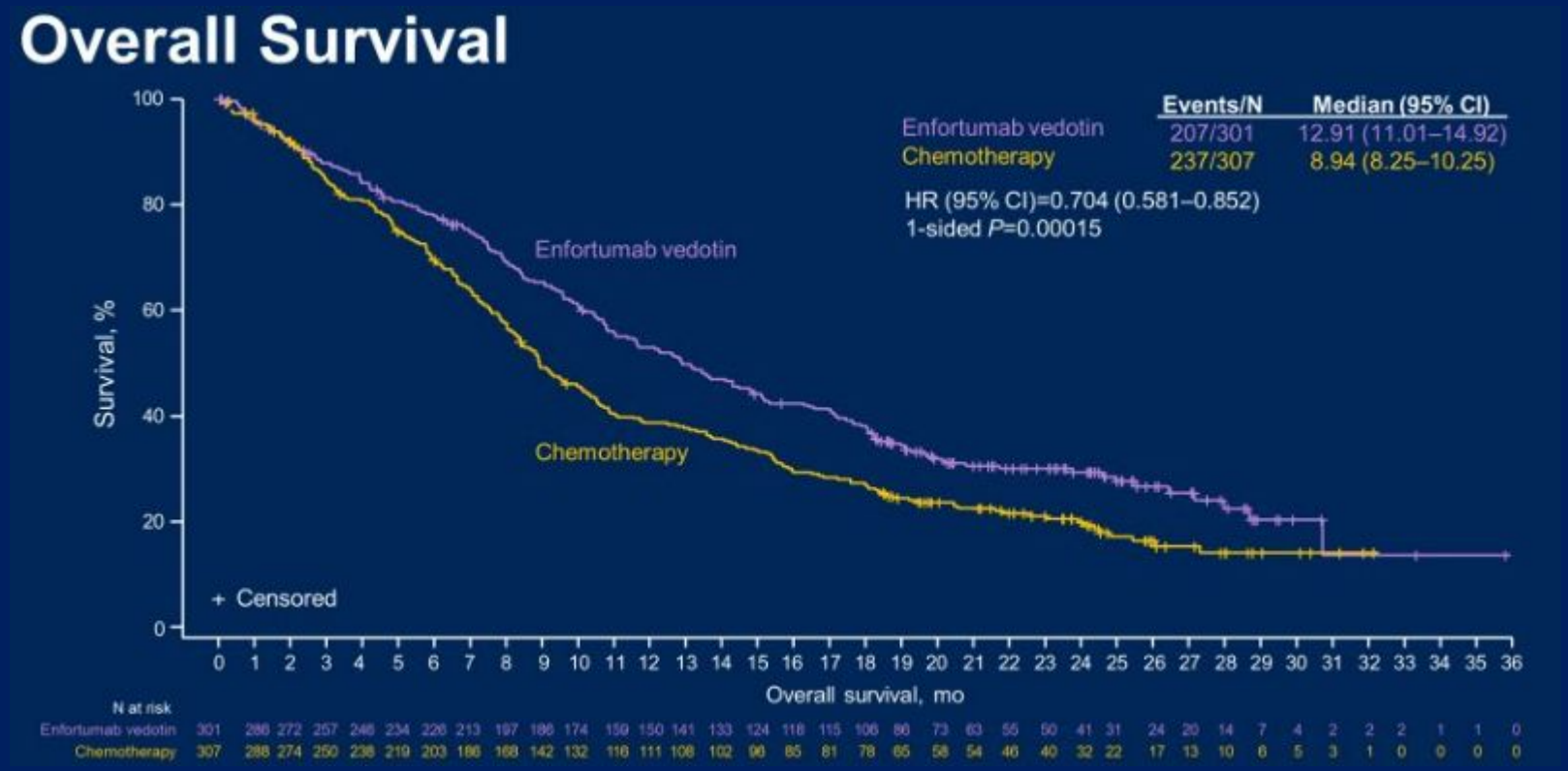
Preselected chemotherapy (N=307)
Docetaxel 75 mg/m² or paclitaxel 175 mg/m² or vinflunine 320 mg/m² on day 1 of each 21-d cycle

Primary end point: Overall survival

Secondary end points:
- Progression-free survival
- Disease control rate
- Overall response rate
- Safety

Investigator-assessed per RECIST v1.1

Findings from the prespecified, event-driven OS analysis when 439 deaths occurred are presented



Rosenberg et al. ASCO Annual Meeting 2022.

Table 2. Treatment-Related Adverse Events (Safety Population).*

Adverse Event	Enfortumab Vedotin Group (N=296)		Chemotherapy Group (N=291)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	278 (93.9)	152 (51.4)	267 (91.8)	145 (49.8)
Alopecia	134 (45.3)	0	106 (36.4)	0
Peripheral sensory neuropathy†	100 (33.8)	9 (3.0)	62 (21.3)	6 (2.1)
Pruritus	95 (32.1)	4 (1.4)	13 (4.5)	0
Fatigue	92 (31.1)	19 (6.4)	66 (22.7)	13 (4.5)
Decreased appetite	91 (30.7)	9 (3.0)	68 (23.4)	5 (1.7)
Diarrhea	72 (24.3)	10 (3.4)	48 (16.5)	5 (1.7)
Dysgeusia	72 (24.3)	0	21 (7.2)	0
Nausea	67 (22.6)	3 (1.0)	63 (21.6)	4 (1.4)
Maculopapular rash	48 (16.2)	22 (7.4)	5 (1.7)	0
Anemia	34 (11.5)	8 (2.7)	59 (20.3)	22 (7.6)
Decreased neutrophil count	30 (10.1)	18 (6.1)	49 (16.8)	39 (13.4)
Neutropenia	20 (6.8)	14 (4.7)	24 (8.2)	18 (6.2)
Decreased white-cell count	16 (5.4)	4 (1.4)	31 (10.7)	20 (6.9)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

Powels et al. NEJM 2021.

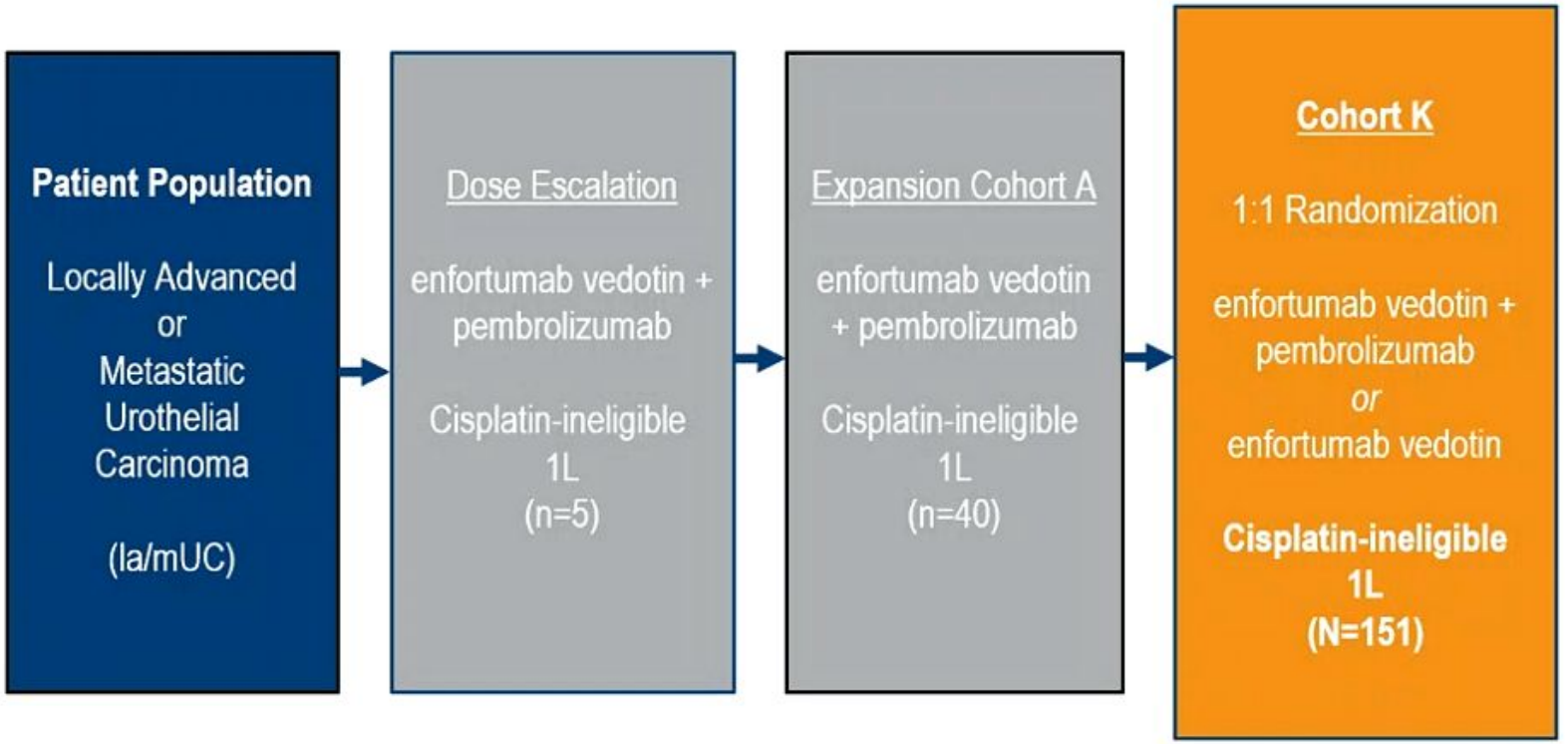
EV-301: Enfotumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Treatment-Related Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Skin Reactions[a]	**47%**	**15%**	**16%**	**1%**
Rash	44%	15%	10%	0[c]
Severe cutaneous adverse reactions[b]	20%	5%	8%	1%
Peripheral neuropathy	**46%**	**5%**	**31%**	**2%**
Sensory events	44%	4%	30%	2%
Motor events	7%	2%	2%	0
Hyperglycemia	**6%**	**4%**	**0[c]**	**0**

The majority of TRAEs of special interest were mild-to-moderate in severity.

Powles et al. GU ASCO 2021.

EV-103: Enfortumab Vedotin +/- Pembrolizumab



- **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 endpoint:** confirmed ORR by RECIST v1.1 per BICR
- **Key secondary endpoints:** confirmed ORR per RECIST v1.1 by investigator, DOR, DCR, PFS, OS, safety/ tolerability, and lab abnormalities

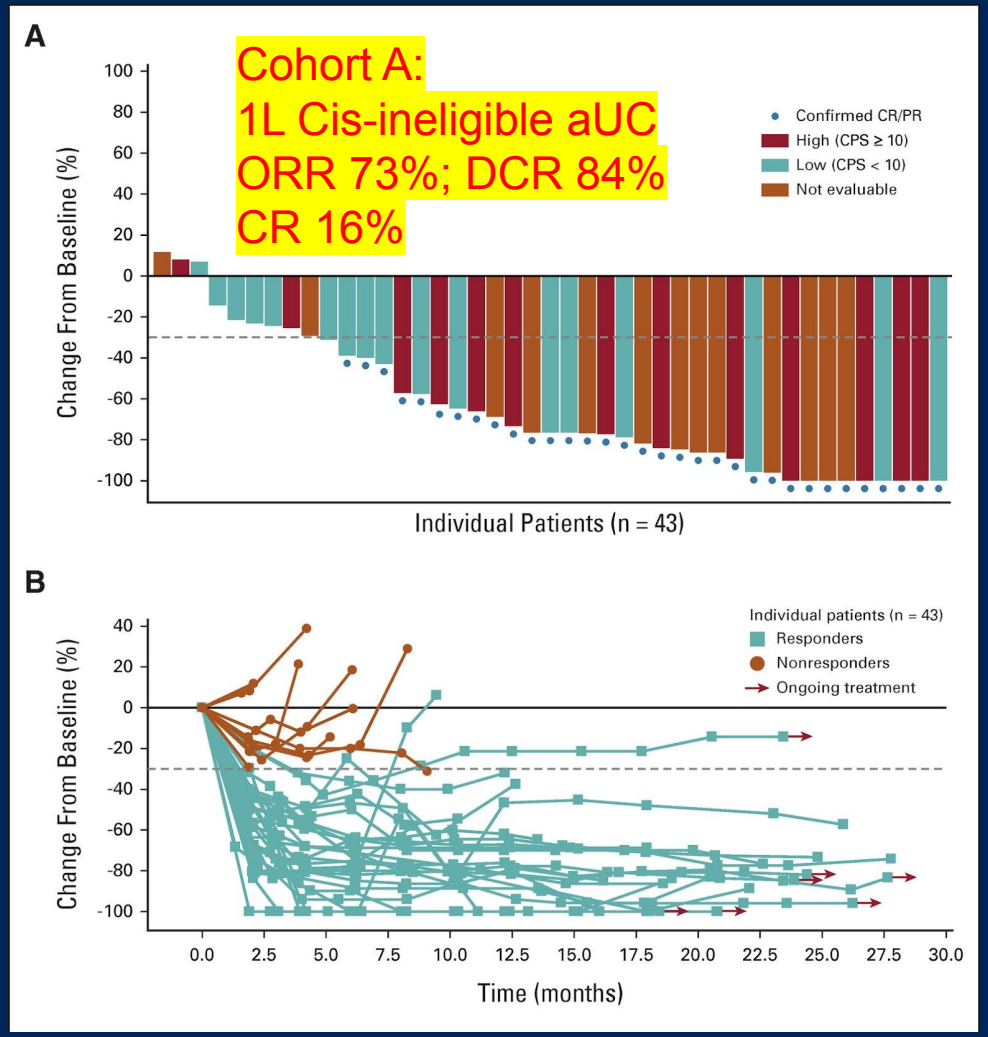
Statistical considerations

- The sample size was based on precision of the estimate for ORR characterized by 95%CIs
- No formal statistical comparisons between the 2 treatment arms

Stratification factors: Liver metastases (present/absent) and ECOG PS (0 or 1/2); **Exploratory endpoints**: pharmacokinetics, antitherapeutic antibody, biomarkers of activity including baseline PD-L1 status and Nectin-4 expression, progression-free survival on subsequent therapy by investigator, patient reported outcomes; **Cohort K** completed enrollment on 11 Oct 2021; **Data cutoff was 10 Jun 2022**

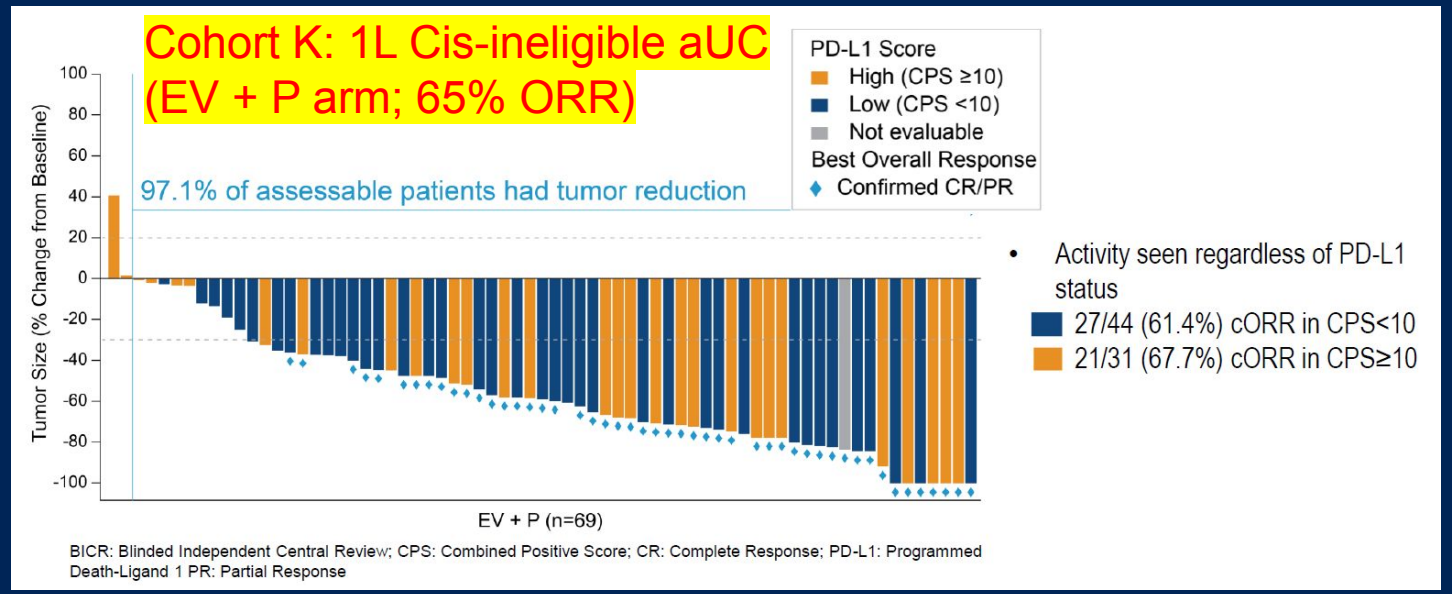
Rosenberg et al. ESMO 2022.

EV-103: Pembrolizumab + Enfortumab Vedotin



ORR, objective response rate

Hoimes et al, JCO 2023



TRAEs **Any Grades** by Preferred Term **≥20% of Patients**	**EV+P (N=76) n (%)**	
	Any Grade	**Grade ≥3**
Overall	76 (100.0)	48 (63.2)
Fatigue	43 (56.6)	7 (9.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)
Alopecia	35 (46.1)	0
Rash maculo-papular	35 (46.1)	13 (17.1)
Pruritus	30 (39.5)	3 (3.9)

Rosenberg et al, ESMO 2022

EV-103 Cohort K: Treatment-Related Adverse Events of Special Interest

TABLE A2. EV Treatment-Related AEs of Special Interest

	EV + Pembro (N = 76)			EV Monotherapy (N = 73)		
Adverse Event	Any Grade, No. (%)	Grade ≥3, No. (%)	Time to Onset, Any Grade, Median, Months	Any Grade, No. (%)	Grade ≥3, No. (%)	Time to Onset, Any Grade, Median, Months
Skin reactions	51 (67.1)	16 (21.1)	0.53	33 (45.2)	6 (8.2)	0.95
Rashes	50 (65.8)	15 (19.7)	NA	32 (43.8)	5 (6.8)	NA
Severe cutaneous AEs	14 (18.4)	2 (2.6)	NA	13 (17.8)	3 (4.1)	NA
Peripheral neuropathy	46 (60.5)	2 (2.6)	2.99	40 (54.8)	2 (2.7)	2.48
Ocular disorders	20 (26.3)	0	NA	21 (28.8)	0	NA
Dry eye	19 (25.0)	0	1.64	21 (28.8)	0	2.04
Blurred vision	2 (2.6)	0	6.93	5 (6.8)	0	3.45
Corneal disorders	0	0	NA	4 (5.5)	0	3.48
Hyperglycemia	11 (14.5)	5 (6.6)	0.53	8 (11.0)	7 (9.6)	0.69
Infusion-related reactions	3 (3.9)	0	NA	4 (5.5)	0	NA

NOTE. Treatment relatedness is determined by investigator.
Abbreviations: AE, adverse event; EV, enfortumab vedotin; NA, not available; Pembro, pembrolizumab.

