The growing landscape of antibody-drug conjugates

BLADDR 2022 ATHENS!

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Bladder Cancer Advocacy Network BCAN Leading the way to awareness and a cure

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

UNIVERSITY of WASHINGTON

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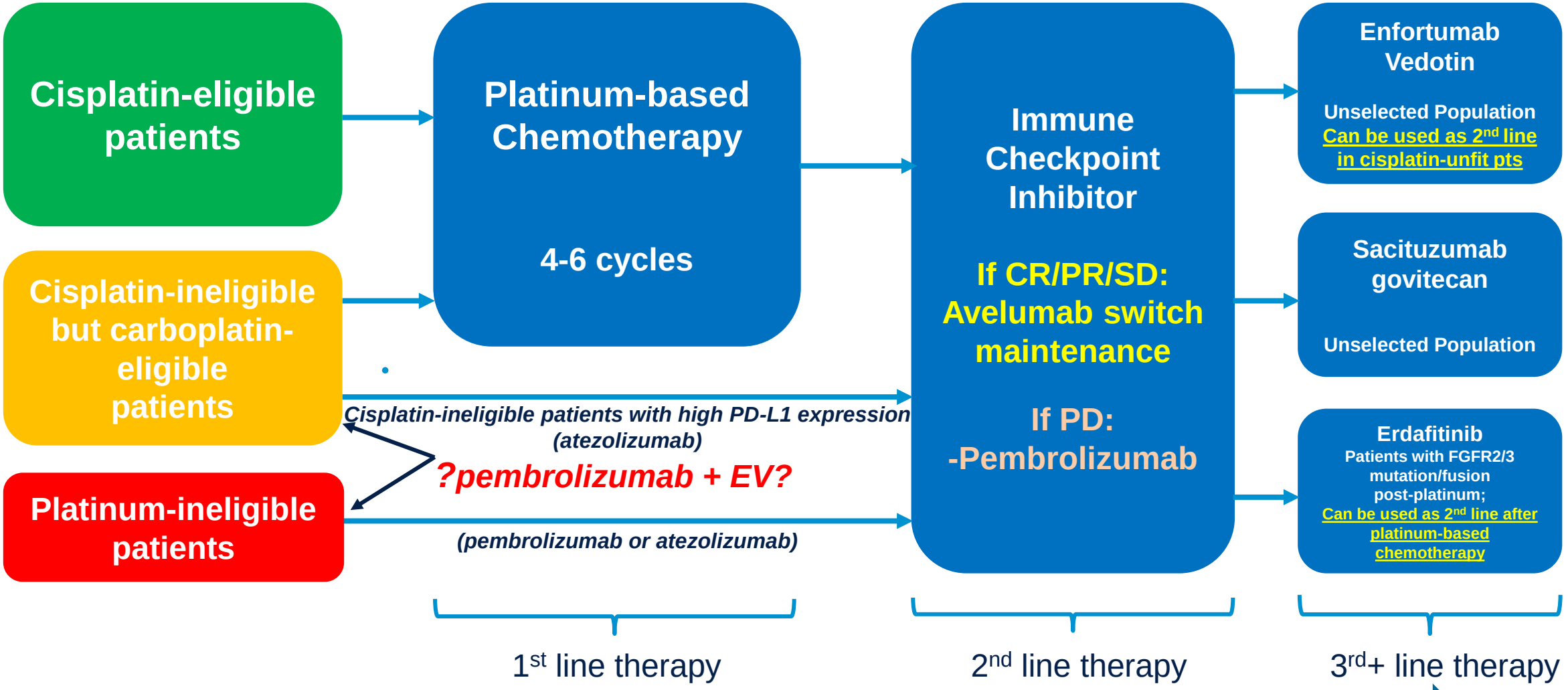
Disclosures

- **Institutional research funding: Bavarian Nordic; Bristol-Myers Squibb; Clovis Oncology; Debiopharm; EMD Serono; Gilead; Pfizer; Merck; QED Therapeutics; GlaxoSmithKline; Mirati Therapeutics, G1 Therapeutics**

- **Consulting: AstraZeneca; Astellas Pharma, BMS; Boston Gene, Dyania Health; EMDSerono; Exelixis; Lucence Health; Fresenius Kabi, G1 Therapeutics; Gilead; Guardant Health; Infinity Pharmaceuticals; Janssen; Merck; Mirati Therapeutics; Genentech/Roche; Pfizer; PureTech; Regeneron Pharmaceuticals; QED Therapeutics; Seattle Genetics, 4D Pharma PLC, UroGen, Silverback Therapeutics**

Treatment Landscape in Advanced Urothelial Carcinoma (present->2023)



Vadim Koshkin & Petros Grivas

EV-103: Phase 1b/2 Trial of EV + Pembrolizumab *Cohort A*

Patients with 1L **cisplatin-ineligible** la/mUC (N=45)

Dose escalation	Dose expansion cohort A
EV + pembro	EV + pembro
(n=5)	(n=40)

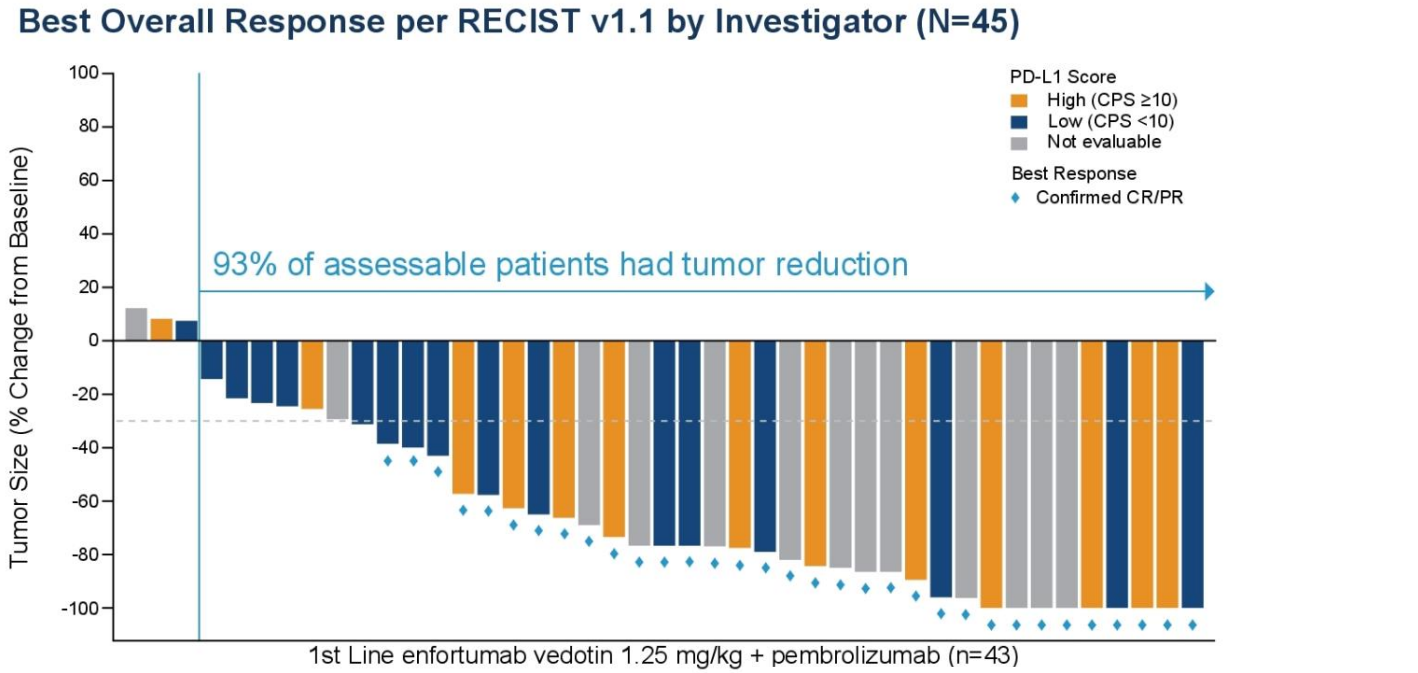
EV 1.25 mg/kg days 1 and 8 of a 3-week cycle
+
Pembrolizumab 200 mg on day 1 of a 3-week cycle

- 84% of patients had visceral disease, and 31% had liver metastasis
- 31% of patients had PD-L1 CPS ≥10

Confirmed ORR 95% CI	**73%** (33/45) (58.1, 85.4)
Complete response	16% (7/45)
Partial response	58% (26/45)

- 57% confirmed ORR in patients with liver metastases

Maximum Target Lesion Reduction from Baseline by PD-L1 Status



la = locally advanced.

Friedlander TW, et al. Presented at: ASCO Annual Meeting; 2021. Abstract 4528.

Key Demographic and Baseline Disease Characteristics *Cohort K*

Representative of the 1L cisplatin-ineligible la/mUC population

	EV+P (N=76)	EV Mono (N=73)
Male sex, n (%)	54 (71.1)	56 (76.7)
Age (yrs), median (range)	71 (51, 91)	74 (56, 89)
White race, n (%)	61 (80.3)	55 (75.3)
ECOG PS, n (%)		
0	33 (43.4)	28 (38.4)
1	33 (43.4)	35 (47.9)
2	10 (13.2)	10 (13.7)
Primary tumor location, n (%)		
Lower tract	46 (60.5)	51 (69.9)
Upper tract	30 (39.5)	21 (28.8)

	EV+P (N=76)	EV Mono (N=73)
Metastasis disease sites, n (%)		
Bone	19 (25.0)	21 (28.8)
Liver	13 (17.1)	13 (17.8)
Lung	37 (48.7)	30 (41.1)
Metastasis category, n (%)		
Lymph node only	10 (13.2)	12 (16.4)
Visceral disease	64 (84.2)	60 (82.2)
Not applicable[1]	2 (2.6)	1 (1.4)
PD-L1 status by combined positive score,[2] n (%)		
CPS<10	44 (57.9)	38 (52.1)
CPS≥10	31 (40.8)	28 (38.4)
Not Evaluable	1 (1.3)	7 (9.6)

CPS: Combined Positive Score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Mono: monotherapy; PD-L1: Programmed death-ligand 1

[1]Patients had locally advanced disease without metastasis to lymph nodes or distant organs.