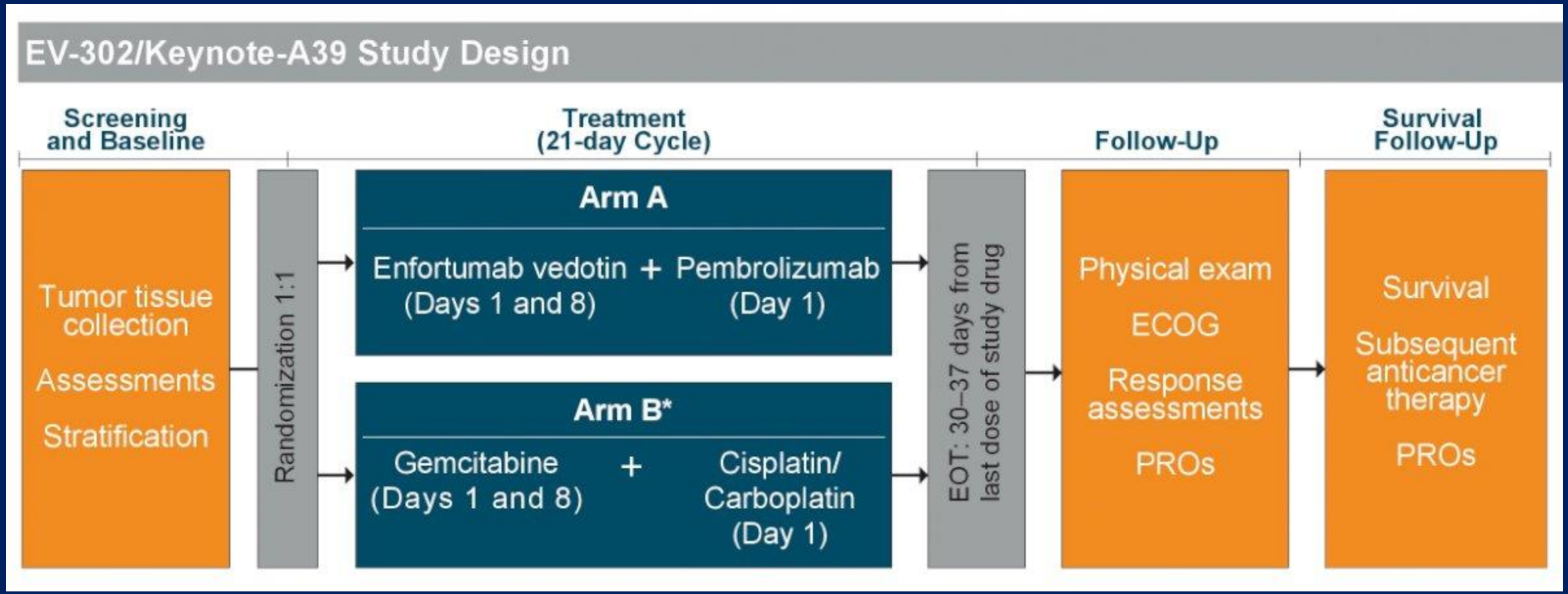
O'Donnell P.H. et al. JCO.2023.

FDA grants accelerated approval to enfortumab vedotin-ejfv with pembrolizumab for locally advanced or metastatic urothelial carcinoma

Apr 3, 2023

- Cisplatin-ineligible patients
- Combination of dose escalation, cohort A, and cohort K
- 121 patients: ORR 68%, CR 12%
  - Cohort A median DoR 25.6 months
  - Cohort K median DoR not reached

ORR, objective response rate; DoR, duration or response



Van Der Heijden, ASCO GU 2022 TIP

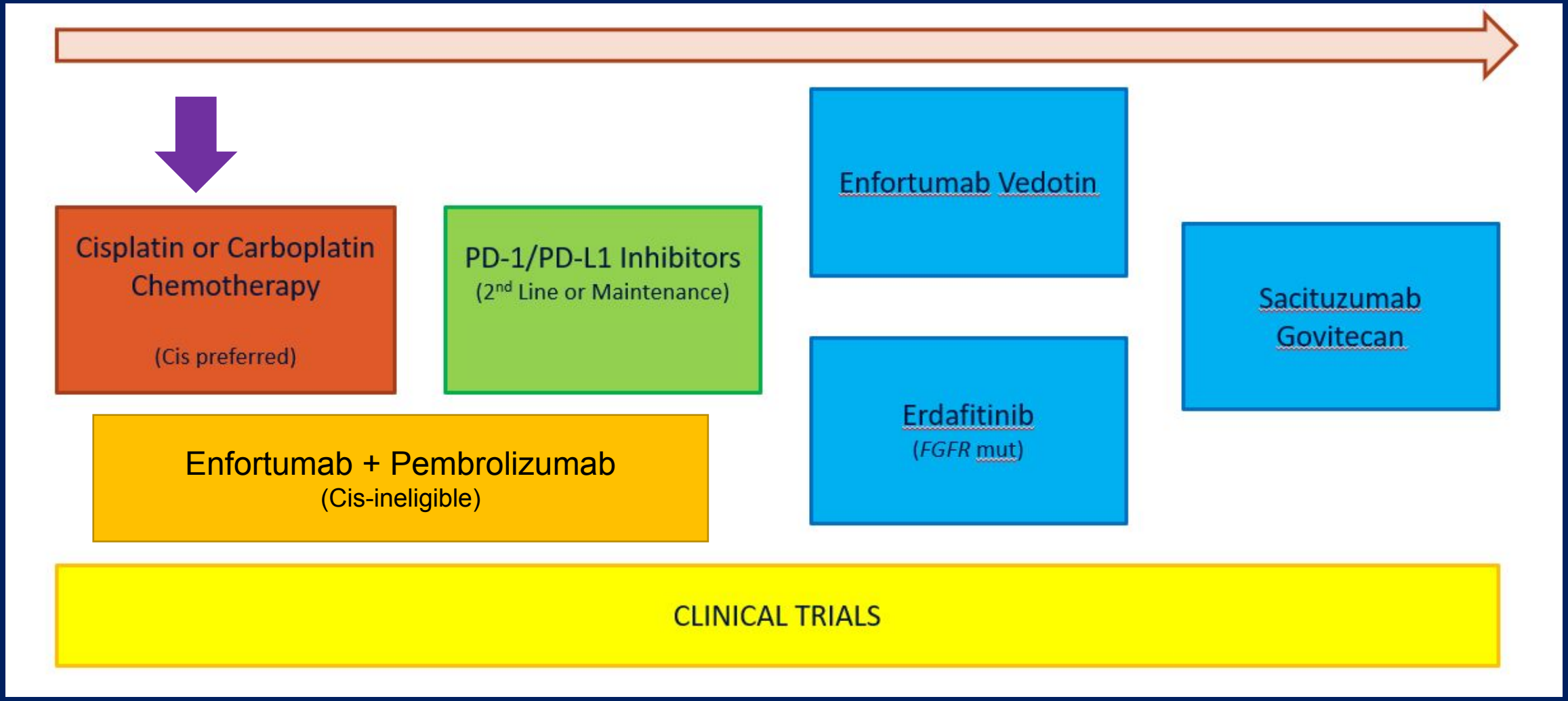
Expression of Nectin-4 and PD-L1 in Bladder Cancer with Variant Histology

Nectin-4 and PD-L1 staining results among BCVH subtypes.

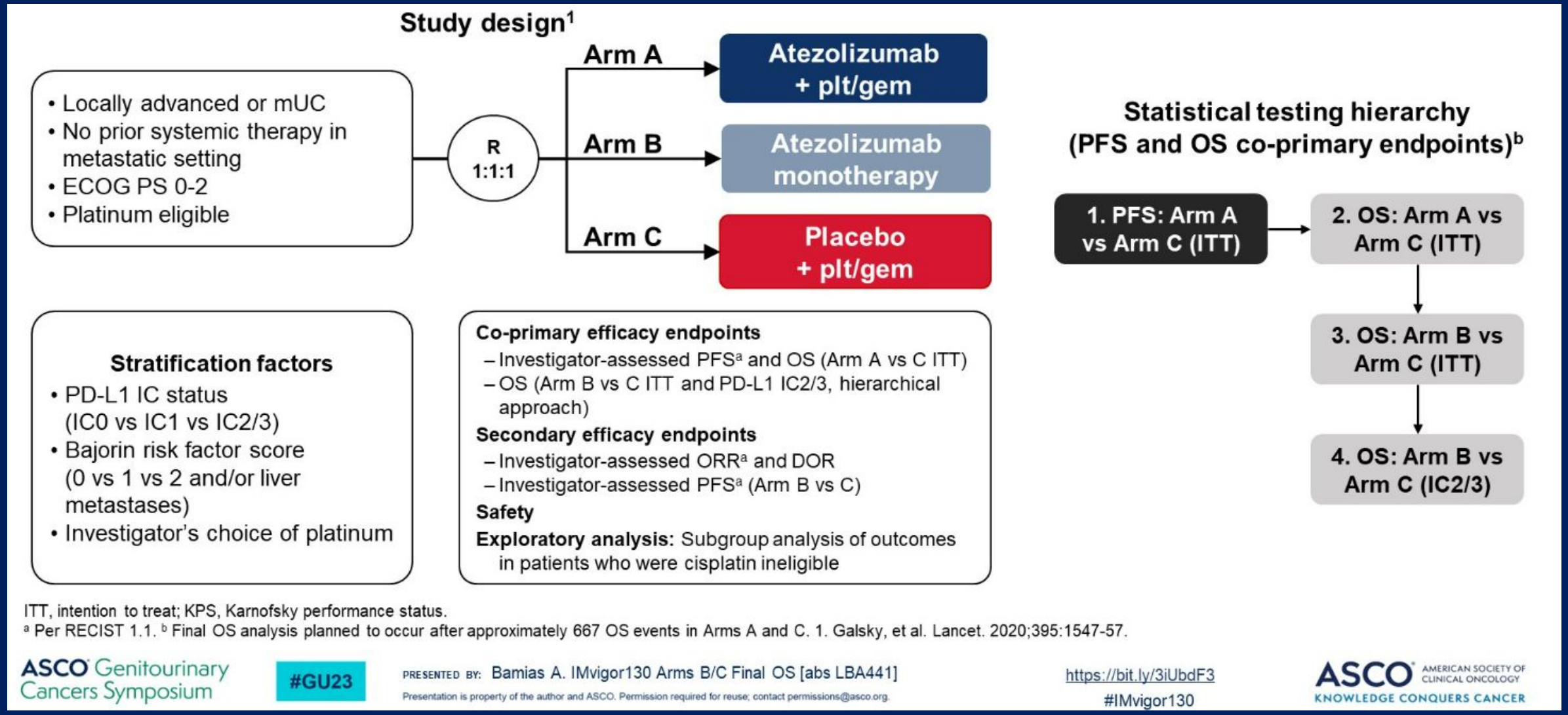
			Nectin-4 H-score		PD-L1
Histology	No. of specimens	% of total (N = 117)	Mean	Median (range)	CPS ≥ 10 n(%)
Squamous	31	26.5	207.7	219.5 (17-300)	15/30 (50)
Adenocarcinoma	24	20.5	166.9	140.0 (45-299)	4/24 (16.7)
Sarcomatoid	24	20.5	52.3	2.5 (0-300)	17/24 (70.8)
Plasmacytoid	20	17.1	253.5	257.5 (108-300)	1/20 (5)
Small cell	10	8.5	46.8	0 (0-233)	2/10 (20)
Mixed	8	6.8	122	105 (20-265)	2/8 (25)

Case K et al. GU ASCO 2022.

Metastatic Urothelial Carcinoma



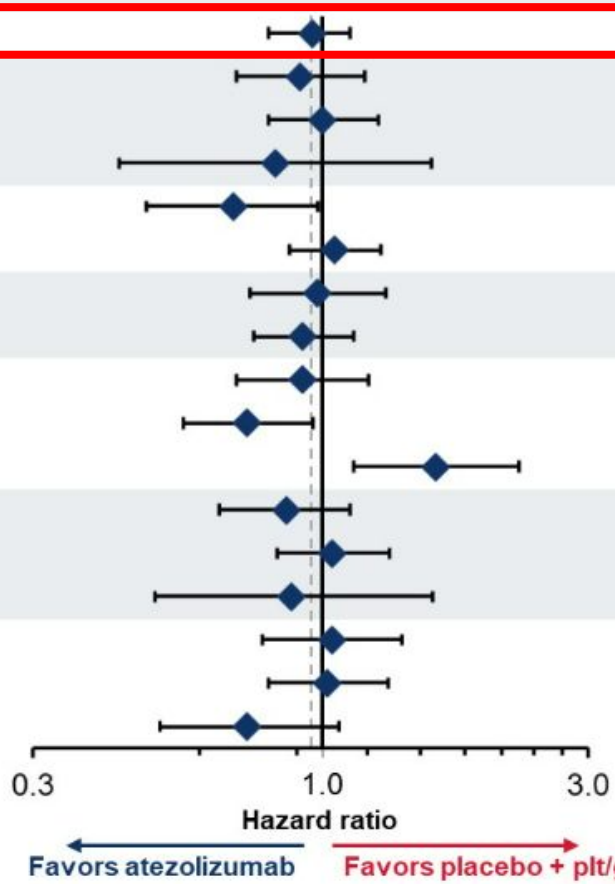
IMvigor130: a global, randomized, Phase III study (NCT02807636)



ITT, intention to treat; KPS, Karnofsky performance status.
[a] Per RECIST 1.1. [b] Final OS analysis planned to occur after approximately 667 OS events in Arms A and C. 1. Galsky, et al. Lancet. 2020;395:1547-57.

IMvigor130: OS by Clinical Subgroup

Baseline risk factors	Arm B n	Arm B Median OS, mo	Arm C[a] n	Arm C[a] Median OS, mo	Hazard ratio (95% CI)[b]
All patients	360	15.2	359	13.3	0.96 (0.80, 1.12)
Age <65 years	142	16.0	145	12.6	0.91 (0.70, 1.19)
Age 65-80 years	192	14.7	192	14.6	1.00 (0.80, 1.26)
Age ≥80 years	26	14.9	22	11.3	0.82 (0.43, 1.57)
Female	81	17.7	95	12.2	0.69 (0.48, 0.98)
Male	279	14.6	264	14.3	1.05 (0.87, 1.27)
Investigator's choice of cisplatin	135	16.3	136	13.4	0.98 (0.74, 1.30)
Investigator's choice of carboplatin	225	14.6	223	13.0	0.92 (0.75, 1.14)
Bajorin risk factor score 0	150	22.4	149	19.9	0.92 (0.70, 1.21)
Bajorin risk factor score 1	133	16.0	134	11.7	0.73 (0.56, 0.96)
Bajorin risk factor score 2 or liver metastasis	77	3.6	76	10.0	1.60 (1.14, 2.26)
ECOG PS 0	157	20.3	161	18.9	0.86 (0.65, 1.12)
ECOG PS 1	172	11.0	171	11.2	1.04 (0.83, 1.32)
ECOG PS 2	31	2.9	27	8.4	0.88 (0.50, 1.58)
PD-L1 IC0	113	12.1	115	12.8	1.04 (0.78, 1.39)
PD-L1 IC1	159	14.2	159	13.1	1.02 (0.80, 1.31)
PD-L1 IC2/3	88	27.5	85	16.7	0.73 (0.51, 1.07)

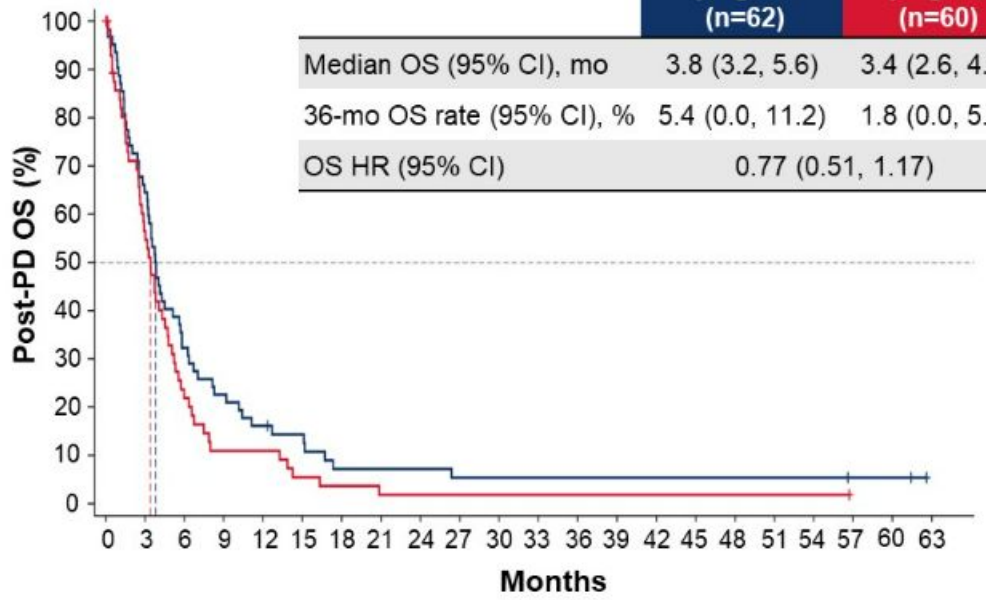


[a] Comparison included only patients concurrently enrolled with Arm B. [b] Unstratified.