[2]PD-L1 tested using the PD-L1 IHC 22C3 pharmDx assay from Agilent

Overall Response Rate by BICR

EV+P: 64.5% confirmed ORR with rapid responses

	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

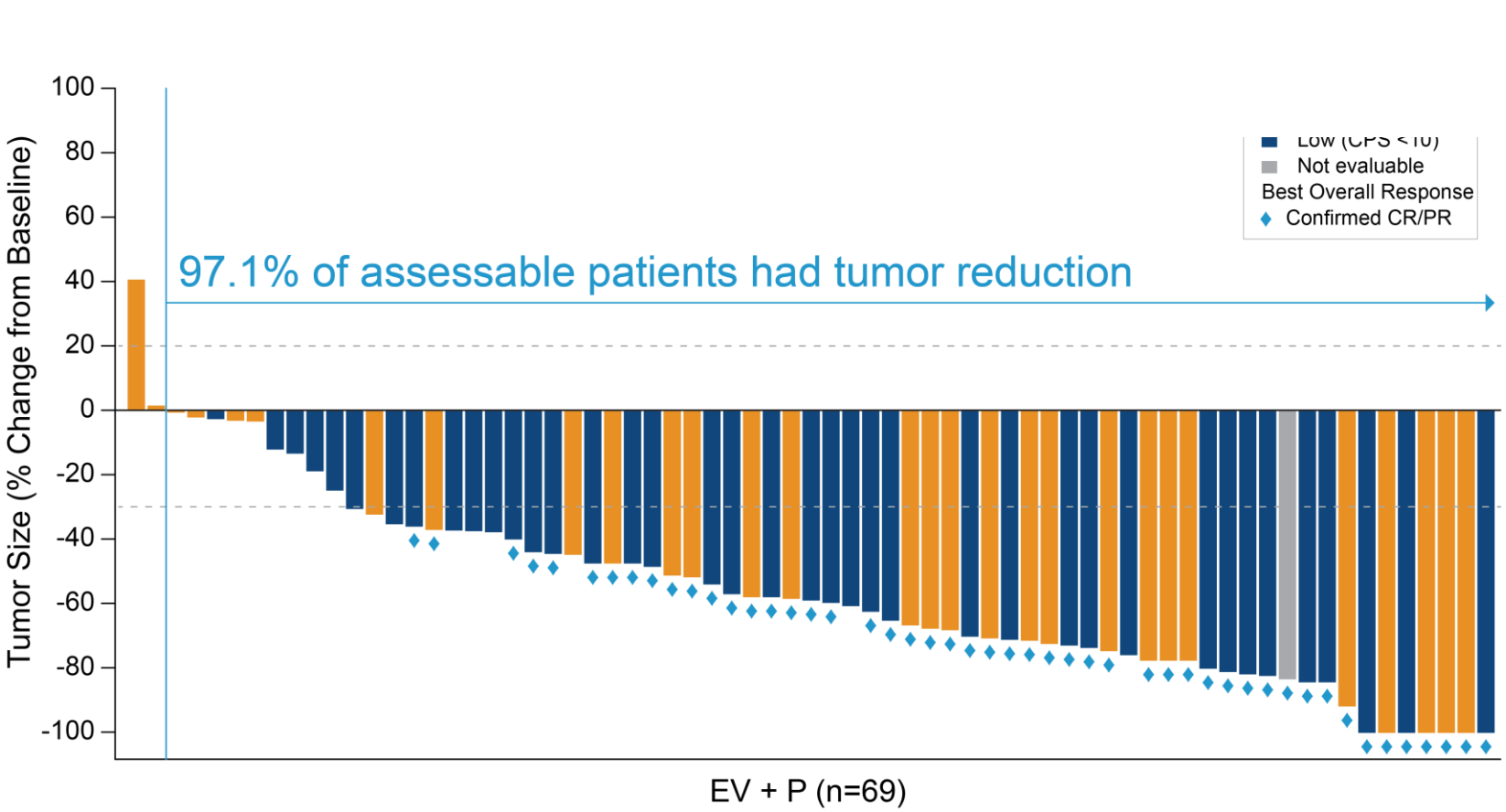
EV+P

- 41/49 (85.7%) of responses observed at first assessment (week 9±1 wk)
- cORRs were consistent across all pre-specified subgroups
- 7/13 (53.8%) cORR observed in patients with liver metastases

EV monotherapy

- Activity is consistent with prior results in 2L+ la/mUC

EV+P: Maximum Percent Reduction from Baseline of Target Lesion by BICR



PD-L1 Score
- High (CPS ≥10)
- Low (CPS <10)
- Not evaluable

Best Overall Response
- Confirmed CR/PR

- Activity seen regardless of PD-L1 status
  - 27/44 (61.4%) cORR in CPS<10
  - 21/31 (67.7%) cORR in CPS≥10

BICR: Blinded Independent Central Review; CPS: Combined Positive Score; CR: Complete Response; PD-L1: Programmed Death-Ligand 1 PR: Partial Response

Treatment-Related Adverse Events (TRAEs)

Most common AEs with EV+P were fatigue, peripheral sensory neuropathy, alopecia, and maculo-papular rash

TRAEs **Any Grades** by Preferred Term **≥20% of Patients**	EV+P (N=76) n (%)		EV Mono (N=73) n (%)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Overall	76 (100.0)	48 (63.2)	68 (93.2)	35 (47.9)
Fatigue	43 (56.6)	7 (9.2)	29 (39.7)	6 (8.2)
Peripheral sensory neuropathy	39 (51.3)	1 (1.3)	32 (43.8)	2 (2.7)
Alopecia	35 (46.1)	0	26 (35.6)	0
Rash maculo-papular	35 (46.1)	13 (17.1)	21 (28.8)	1 (1.4)
Pruritus	30 (39.5)	3 (3.9)	19 (26.0)	1 (1.4)
Dysgeusia	23 (30.3)	0	25 (34.2)	0
Weight decreased	23 (30.3)	3 (3.9)	21 (28.8)	1 (1.4)
Diarrhea	22 (28.9)	5 (6.6)	20 (27.4)	4 (5.5)
Decreased appetite	20 (26.3)	0	28 (38.4)	0
Nausea	19 (25.0)	0	25 (34.2)	1 (1.4)
Dry eye	15 (19.7)	0	8 (11.0)	0

Serious TRAEs

- **18 (23.7%) EV+P**
- **11 (15.1%) EV Mono**

TRAEs leading to death (per investigator)

- **3 (3.9%) EV+P (Pneumonitis, Respiratory failure, Sepsis)**
- **2 (2.7%) EV Mono (Multiple organ dysfunction, Respiratory failure)**

KEY FINDINGS (3)

Safety : Pembro may increase EV G≥3 TRAE

Δ~15%

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EV Mono (n= 301) from EV 301 L3 trial

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

Adverse Event	Enfortumab Vedotin Group (N = 296)	
	Any Grade	Grade ≥3
		number of patient
Any adverse event	278 (93.9)	152 (51.4)
Alopecia	134 (45.3)	0
Peripheral sensory neuropathy†	100 (33.8)	9 (3.0)
Pruritus	95 (32.1)	4 (1.4)
Fatigue	92 (31.1)	19 (6.4)
Decreased appetite	91 (30.7)	9 (3.0)
Diarrhea	72 (24.3)	10 (3.4)
Dysgeusia	72 (24.3)	0
Nausea	67 (22.6)	3 (1.0)
Maculopapular rash	48 (16.2)	22 (7.4)
Anemia	34 (11.5)	8 (2.7)
Decreased neutrophil count	30 (10.1)	18 (6.1)
Neutropenia	20 (6.8)	14 (4.7)
Decreased white-cell count	16 (5.4)	4 (1.4)
Febrile neutropenia	2 (0.7)	2 (0.7)

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EV-302: Randomized Phase 3 Trial of Enfortumab Vedotin + Pembrolizumab vs Chemotherapy

Key eligibility criteria:

- Untreated locally advanced or metastatic urothelial cancer
- Eligible for platinum-based chemotherapy and for pembrolizumab