Imvigor: Post-progression OS in patients with PD: by Chemotherapy Type

Carboplatin-treated patients

	Atezo + plt/gem (n=62)	Placebo + plt/gem (n=60)
Median OS (95% CI), mo	3.8 (3.2, 5.6)	3.4 (2.6, 4.5)
36-mo OS rate (95% CI), %	5.4 (0.0, 11.2)	1.8 (0.0, 5.4)
OS HR (95% CI)	0.77 (0.51, 1.17)	

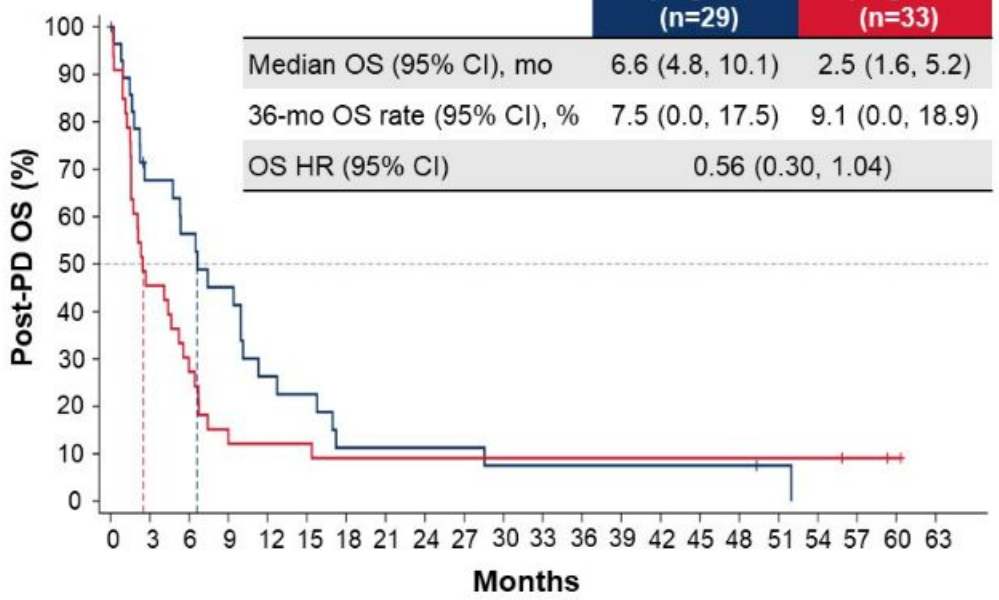


No. at risk

Atezo + plt/gem	62	40	20	14	10	8	4	4	4	3	3	3	3	3	3	3	3	3	2	2	0
Placebo + plt/gem	60	31	12	6	6	3	2	1	1	1	1	1	1	1	1	1	1	1	0	0	0

Cisplatin-treated patients

	Atezo + plt/gem (n=29)	Placebo + plt/gem (n=33)
Median OS (95% CI), mo	6.6 (4.8, 10.1)	2.5 (1.6, 5.2)
36-mo OS rate (95% CI), %	7.5 (0.0, 17.5)	9.1 (0.0, 18.9)
OS HR (95% CI)	0.56 (0.30, 1.04)	



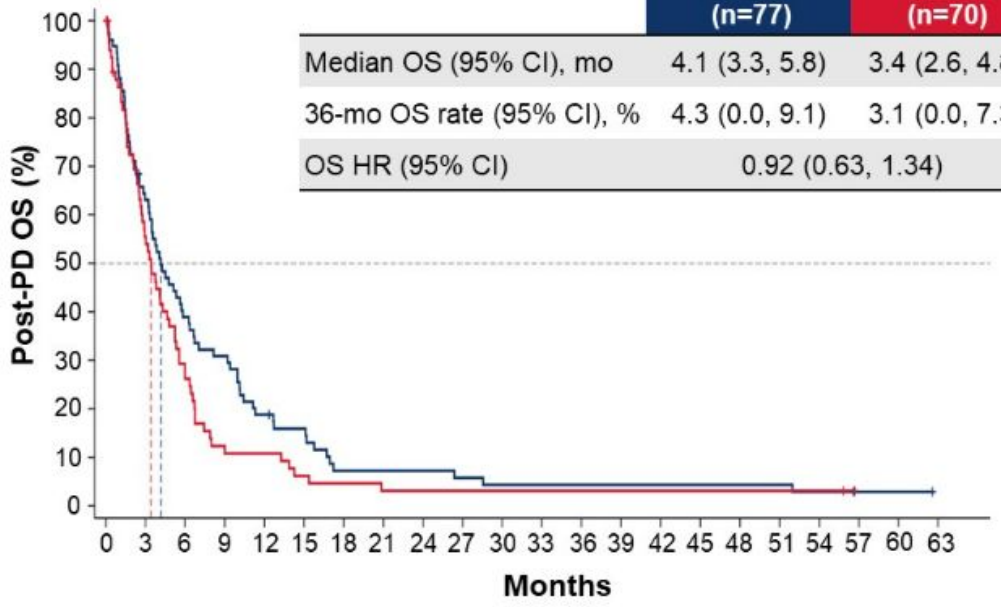
No. at risk

Atezo + plt/gem	29	18	15	12	7	6	3	3	3	3	2	2	2	2	2	2	1	0	0	0	0
Placebo + plt/gem	33	15	9	5	4	4	3	3	3	3	3	3	3	3	3	3	3	3	2	1	0

IMvigor 130: Post-progression OS in patients with PD: by PD-L1 Status

PD-L1 IC0/1

	Atezo + plt/gem (n=77)	Placebo + plt/gem (n=70)
Median OS (95% CI), mo	4.1 (3.3, 5.8)	3.4 (2.6, 4.8)
36-mo OS rate (95% CI), %	4.3 (0.0, 9.1)	3.1 (0.0, 7.3)
OS HR (95% CI)	0.92 (0.63, 1.34)	

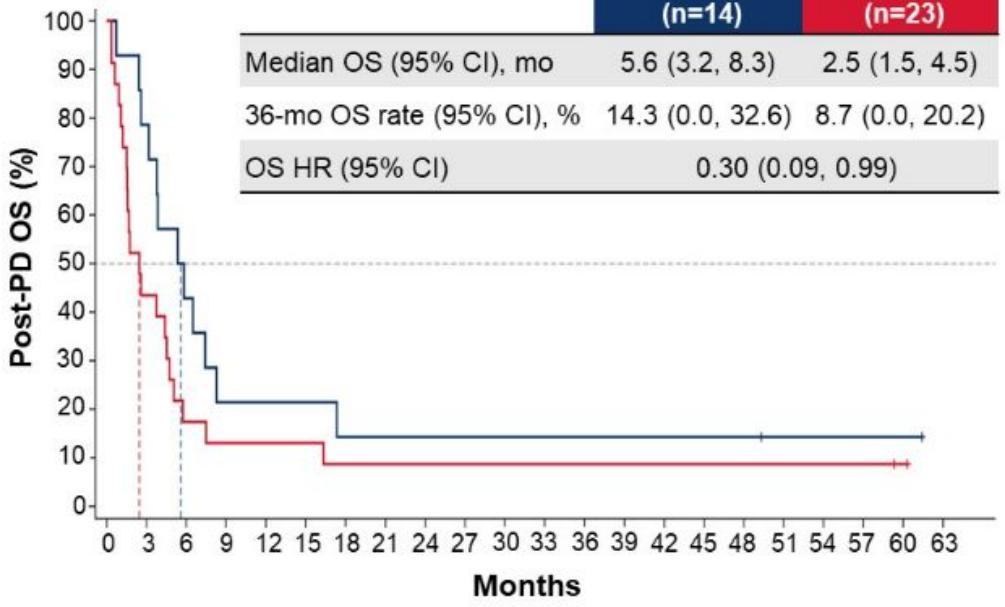


No. at risk

Atezo + plt/gem	77	47	29	23	14	11	5	5	5	4	3	3	3	3	3	3	3	3	2	1	1	0
Placebo + plt/gem	70	36	17	8	7	4	3	2	2	2	2	2	2	2	2	2	2	2	0	0	0	

PD-L1 IC2/3

	Atezo + plt/gem (n=14)	Placebo + plt/gem (n=23)
Median OS (95% CI), mo	5.6 (3.2, 8.3)	2.5 (1.5, 4.5)
36-mo OS rate (95% CI), %	14.3 (0.0, 32.6)	8.7 (0.0, 20.2)
OS HR (95% CI)	0.30 (0.09, 0.99)	



No. at risk

Atezo + plt/gem	14	11	6	3	3	3	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	0								
Placebo + plt/gem	23	10	4	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	0								

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]

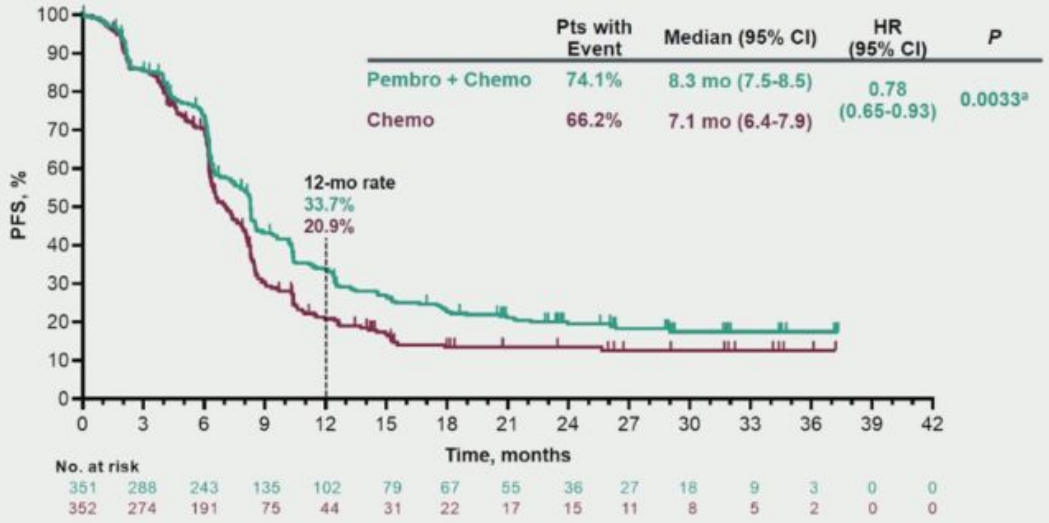
Stratification Factors
- PD-L1 expression[a] (CPS ≥10 vs <10)
- Choice of platinum

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

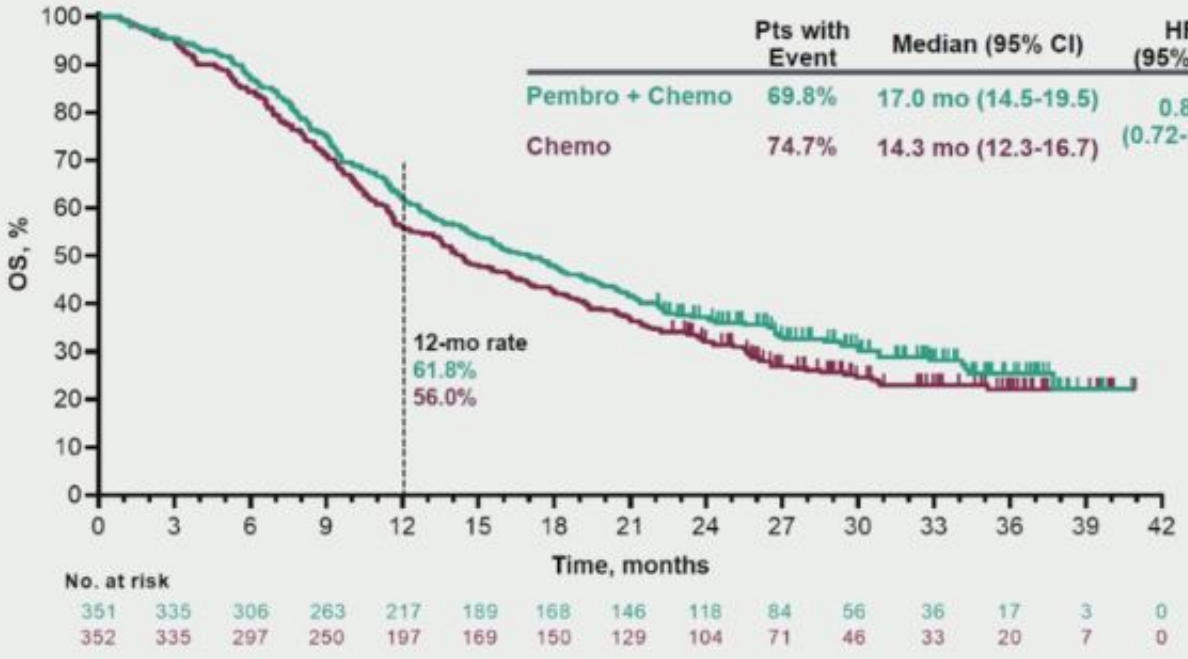
- Dual primary endpoints: PFS per RECIST v1.1 by BICR and OS
- Secondary endpoints: ORR, DCR, and DOR by BICR per RECIST v1.1, safety

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



	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	74.1%	8.3 mo (7.5-8.5)	0.78 (0.65-0.93)	0.0033[a]
Chemo	66.2%	7.1 mo (6.4-7.9)		

OS: Pembro + Chemo vs Chemo, ITT Population



	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407[a]
Chemo	74.7%	14.3 mo (12.3-16.7)		

Neither PFS or OS reached statistical significance via predetermined plan

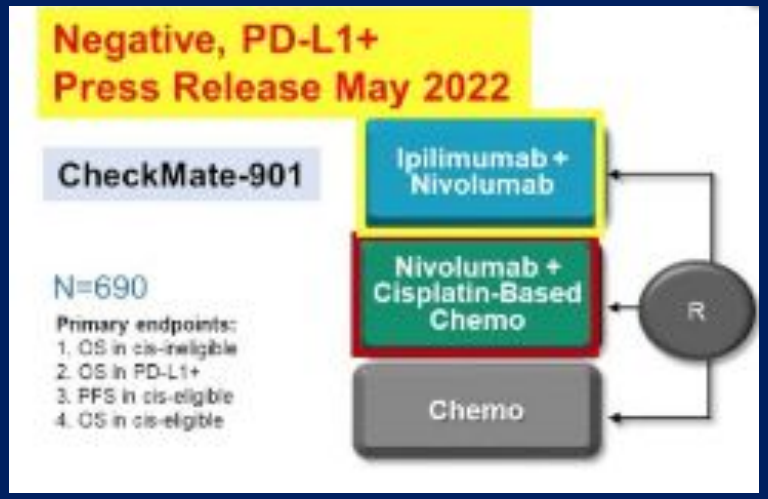
Alva et al. ESMO 2020.
Powles et al. NEJM 2021.

(nivolumab) in Combination with Cisplatin-Based Chemotherapy Shows Overall Survival and Progression-Free Survival Benefit for Cisplatin-Eligible Patients with Unresectable or Metastatic Urothelial Carcinoma in the Phase 3 CheckMate -901 Trial

07/11/2023

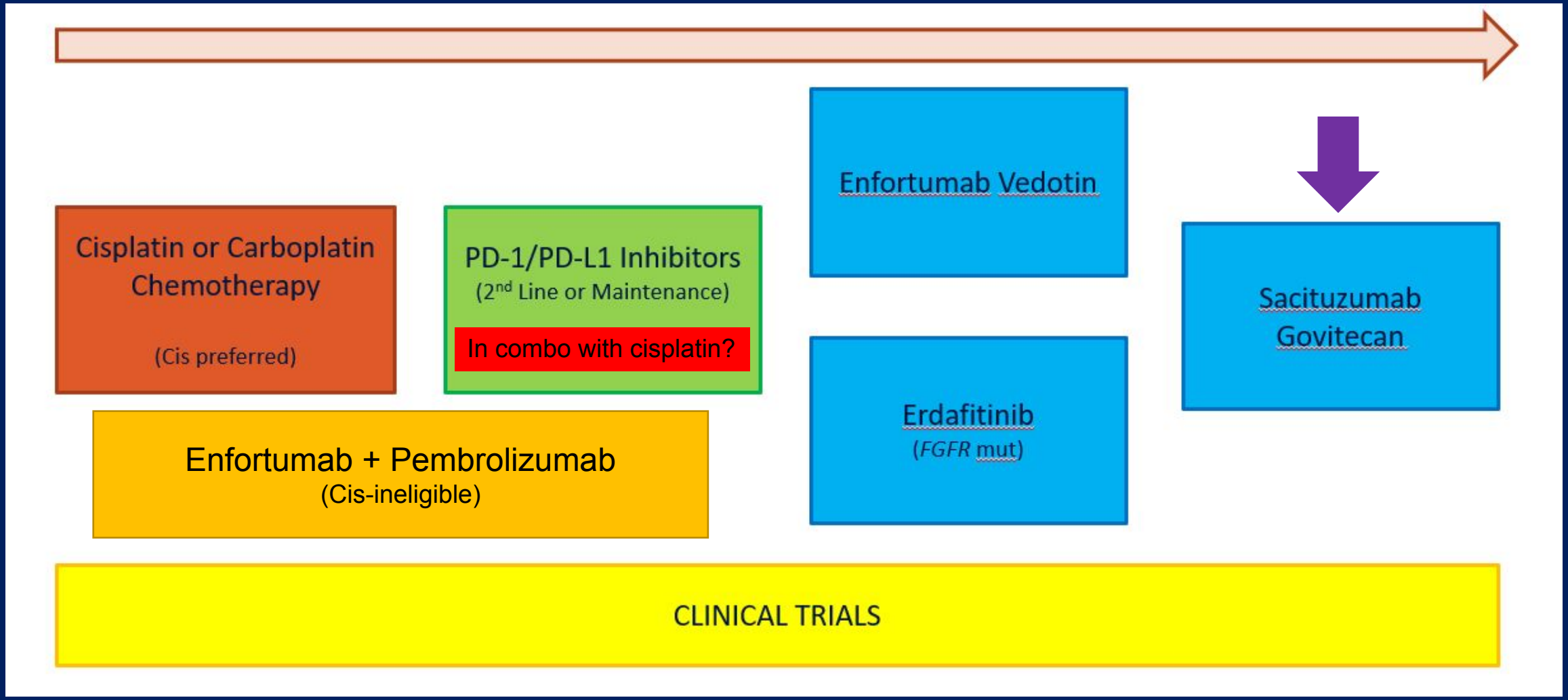
CATEGORY: Corporate/Financial News

CheckMate -901 is the first and only Phase 3 trial with an immunotherapy-based combination to demonstrate a survival benefit compared to standard-of-care cisplatin-based combinations in the first-line treatment of this patient population

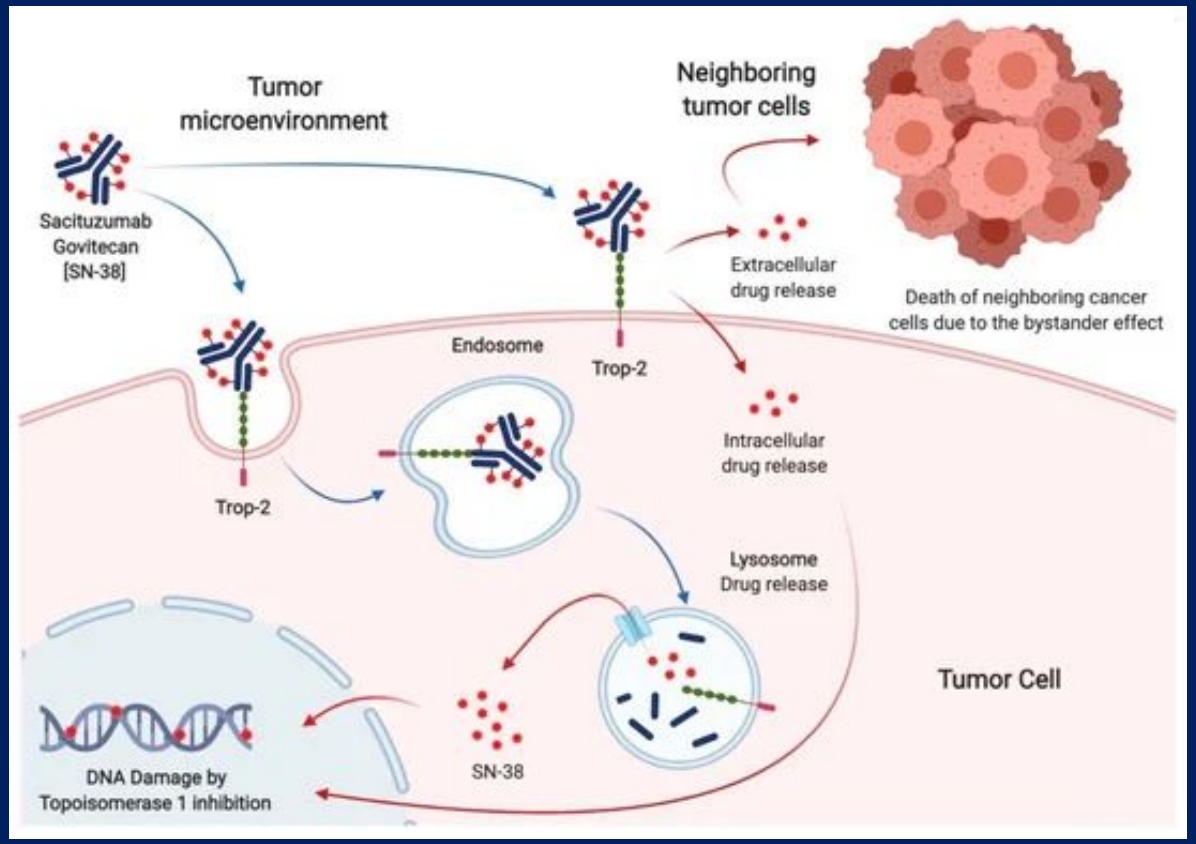


Apolo et al. ASCO 2023.