1:1 randomization

Enfortumab vedotin
(Days 1 and 8)
+
Pembrolizumab
(Day 1)
Every 3-week cycle

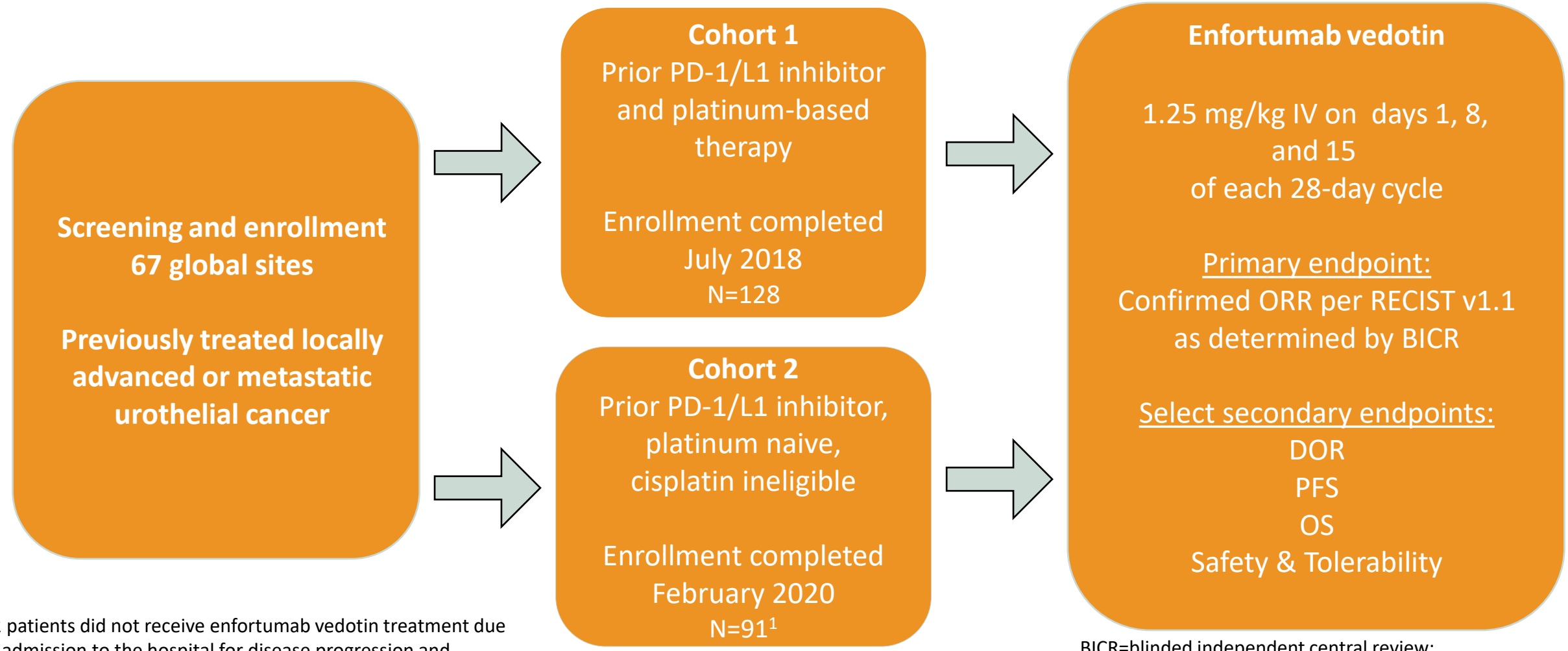
Gemcitabine
(Days 1 and 8)
+
Cisplatin or Carboplatin
(Day 1)

Every 3-week Cycle

Primary Objectives
- PFS per RECIST by central review
- OS

Secondary Objectives
- PFS per RECIST by investigator
- ORR
- DOR
- DCR
- QOL
- Safety and tolerability

Enfortumab Vedotin (EV-201) Phase 2 Trial



[1] 2 patients did not receive enfortumab vedotin treatment due to admission to the hospital for disease progression and pursuing hospice care, respectively

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

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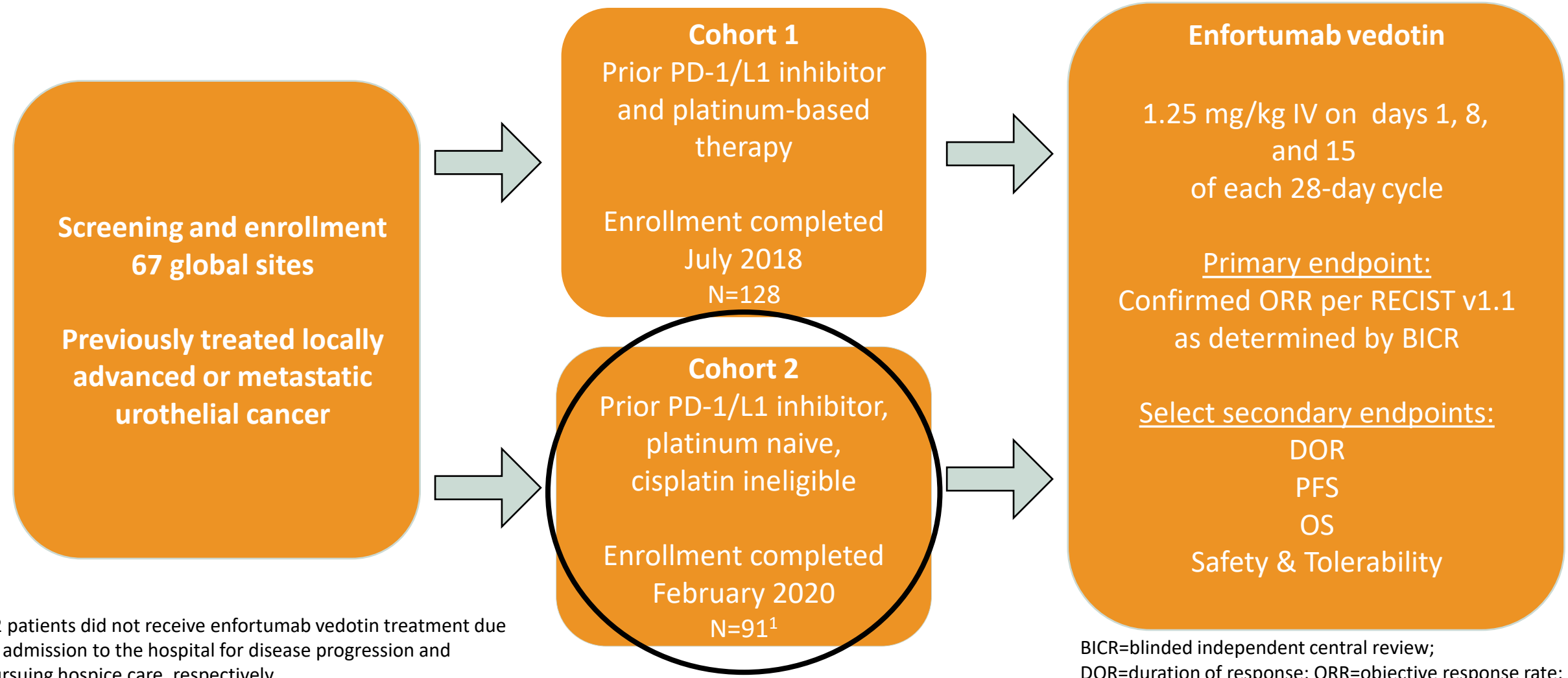

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EV-201 Cohort 2 Confirmed Best Overall Response per BICR

ORR per RECIST v 1.1 assessed by BICR	Patients (N=89) %
Confirmed ORR, 95% CI[1]	52 (40.8, 62.4)
Best overall response	%
Complete response	20
Partial response	31
Stable disease	30
Progressive disease	9
Not evaluable[2]	9

ORR = Objective Response Rate; BICR = Blinded Independent Central Review

[1] CI = Confidence Interval, Computed using the Clopper-Pearson method

[2] Includes five subjects who did not have response assessment post-baseline, two subjects whose post-baseline assessment did not meet the minimum interval requirement for stable disease, and one subject whose response cannot be assessed due to incomplete anatomy.

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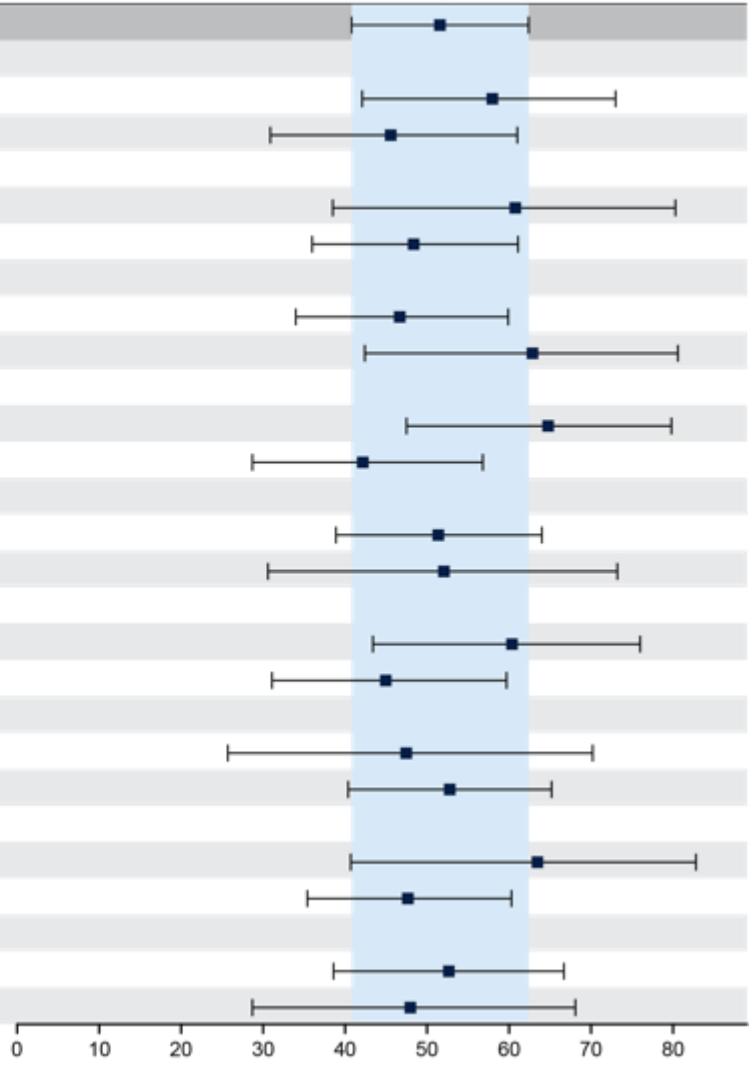
EV-201 Cohort 2 Overall Response Rates by Subgroup

Subjects (N=89)

Subgroup	n/N	% (95% CI)
Overall	46/89	52 (40.8, 62.4)
Age		
<75 years	25/43	58 (42.1, 73)
≥75 years	21/46	46 (30.9, 61)
Sex		
Female	14/23	61 (38.5, 80.3)
Male	32/66	48 (36, 61.1)
Race		
White	29/62	47 (34, 59.9)
Non-white	17/27	63 (42.4, 80.6)
ECOG PS		
0	24/37	65 (47.5, 79.8)
1–2	22/52	42 (28.7, 56.8)
Bellmunt risk score		
0–1	34/66	52 (38.9, 64)
≥2	12/23	52 (30.6, 73.2)
Primary tumor sites		
Upper tract	23/38	61 (43.4, 76)
Bladder/Other	23/51	45 (31.1, 59.7)
Liver metastasis		
Yes	10/21	48 (25.7, 70.2)
No	36/68	53 (40.4, 65.2)
Best response to prior CPI		
Responder	14/22	64 (40.7, 82.8)
Non-responder	32/67	48 (35.4, 60.3)
PD-L1 expression		
CPS <10	28/53	53 (38.6, 66.7)
CPS ≥10	13/27	48 (28.7, 68.1)



Responses were observed across all subgroups, including patients:

- with liver metastasis (48%)
- with primary tumor sites in the upper tract (61%)
- who did not respond to prior PD-1/PD-L1 inhibitors (48%)

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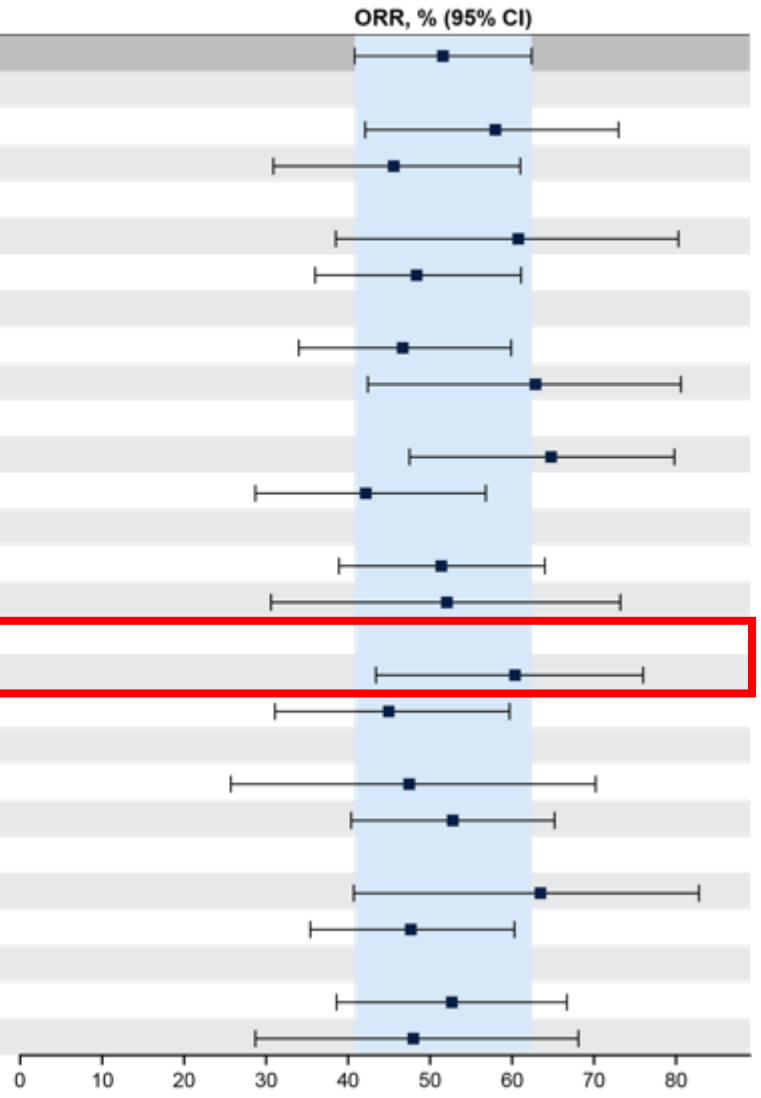