Metastatic Urothelial Carcinoma



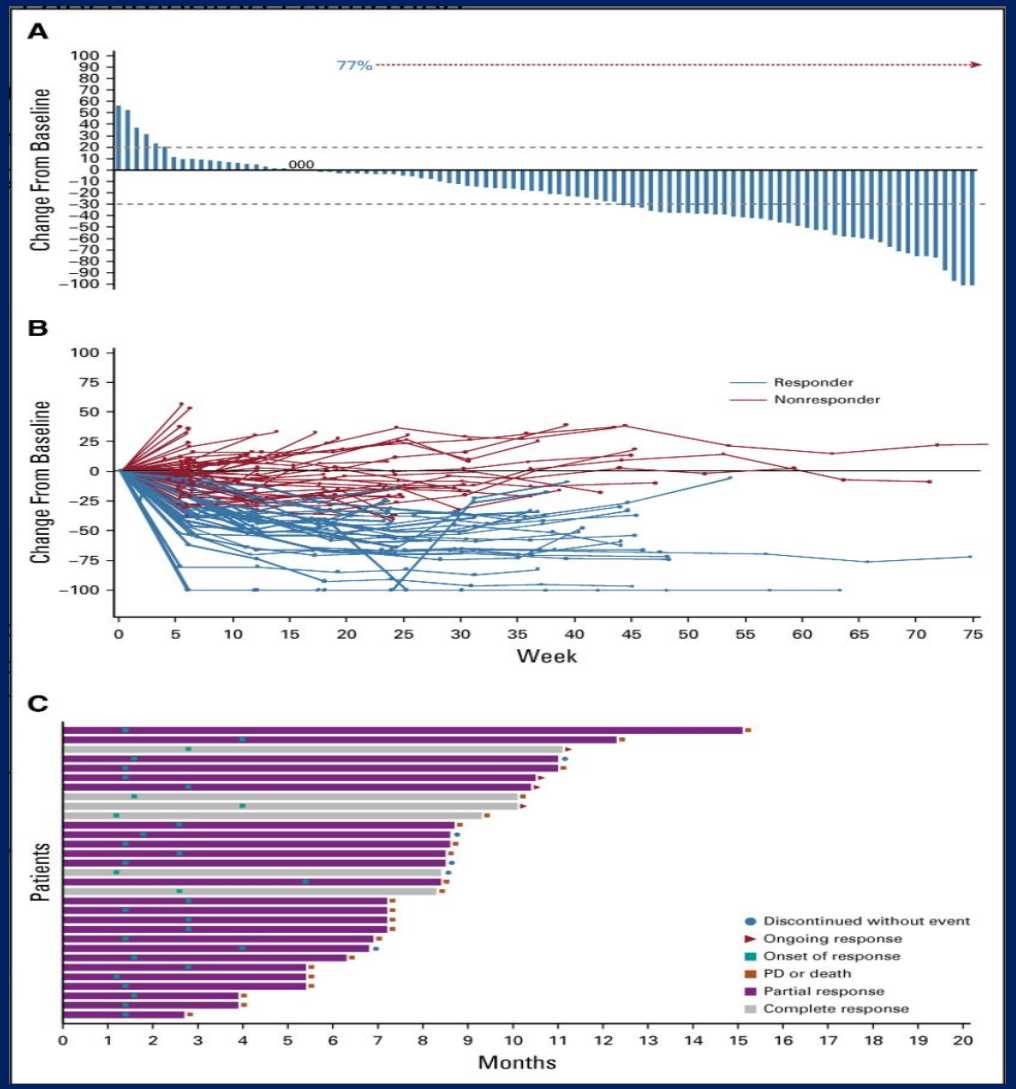
Sacituzumab Govitecan (SG): Trop-2-Directed ADC



- SG is an ADC composed of Trop-2 antibody coupled to SN-38, the active metabolite of irinotecan
- SG was granted FDA –accelerated approval for patients with locally advanced or mUC who have previously received a platinum-chemotherapy and a CPI.

Pavone G et al. Molecules 2021.
Bardia A et al. Ann Oncol 2021.
Tagawa ST et al. J Clin Oncol 2021.

TROPHY-U-01 Cohort 1: Prior Platinum and Immunotherapy



- 113 patients
- ORR 27.4%, including 6 CR (5.3%) and 25 PR (22.1%)
- Median DOR 7.2 mo (95% CI, 4.7 – 8.6m)
- mPFS 5.4mo (95% CI, 3.5 - 7.2 m; range 2.4 - 8.9)
- mOS 10.9mo (95% CI 9 - 13 m; range 3.8 -19.8

Petrylak et al. ASCO Annual Meeting 2020.
Tagawa ST et al. J Clin Oncol 2021.

TROPHY-U-01 Cohort 1: Prior Platinum and Immunotherapy

TABLE 3. Most Common TRAEs of Any Grade (Observed in ≥ 20% of Patients) orTRAEs Grade ≥ 3 (Observed in ≥ 5% of Patients) (N = 113)

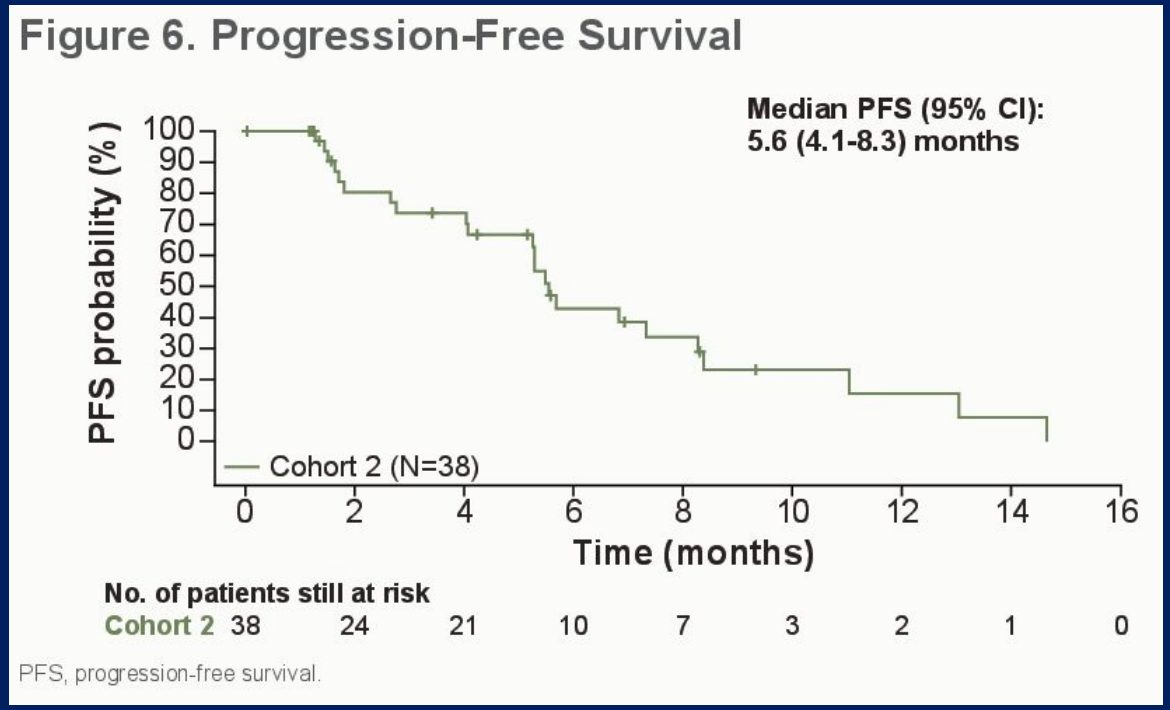
Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	Neutropenia	46	22	12
	Leukopenia	25	12	5
	Anemia	33	14	0
	Lymphopenia	11	5	2
	Febrile neutropenia	10	7	3
GI	Diarrhea	65	9	1
	Nausea	60	4	0
	Vomiting	30	1	0
General disorders and administrative site conditions	Fatigue	52	4	0
Skin and subcutaneous tissue	Alopecia	47	0	0
Metabolism and nutrition	Decreased appetite	36	3	0
Infections and infestations	Urinary tract infection	8	6	0

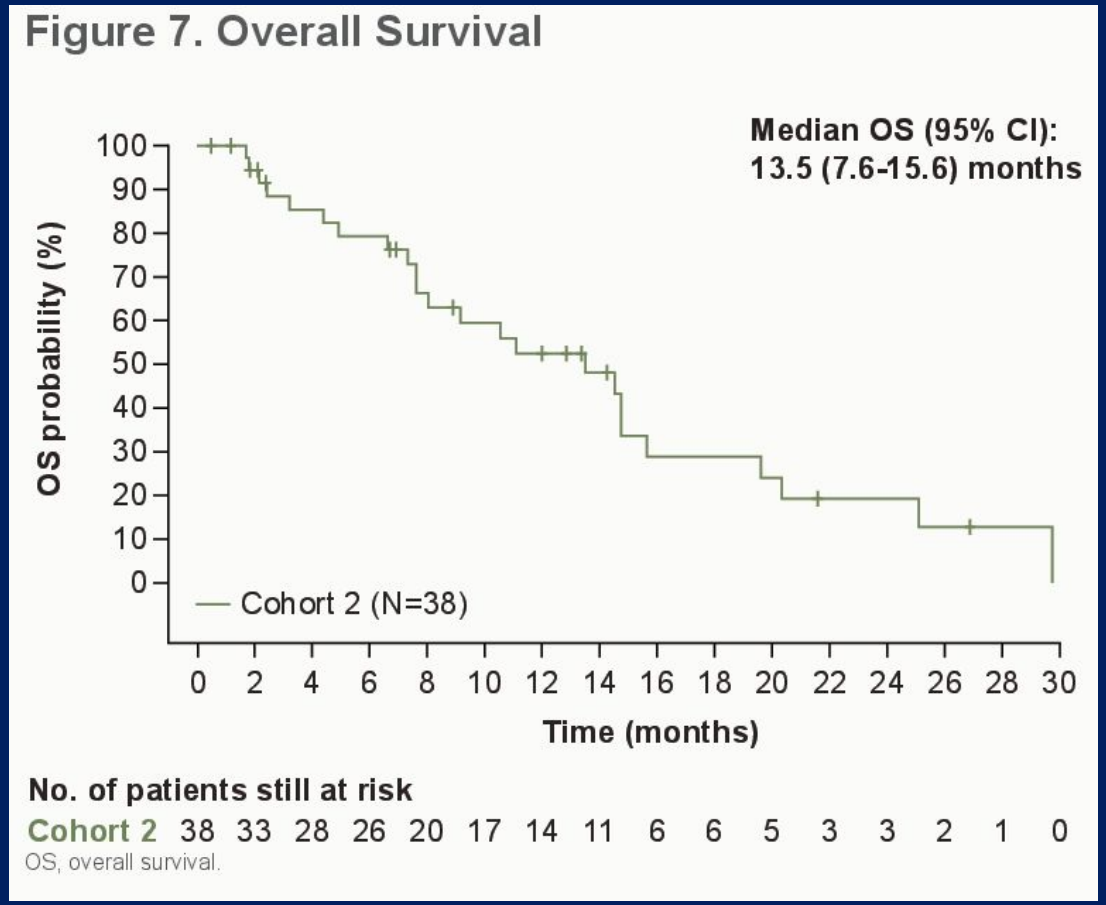
Abbreviation: TRAEs, treatment-related adverse events.

[a]Neutrophil count decreased, WBC count decreased, lymphocyte count decreased, and hemoglobin decreased have been recoded to neutropenia, leukopenia, lymphopenia, and anemia, respectively, for summary purposes.

Tagawa ST et al. J Clin Oncol 2021.

TROPHY-U-01 Cohort 2: Platinum-Ineligible and CPI-exposed

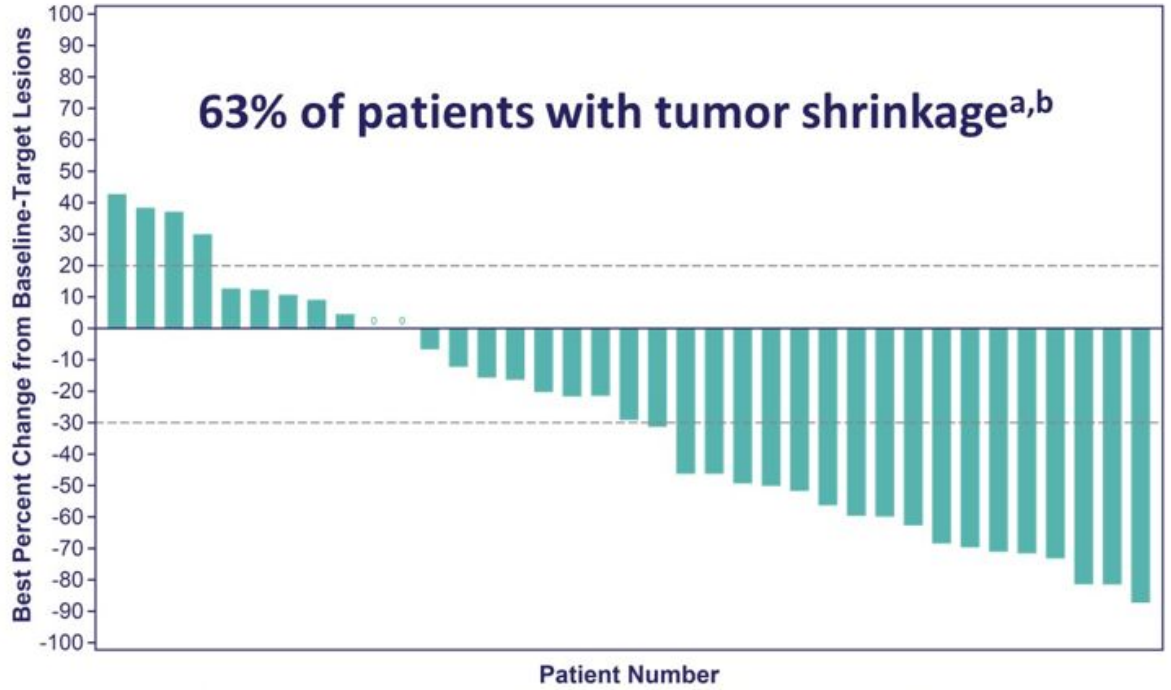




Petrylak, D.P. et al. GU ASCO. 2023. Abstract #520

TROPHY-U-01 Cohort 3: SG + Pembro in pts with mUC who progressed after PLT-based regimens

- Median follow-up: 5.8 months (data cutoff date: 2021-09-24)
- Median time to response: 2 months (1.3–2.8; n=14)
- Median DOR not yet reached: N/A (2.80-N/A)
- Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached



	Cohort 3[a] (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	14 (34) [20.1-50.6]
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	*4 (10)*
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]	25 (61) [44.5-75.8]

- Treatment-related Gr 3-4 AEs in 59% of patients. 39% of pts had SG dose reduction due to TRAE.
- No treatment-related death occurred.

Grivas et al. GU ASCO 2022.