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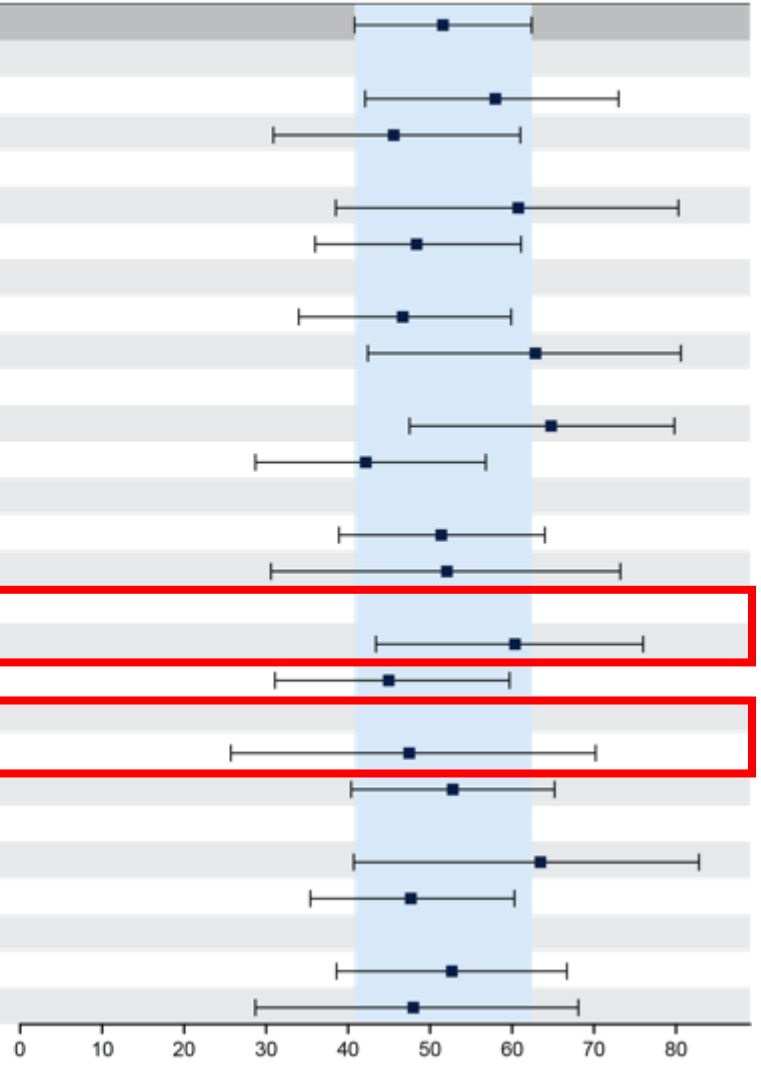
EV-201 Cohort 2 Overall Response Rates by Subgroup

Subjects (N=89)

Subgroup	n/N	% (95% CI)
Overall	46/89	52 (40.8, 62.4)
Age		
<75 years	25/43	58 (42.1, 73)
≥75 years	21/46	46 (30.9, 61)
Sex		
Female	14/23	61 (38.5, 80.3)
Male	32/66	48 (36, 61.1)
Race		
White	29/62	47 (34, 59.9)
Non-white	17/27	63 (42.4, 80.6)
ECOG PS		
0	24/37	65 (47.5, 79.8)
1–2	22/52	42 (28.7, 56.8)
Bellmunt risk score		
0–1	34/66	52 (38.9, 64)
≥2	12/23	52 (30.6, 73.2)
Primary tumor sites		
Upper tract	23/38	61 (43.4, 76)
Bladder/Other	23/51	45 (31.1, 59.7)
Liver metastasis		
Yes	10/21	48 (25.7, 70.2)
No	36/68	53 (40.4, 65.2)
Best response to prior CPI		
Responder	14/22	64 (40.7, 82.8)
Non-responder	32/67	48 (35.4, 60.3)
PD-L1 expression		
CPS <10	28/53	53 (38.6, 66.7)
CPS ≥10	13/27	48 (28.7, 68.1)



Responses were observed across all subgroups, including patients:

- with liver metastasis (48%)
- with primary tumor sites in the upper tract (61%)
- who did not respond to prior PD-1/PD-L1 inhibitors (48%)

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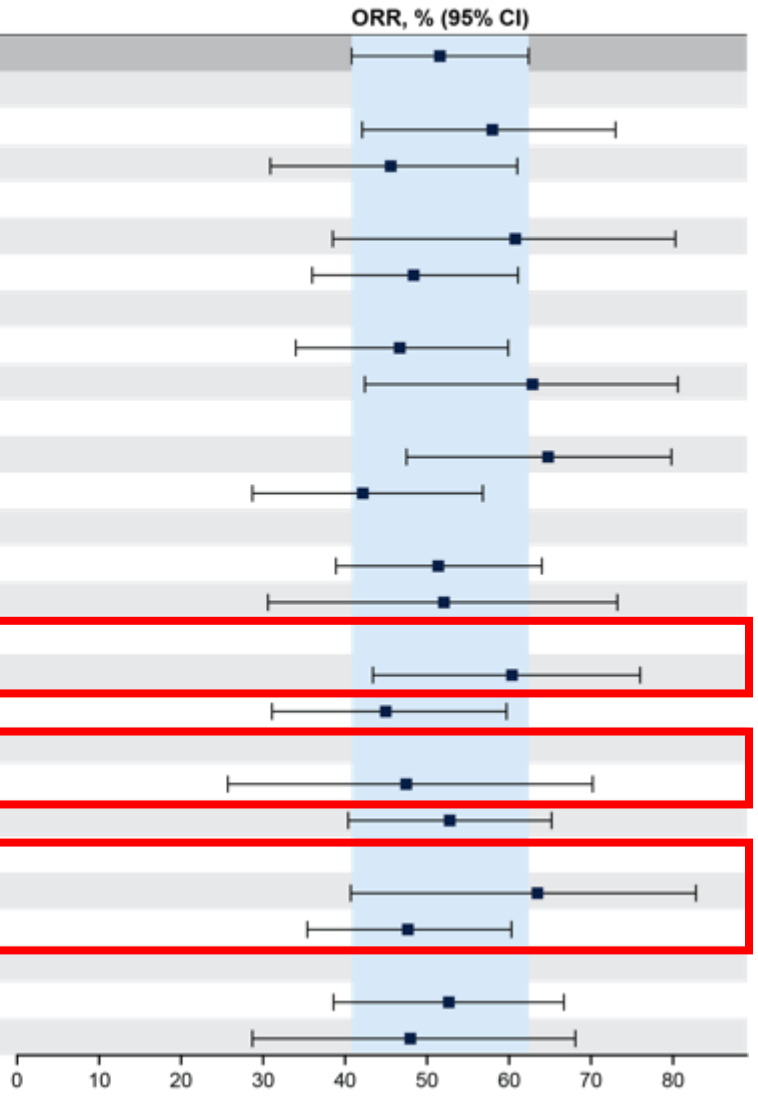

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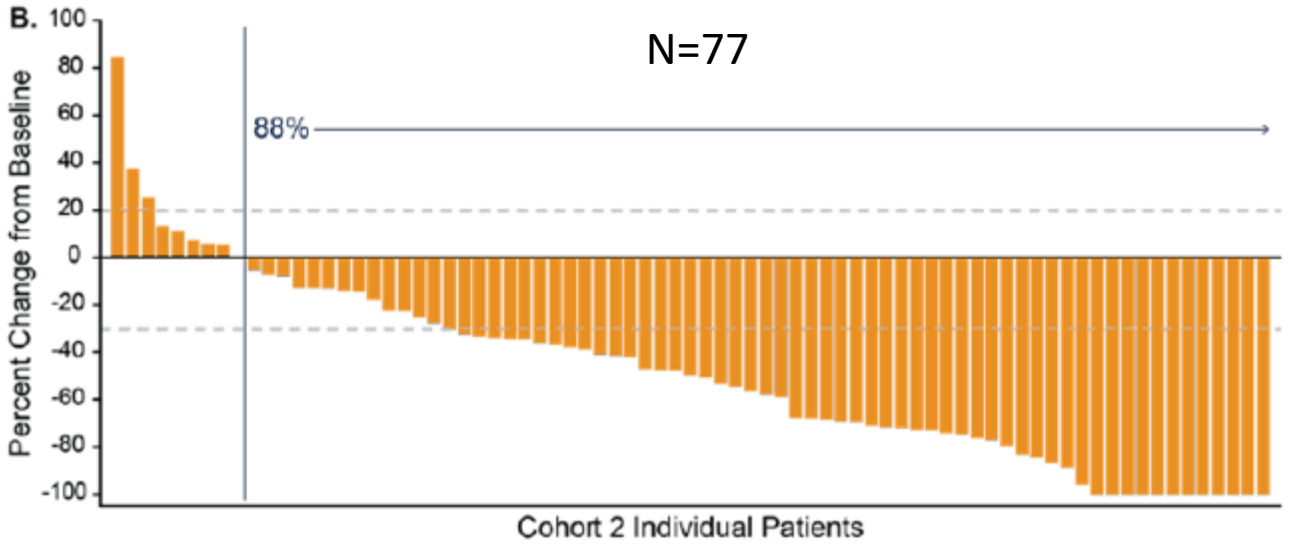
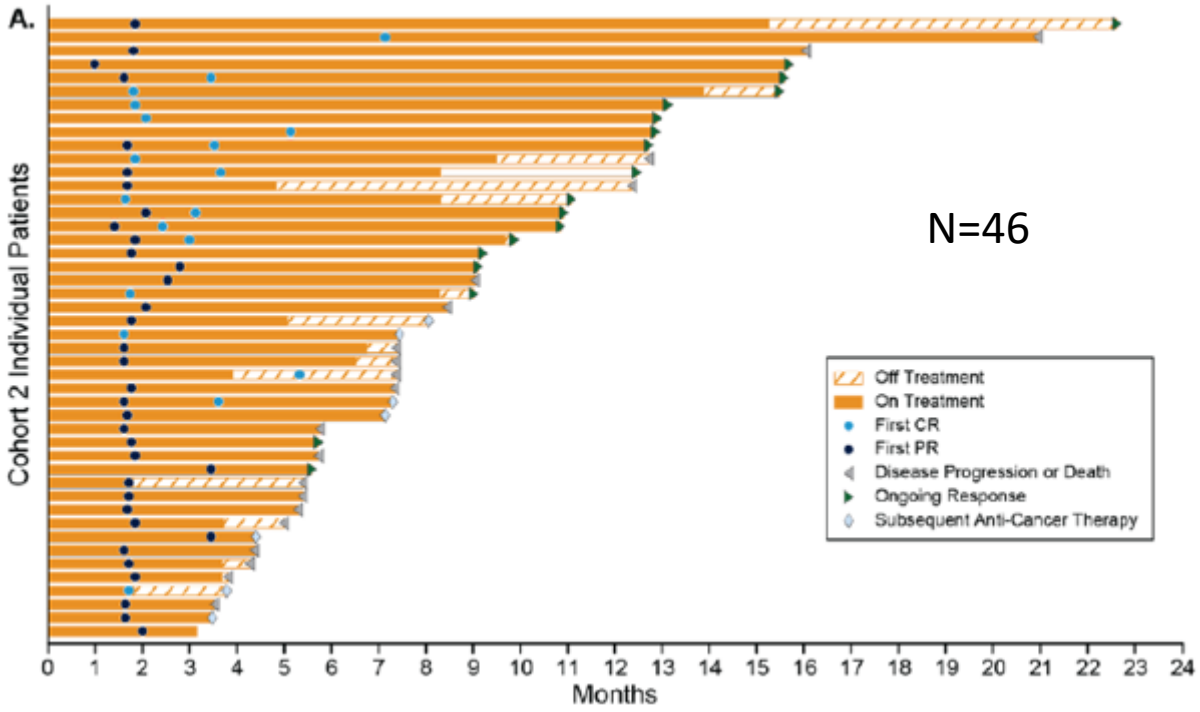
EV-201 Cohort 2 Change in Tumor Measurements and Durability of Response