TROPHY-U-01 Study Design

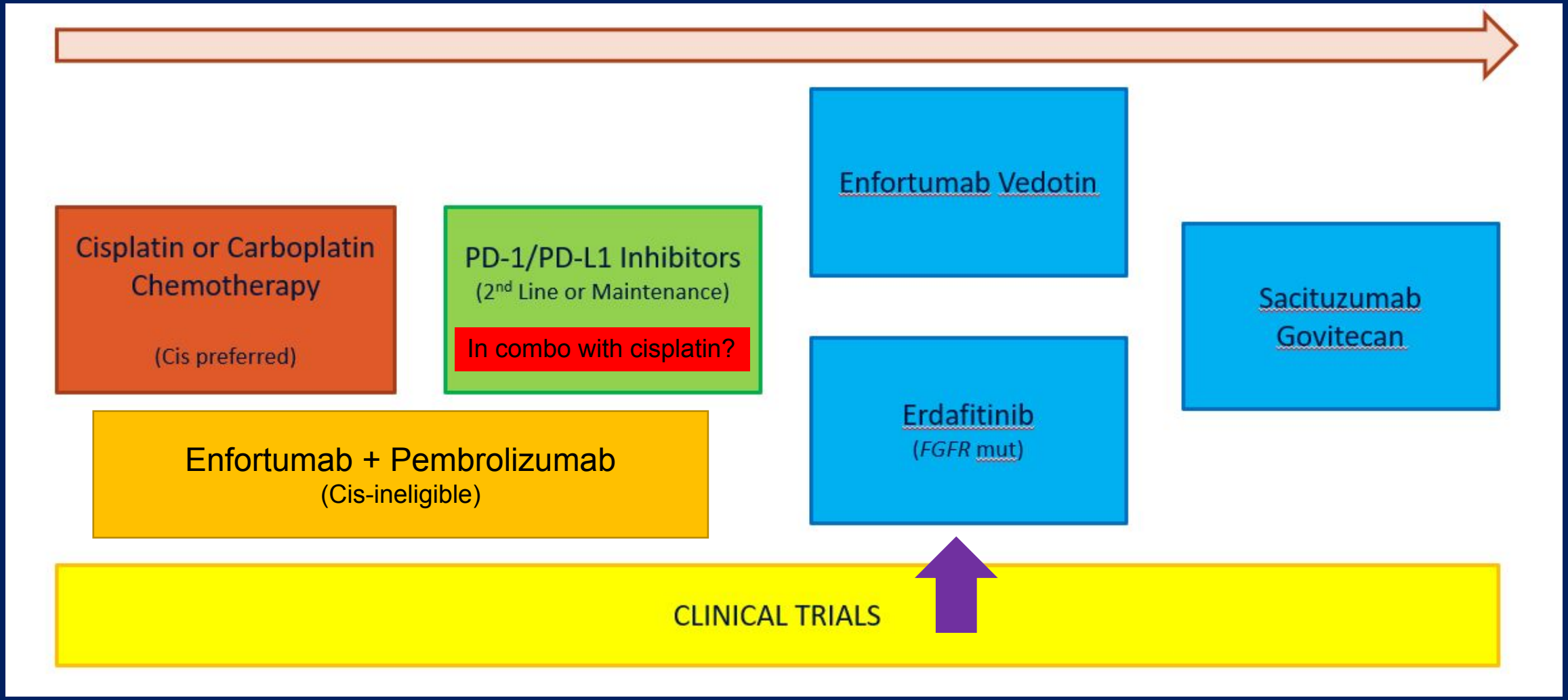
Cohort 1[a] (~100 pts): Pts (≥18 years) with mUC who progressed after prior PT- and CPI-based therapies	→	Tagawa ST, et al.[1,2] SG 10 mg/kg D1 and D8, every 21 D
Cohort 2 (~40 pts): Pts with mUC who progressed after CPI therapy and were PT-ineligible at the start of study	→	Petrylak DP, et al.[3] SG 10 mg/kg D1 and D8, every 21 D
Cohort 3 (up to 61 pts): CPI-naive pts with mUC who progressed after prior PT-therapies	→	Grivas P, et al.[4] SG 10 mg/kg D1 and D8, every 21 D + Pembrolizumab 200 mg D1 every 21 D
Cohort 4 (up to 57 pts): Pts with cis-eligible, treatment-naive LA or mUC	→	Induction: Cis + SG (6 cycles); Maintenance: (1) SG + avelumab; (2) SG + zim[c]
Cohort 5[b] (~158 pts): Pts with LA or mUC who completed 1L cis + gem without progression	→	Arms: (1) SG + zim; (2): Avelumab; (3): zim
Cohort 6 (up to 226 pts): Pts with cis-ineligible, treatment-naive LA or mUC	→	Arms: (1) SG; (2) SG + zim; (3) SG + zim + dom; (4) carbo + gem + avelumab maintenance

Enrollment of Cohorts 1,2,3 is closed. Currently enrollment is open under PA 9 for cohort 4,5,and 6.

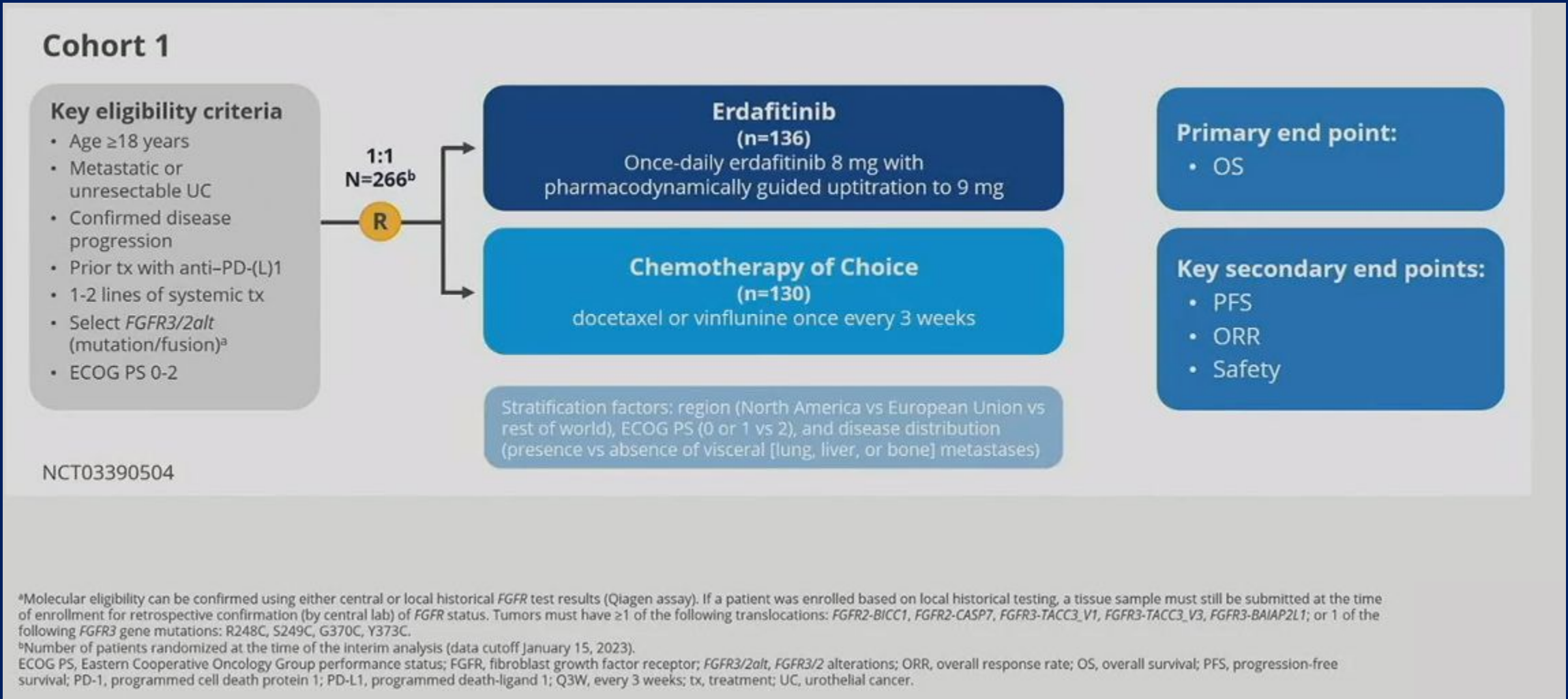
[a]Accelerated FDA approval for treatment of patients with LA or mUC who previously received PT-containing chemotherapy and PD-1/L1 inhibitor9. [b]Patients will complete 4-6 cycles of cis + gem induction before being randomized. [c]After completion of the cohort 5 safety lead-in, patients in the dose expansion of cohort 4 will receive SG + zim in the maintenance phase.

1. Tagawa ST, et al. *J Clin Oncol*. 2021 Aug 1;39(22):2474-2485; 2. Tagawa ST, et al. *J Clin Oncol*. 41, 2023 (suppl 6; abstr 526); 3. Petrylak DP, et al. *J Clin Oncol*. 41, 2023 (suppl 6; abstr 520); 4. Grivas P, et al. *J Clin Oncol*. 41, 2023 (suppl 6; abstr 518)

Metastatic Urothelial Carcinoma



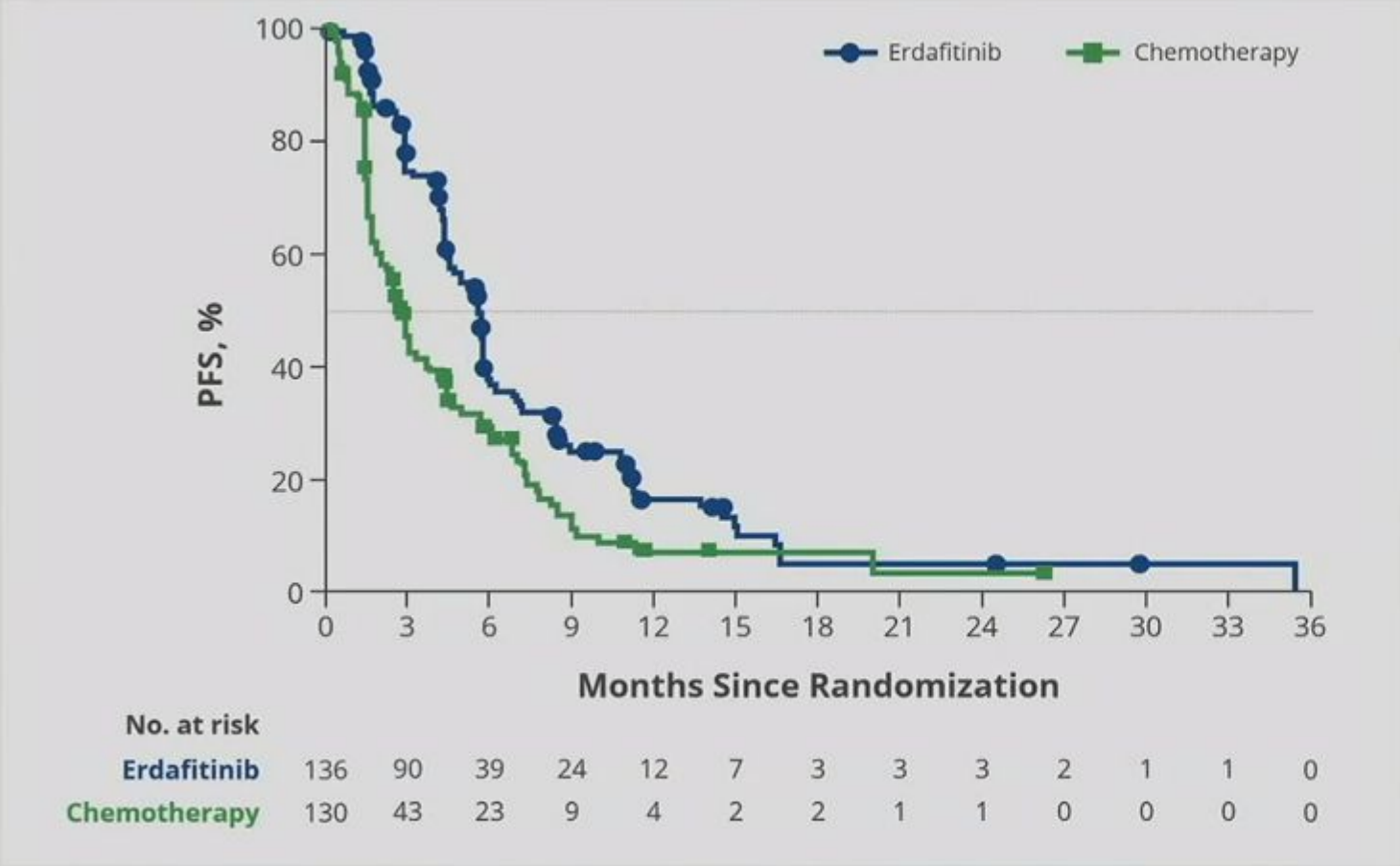
Phase 3 THOR Study: Erdafitinib vs Chemotherapy of Choice in Patients with Advanced Urothelial Cancer and Selected FGFR Aberrations



[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.

Loriot, Y. et al. ASCO Annual Meeting. 2023. Abstract LBA4619

THOR: Erdafitinib Significantly Improved Progression-Free Survival vs Chemotherapy

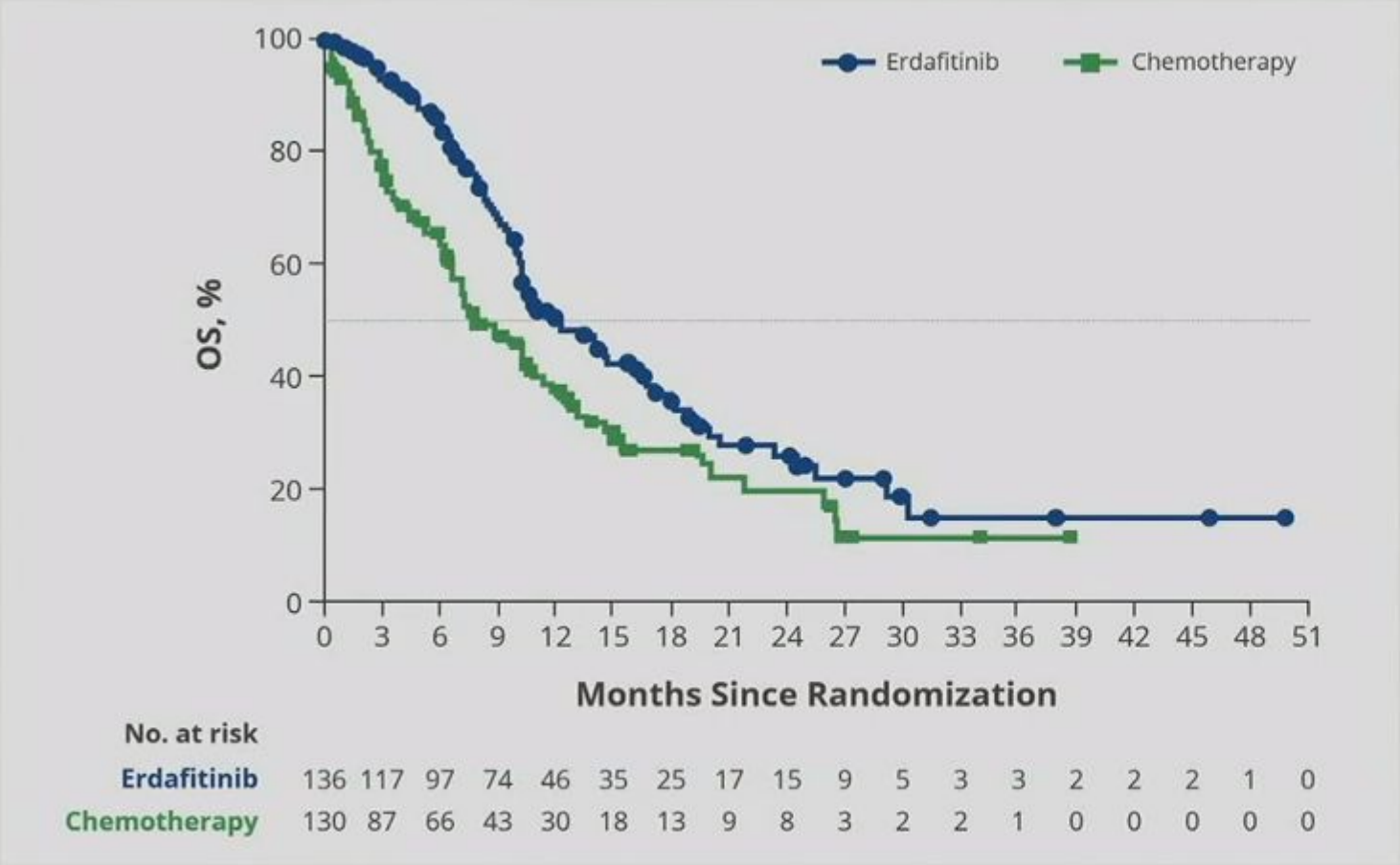


- Median PFS was 5.6 versus 2.7 months for erdafitinib versus chemotherapy
- Erdafitinib reduced the risk of progression or death by 42% versus chemotherapy
  - HR, 0.58 (95% CI, 0.44-0.78; *P* = 0.0002)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Loriot, Y. et al. ASCO Annual Meeting. 2023. Abstract LBA4619

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

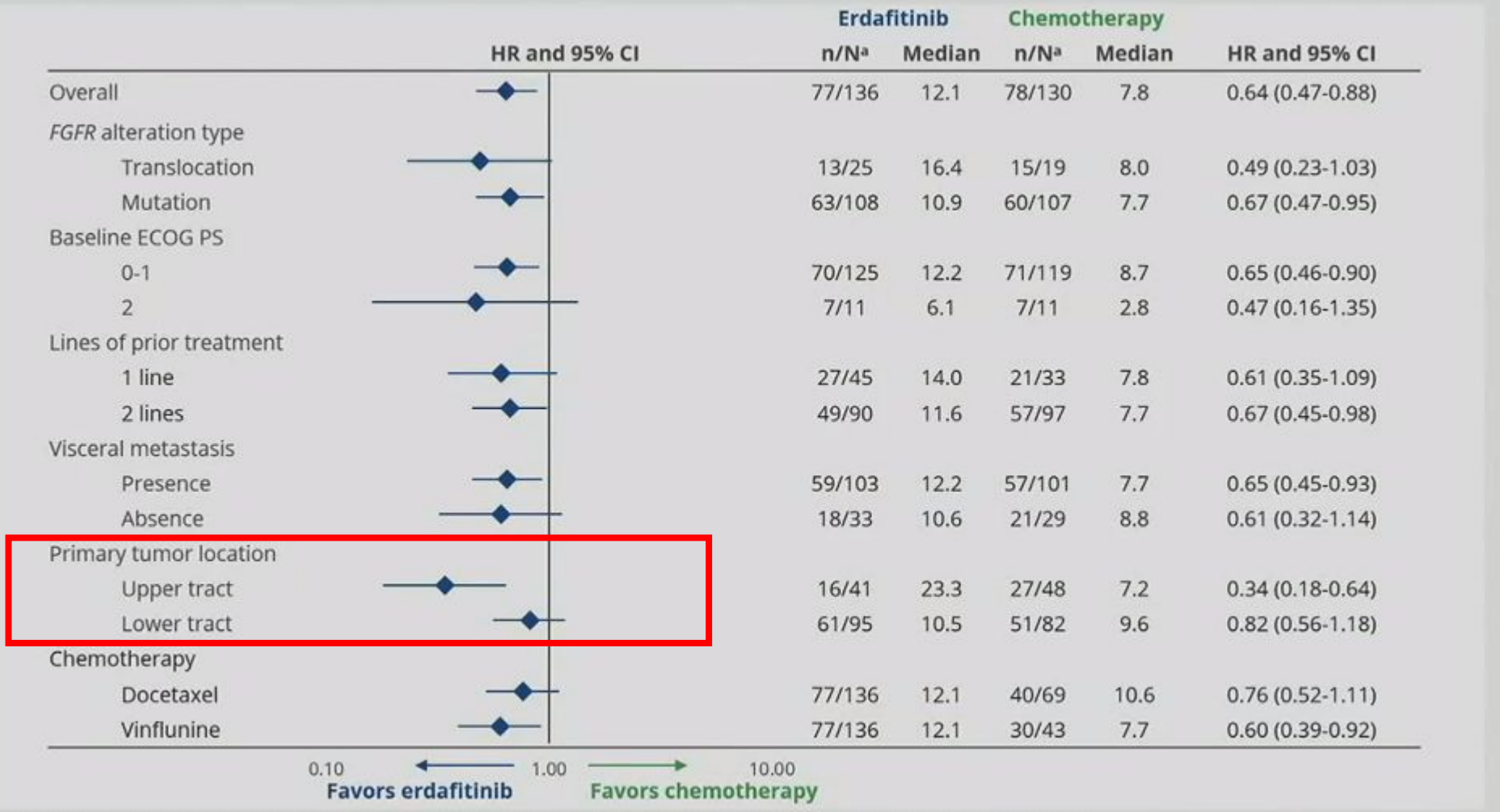


- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; $P = 0.005$)[a]
- Based on these interim analysis results, the IDMC recommended to stop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

Loriot, Y. et al. ASCO Annual Meeting. 2023. Abstract LBA4619

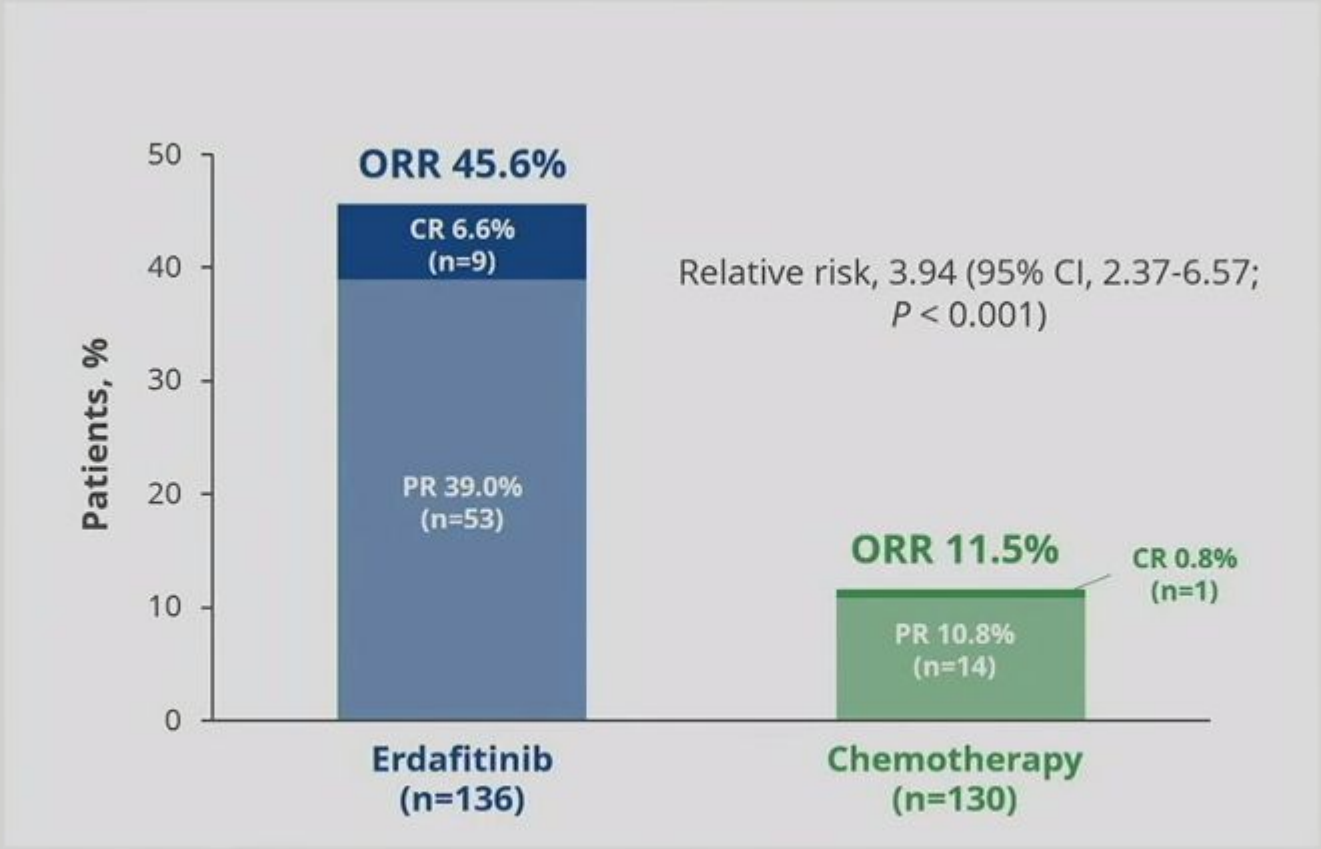
THOR: Overall Survival Benefit with Erdafitinib vs Chemotherapy Was Consistently Observed Across Subgroups



[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.

Loriot, Y. et al. ASCO Annual Meeting. 2023. Abstract LBA4619

THOR: Objective Reponse Rate Was Significantly Higher for Erdafitinib vs Chemotherapy



CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response.
[a]Responses were best overall response per investigator assessment.

Loriot, Y. et al. ASCO Annual Meeting. 2023. Abstract LBA4619

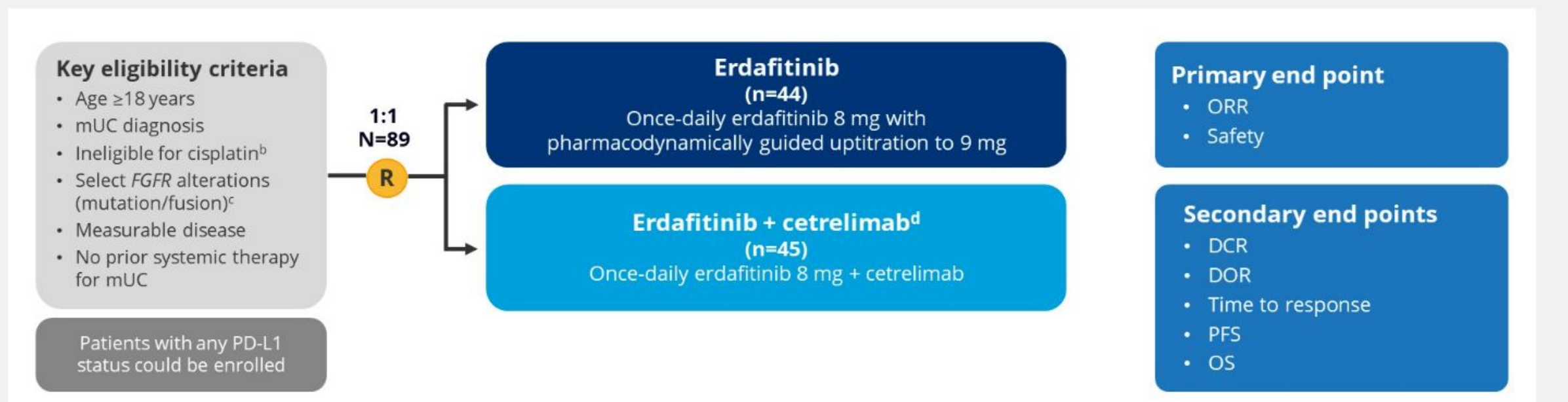
THOR: The Safety Profiles Were Consistent With the Known Profiles of Erdafitinib and Chemotherapy (1/2)

Patients with AEs, n (%)[a]	Erdafitinib (n=135)	
	Any grade	Grade 3-4
≥1 treatment-related AE	131 (97.0)	62 (45.9)
Hyperphosphatemia	106 (78.5)	7 (5.2)
Diarrhea	74 (54.8)	4 (3.0)
Stomatitis	62 (45.9)	11 (8.1)
Dry mouth	52 (38.5)	0
PPE syndrome	41 (30.4)	13 (9.6)
Onycholysis	31 (23.0)	8 (5.9)
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	11 (8.1%)[b]	

Patients with AEs of interest, n (%)	Erdafitinib (n=135)	
	Any grade	Grade 3-4
Nail disorders[a]	90 (66.7)	15 (11.1)
Skin disorders[b]	74 (54.8)	16 (11.9)
Eye disorders (excluding central serous retinopathy)[c]	57 (42.2)	3 (2.2)
Central serous retinopathy[d]	23 (17.0)	3 (2.2)

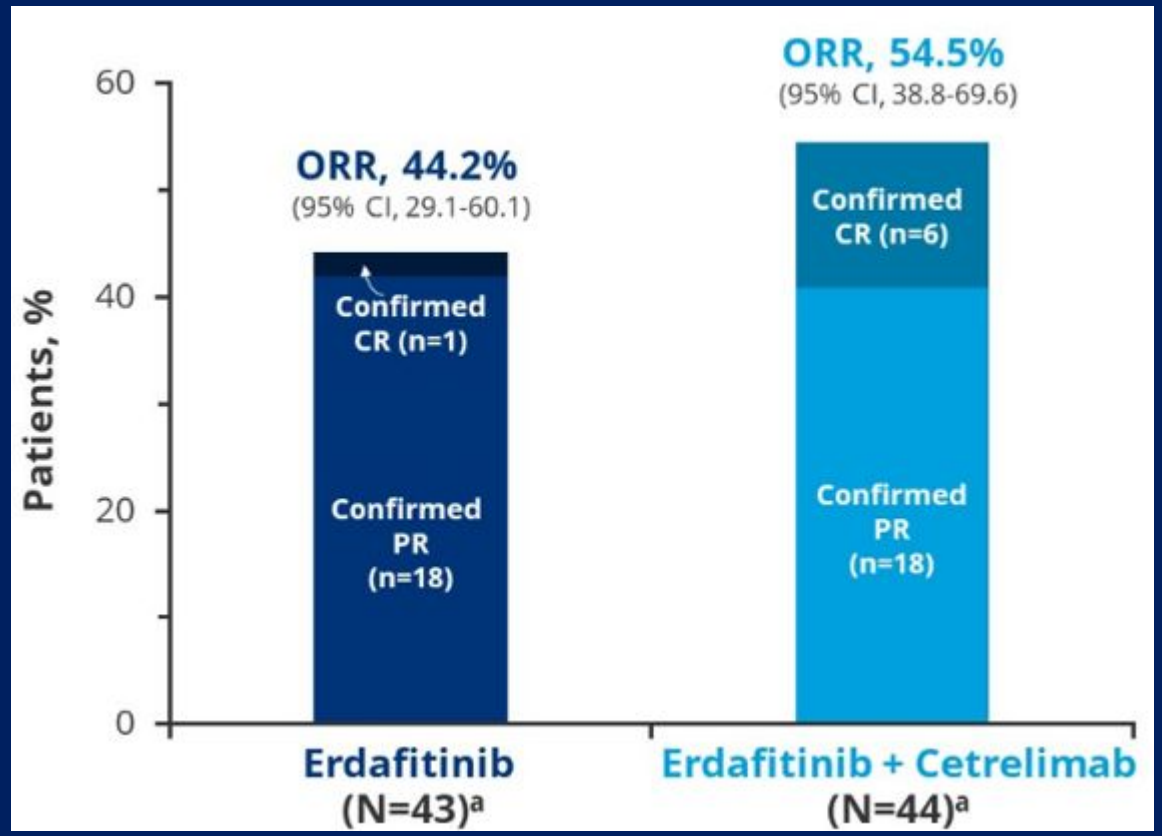
Loriot, Y. et al. ASCO Annual Meeting. 2023. Abstract LBA4619

NORSE: Erdafitinib vs Erdafitinib + Cetrelimab



Siefker-Radtke, A.O. et al. ASCO Annual Meeting. 2023. Abstract #4504

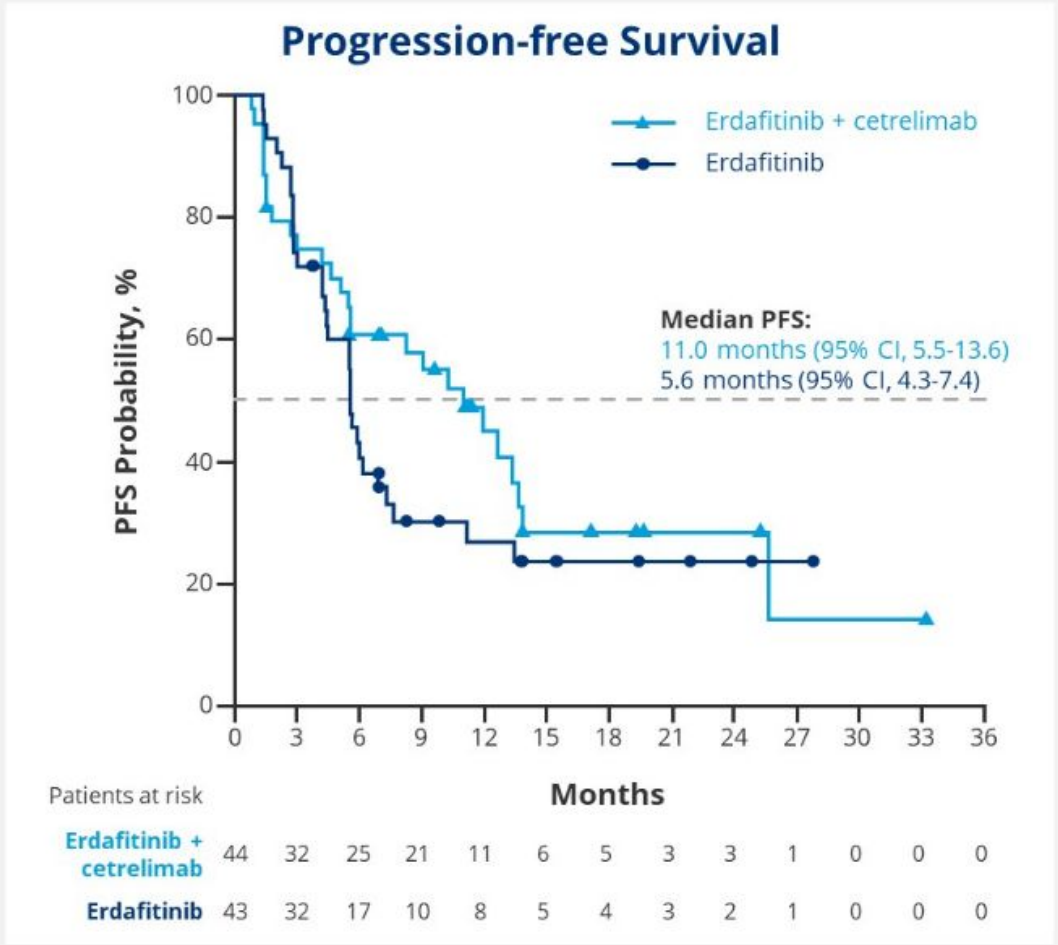
NORSE: Erdafitinib vs Erdafitinib + Cetrelimab

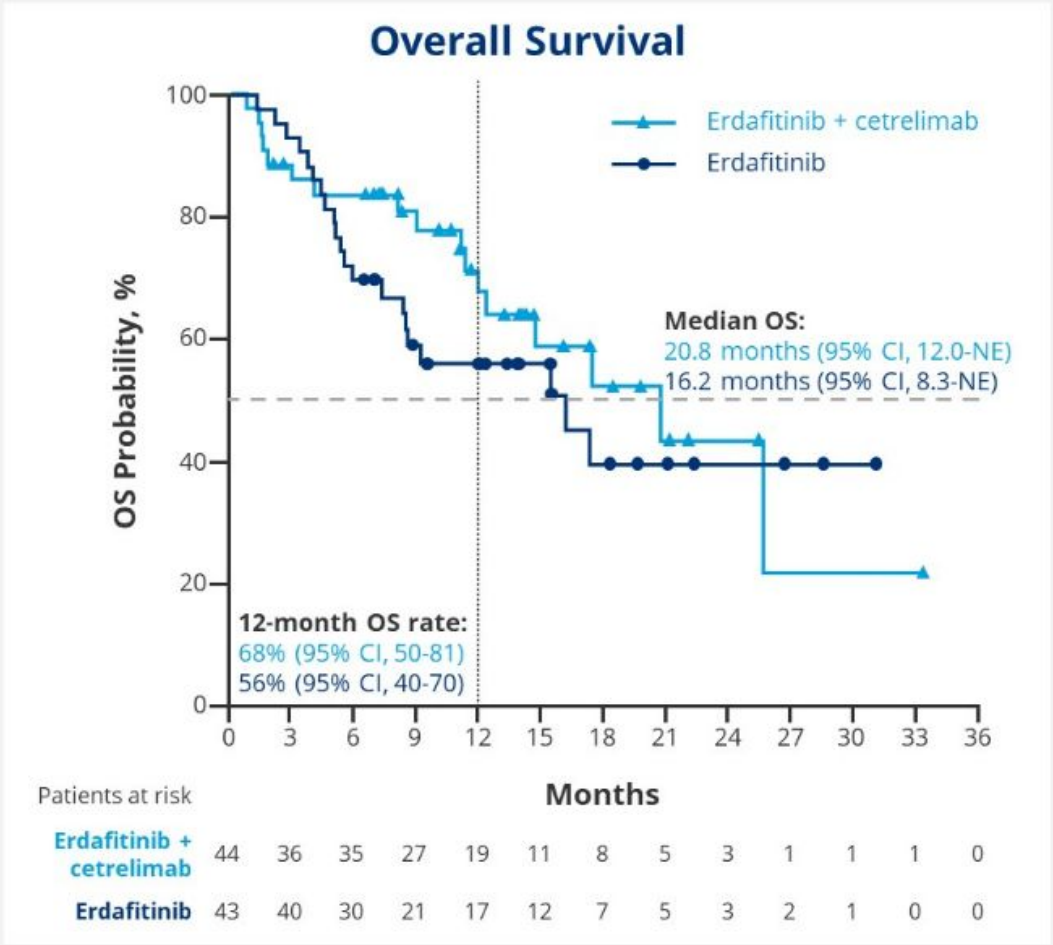


	Erdafitinib (N=43)	Erdafitinib + Cetrelimab (N=44)
DCR, median (95% CI), %	88.4 (74.9-96.1)	79.5 (64.7-90.2)
DOR, median (95% CI), months	9.72 (4.6-NE)	11.10 (8.8-NE)

Siefker-Radtke, A.O. et al. ASCO Annual Meeting. 2023. Abstract #4504

NORSE: Erdafitinib vs Erdafitinib + Cetrelimab

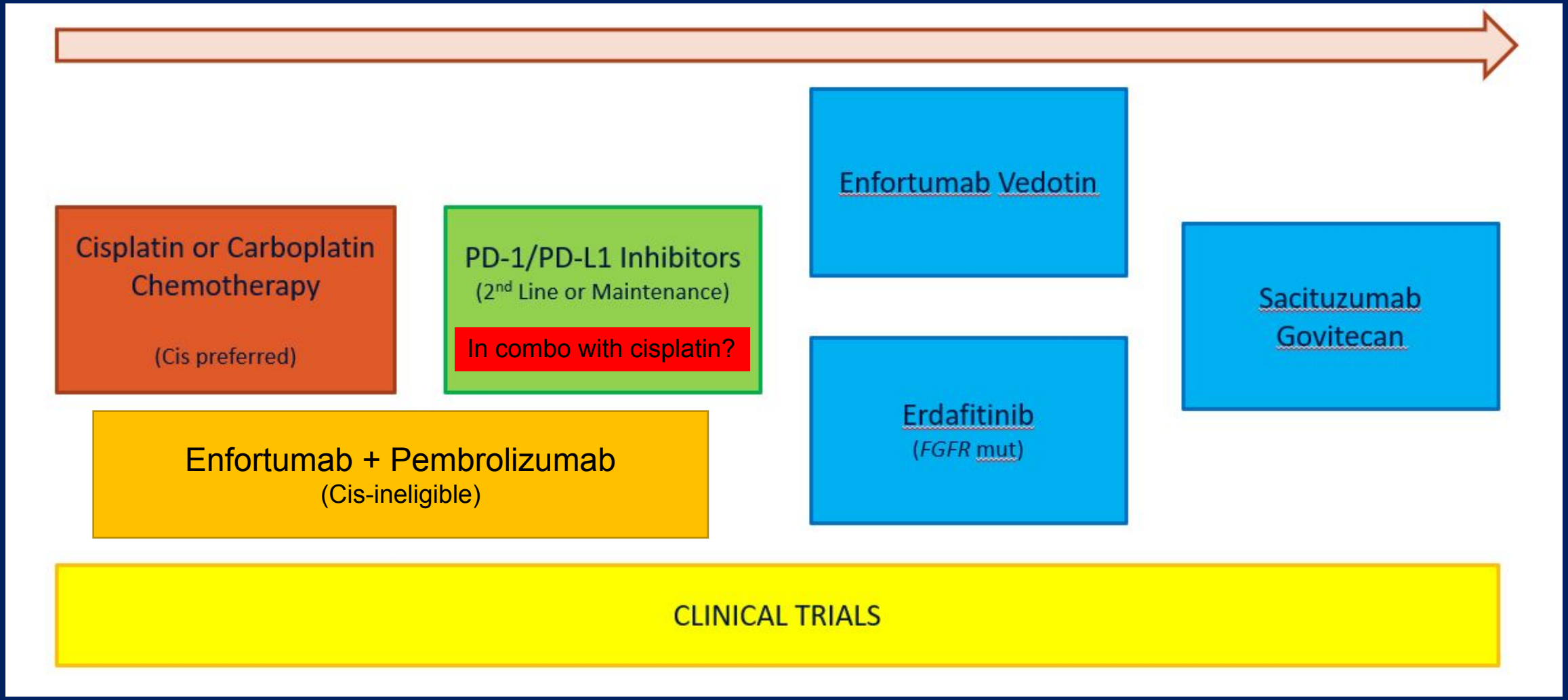




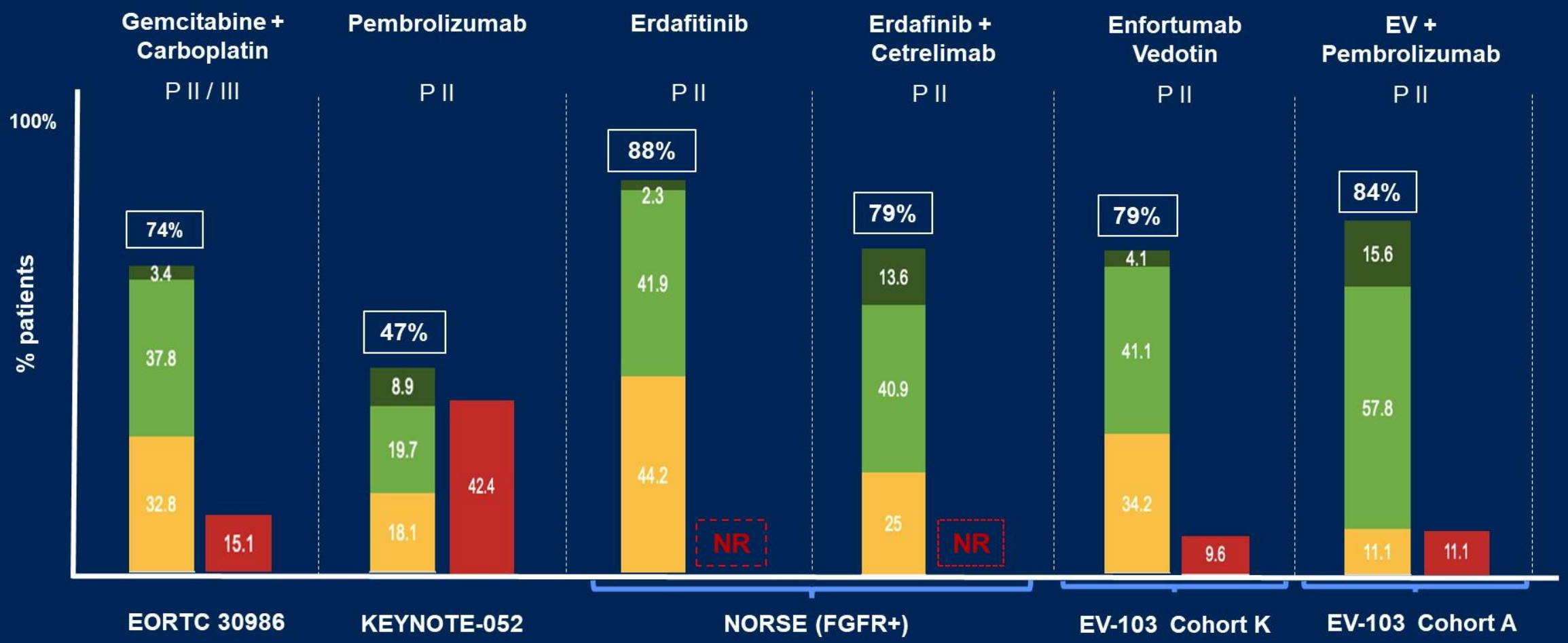
CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

Siefker-Radtke, A.O. et al. ASCO Annual Meeting. 2023. Abstract #4504

Metastatic Urothelial Carcinoma

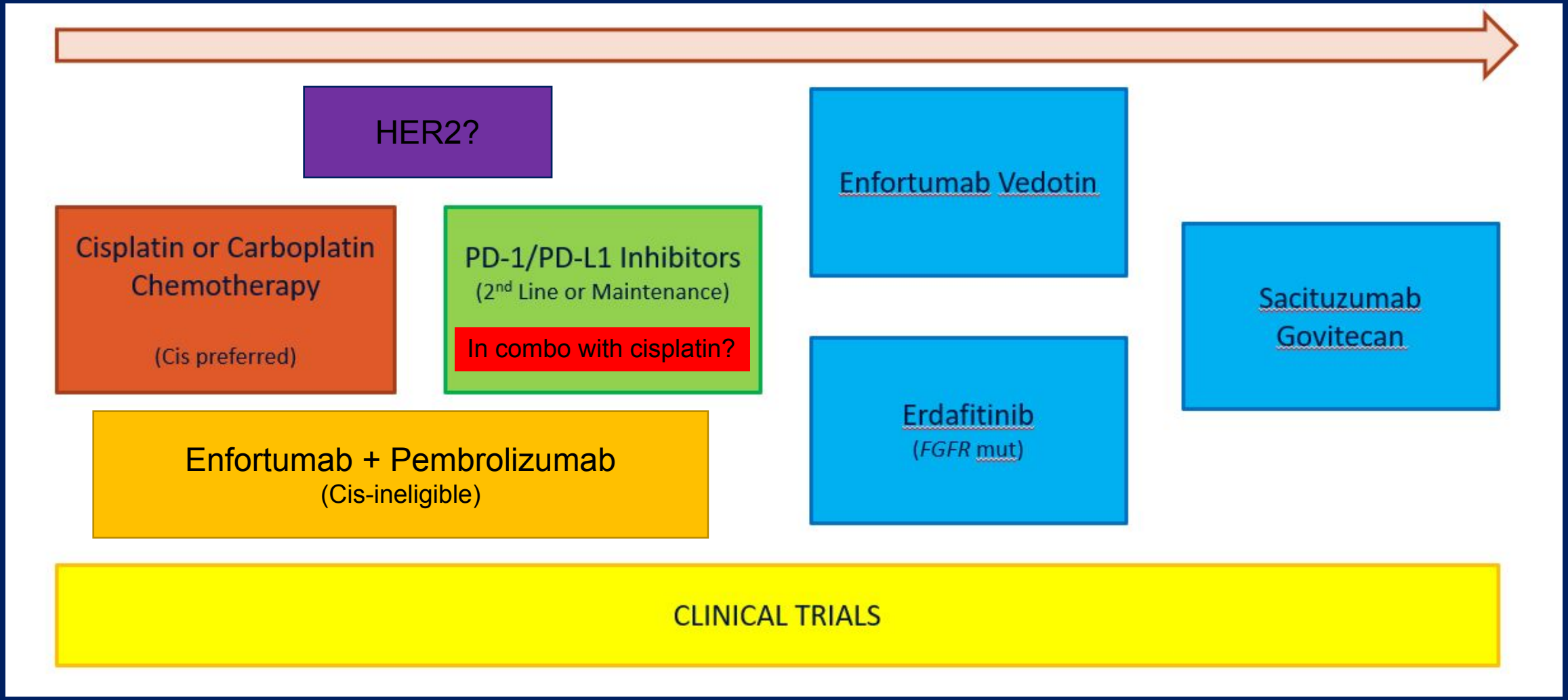


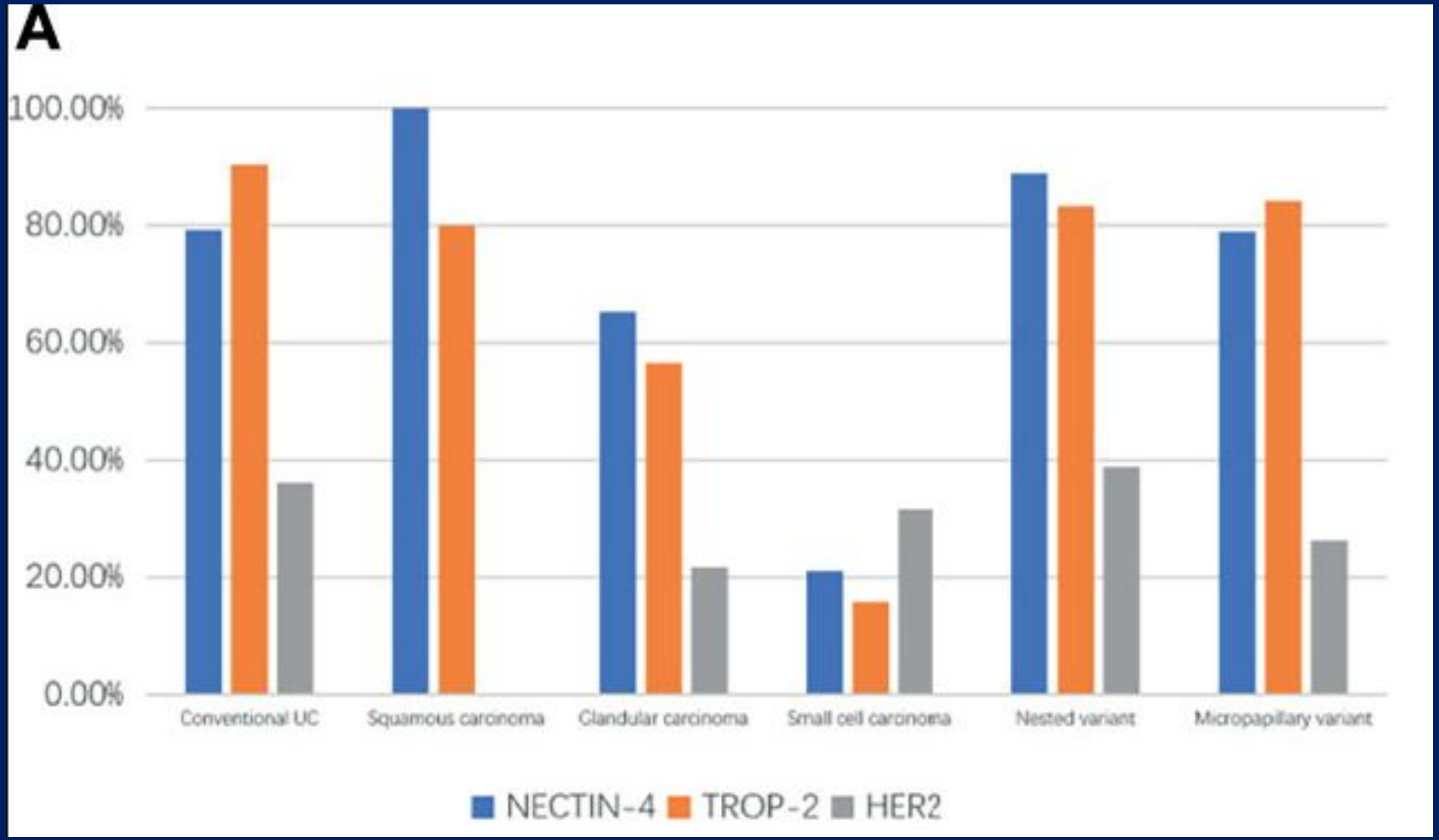
Disease Control Rate (DCR) in cisplatin ineligible



1. De Santis M, et al. J Clin Oncol 2012
2. Vuky J, et al. J Clin Oncol 2020
3. Siefker-Radtke A, et al. ASCO Annual Meeting, 2023. Abstract No. 4504
4. Gupta S, et al. ASCO Annual Meeting, 2023. Abstract No. 4505

Metastatic Urothelial Carcinoma





Fan Y et al. Front Oncol. 2022.

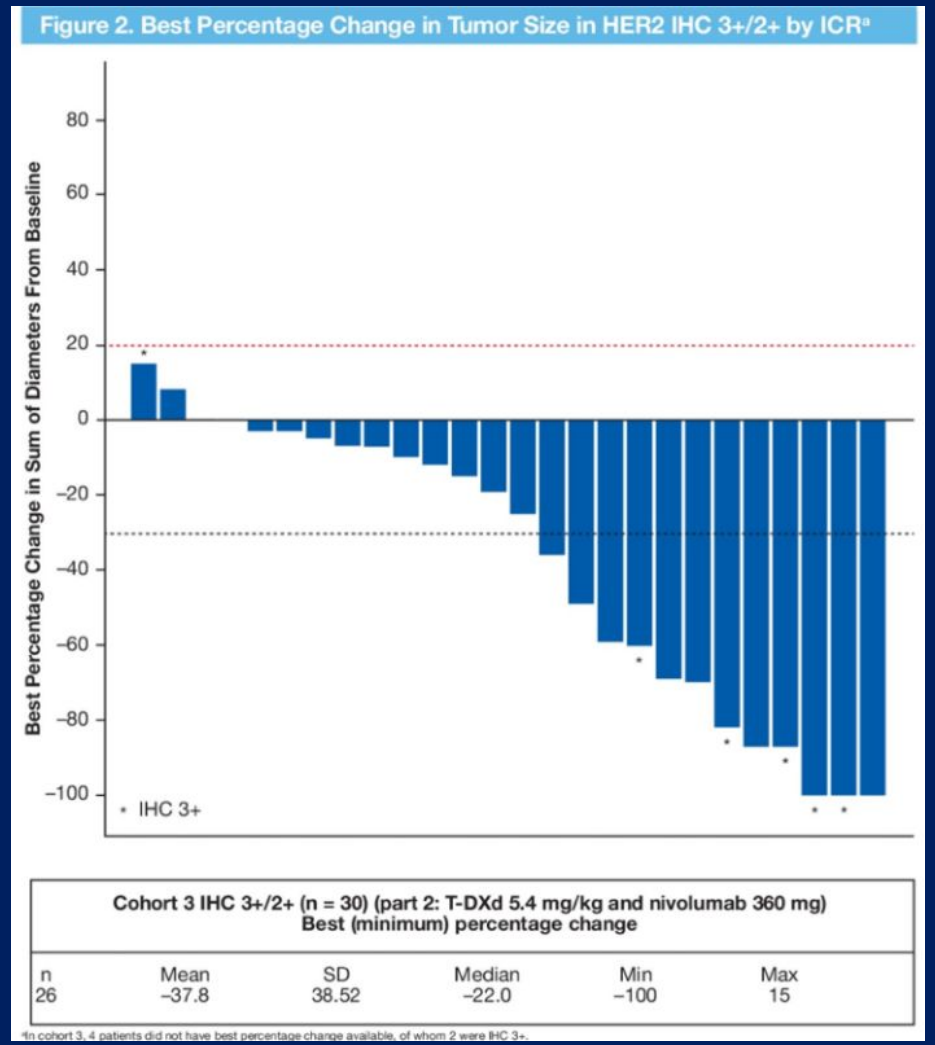
HER2 Failures

- Trastuzumab + Carboplatin, Paclitaxel, Gemcitabine
  - 22.7% suffered cardiac toxicity, 2 deaths
- Platinum/Gemcitabine ± Trastuzumab: No PFS difference (10.2 vs 8.2 m)
- Lapatanib: 3% PR as single-agent
- Lapatanib as maintenance post-chemo (Phase III). No PFS or OS benefit
- Afatanib: 21.7% had a 3 month PFS
- TDM1 basket study without much efficacy in urothelial cancer
- Tucatanib + Trastuzumab basket study ongoing

Hussain MH et al. JCO 2007.
Oudard S et al. European Journal of Cancer. 2015.
Wulfing C et al. Cancer. 2009
PowelsvT et al. JCO. 2017.
Hyman DM et al. Cancer Res. 2017

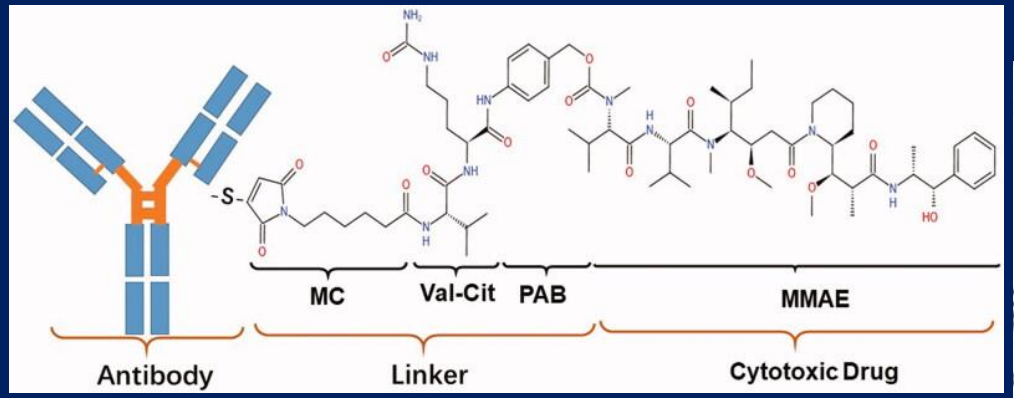
Trastuzumab Deruxtecan + Nivolumab

- Cohort 3, UC HER2 IHC 2/3+ (n=30)
- ORR 36.7%
  - CR 13.3%
  - PR 23.3%
  - SD 40%
- mPFS 6.9m
- mOS 11 m
- No previous IO
- Most common TEAEs: Nausea (73.5%), Fatgiue (52.9%), Vomitting (44.1%).
  - ILD/Pneumonitis in 23.5%. 1 G5.



Galsky et al. GU ASCO 2022.

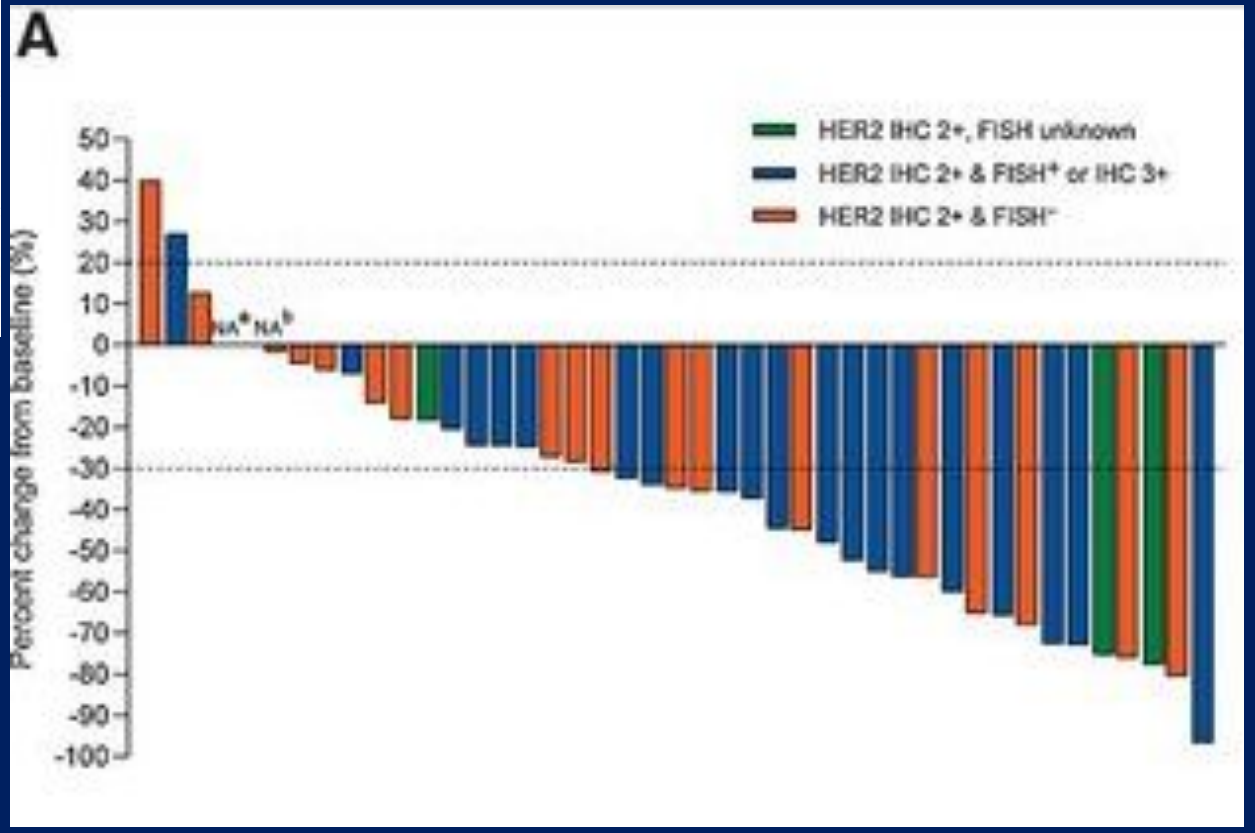
Disitamab vedotin



- mPFS 6.9 months
- mOS 13.9 motns

43 Patients
- CR 0%
- PR 51%
- SD 40%

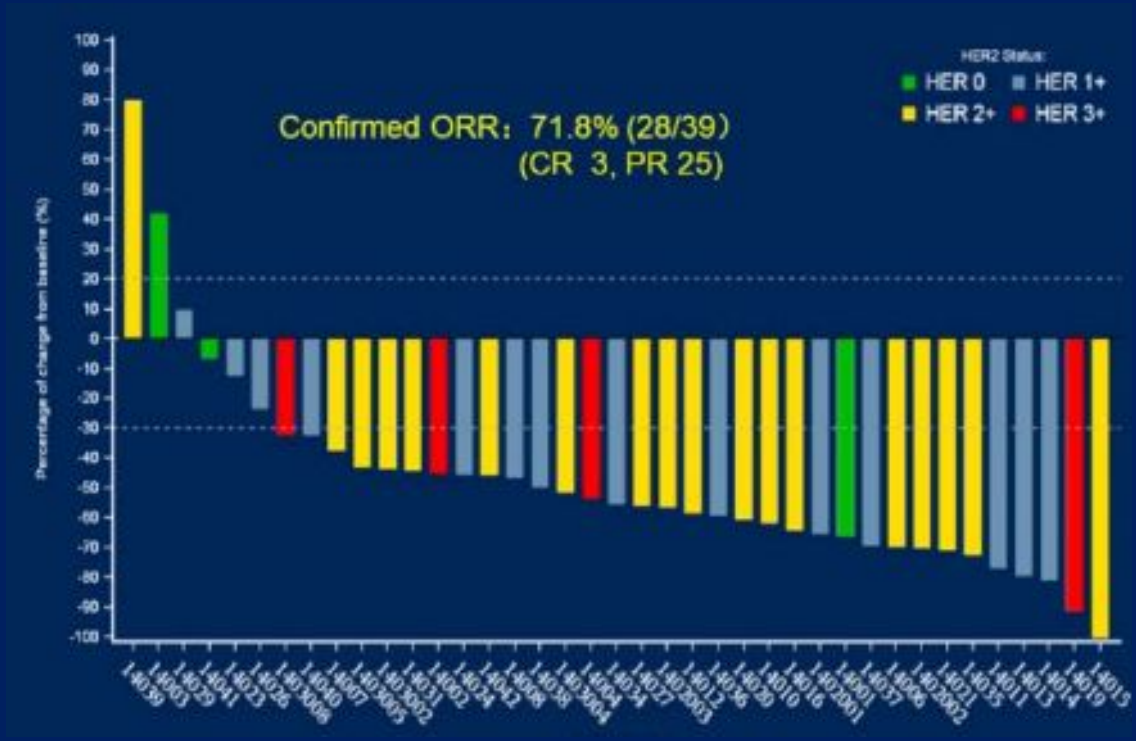
Duration of Response 6.9 m



Sheng X et al. Clin Cancer Res. 2021.

Disitamab vedotin + Torpalimab

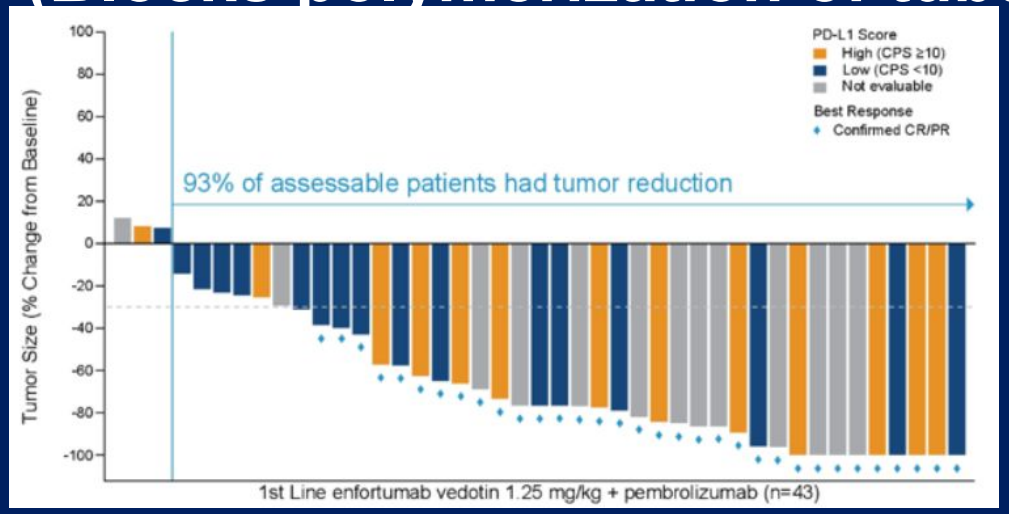
- Phase 1b/II Trial of 41 patients
- 61% had NOT received prior systemic therapy
- 54% HAD visceral metastases; 24% had liver mets
- HER2 IHC 2/3+ in 59%; PD-L1 CPS ≥10 in 32%



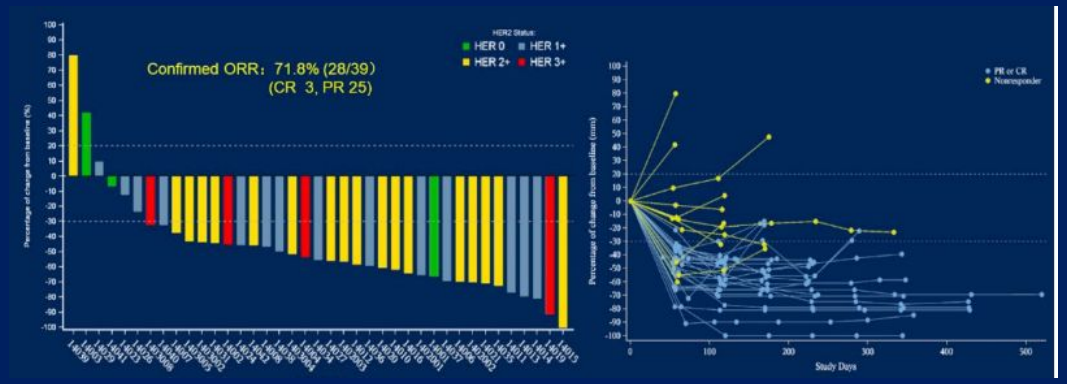
ASCO 2023: ORR 73.2%, CR 9.8%

Sheng X et al. ASCO Annual Meeting 2022.
Sheng X et al. ASCO Annual Meeting 2023.

MMAE Payload (Blocks polymerization of tubulin)

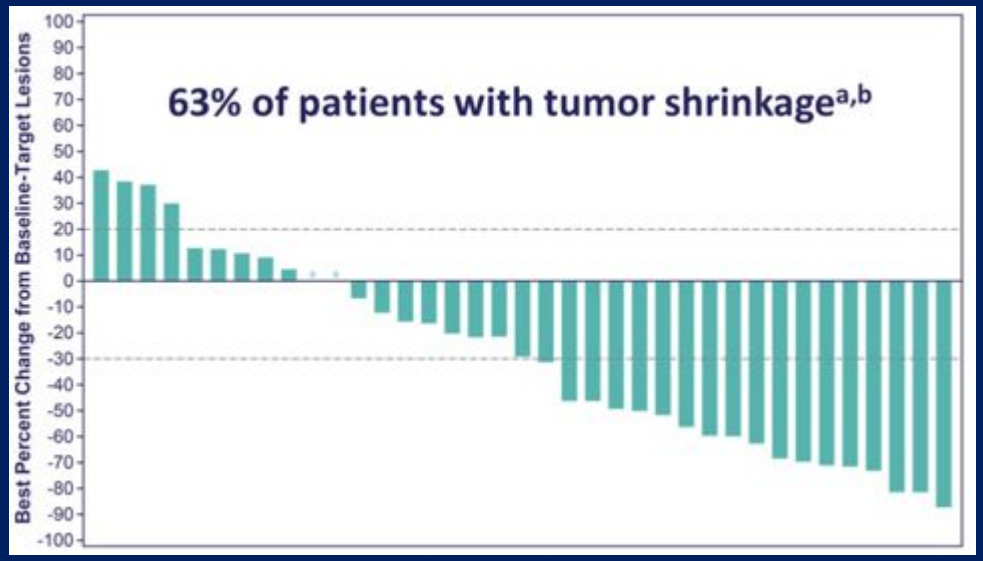


EV + PD1: OR 73%

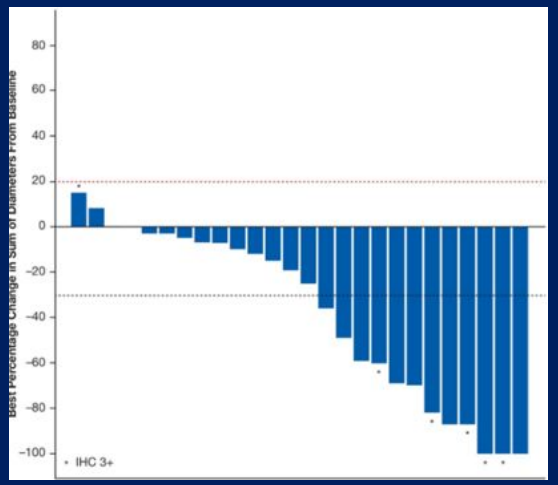


DV + PD1: OR 73%

SN-38 Payload (Topo-1 inh)



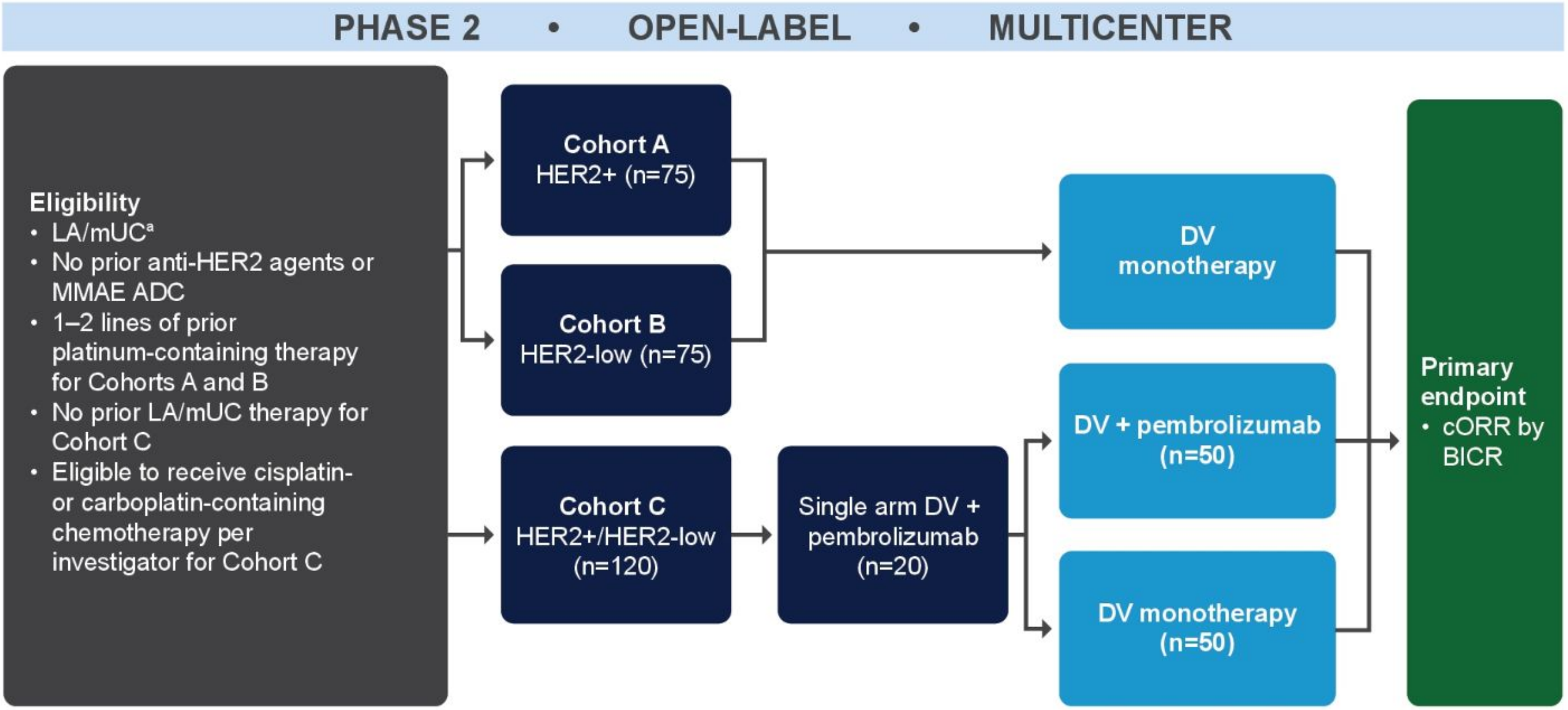
SG + PD1: OR 34%



T-Dxd + PD1: OR 37%

Grivas et al. GU ASCO 2022.
Petrylak et al. ASCO Annual Meeting 2019.
Galsky et al. GU ASCO 2022.
Sheng X et al. ASCO Annual Meeting 2023.

Phase 2: DV +/- Pembrolizumab



[a]Histologically-confirmed, including UC originating from the renal pelvis, ureters, bladder, or urethra.

Thank you!

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Thank you to Molly Altman, Therapeutic Development at SCRI