Data not available for 12 subjects to to no response assessment post-baseline (n=5), incomplete assessment of target lesions post-baseline (n=1), or no measurable disease at baseline per BICR (n=6)

EV-201 Cohort 2 Treatment-Related Adverse Events

Treatment-related AEs by preferred term in ≥20% of patients (any Grade) or ≥5% (≥Grade 3)	Patients (N=89) n (%)	
	Any Grade	≥Grade 3
Alopecia	45 (51)	–
Peripheral sensory neuropathy	42 (47)	3 (3)
Fatigue	30 (34)	6 (7)
Decreased appetite	29 (33)	5 (6)
Pruritus	27 (30)	3 (3)
Rash maculo-papular	27 (30)	7 (8)
Dysgeusia	24 (27)	–
Weight decreased	23 (26)	1 (1)
Anemia	22 (25)	5 (6)
Diarrhea	20 (22)	5 (6)
Nausea	20 (22)	1 (1)
Neutropenia	11 (12)	8 (9)
Hyperglycemia	8 (9)	5 (6)
Lipase increased	7 (8)	5 (6)

Treatment-related AEs led to discontinuations in 16% of patients with peripheral sensory neuropathy as the most common reason (4%)

Treatment-Related AEs leading to death:

4 deaths considered to be treatment related by the investigator:

- acute kidney injury
- metabolic acidosis
- multiple organ dysfunction syndrome
- pneumonitis (occurred >30 days of last dose)

3 of these deaths occurred within 30 days of first dose of EV occurred in patients with BMI ≥30 kg/m^2

All 4 deaths: confounded by age (≥75 years) and other comorbidities

EV-301 Randomized Phase 3 Trial

Key Inclusion Criteria:

- Locally advanced, unresectable or metastatic UC (squamous differentiation and mixed histologies allowed)
- Progression or relapse after PD-1/PD-L1 therapy
- Receipt of prior platinum chemotherapy (if perioperative receipt must have progressed within 12 months)
- ECOG PS 0 or 1

→ **1:1** RANDOMIZE

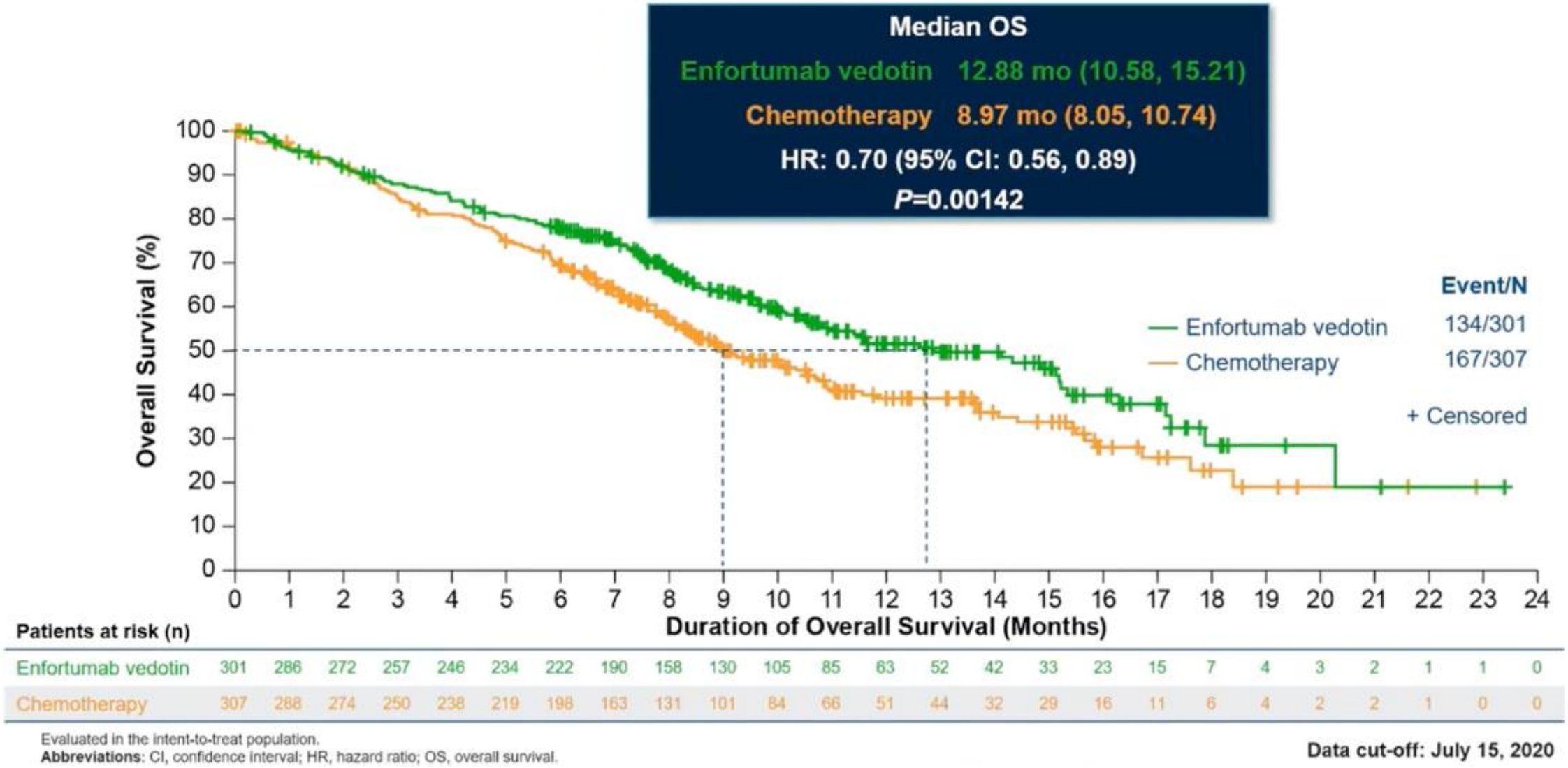
- Enfortumab vedotin 1.25 mg/kg IV on day 1, 8 and 15 of each 28 day cycle, N =301
- Docetaxel, Vinflunine, or Paclitaxel IV Day 1 of a 21-day cycle, N =307

Disease progression or other withdrawal criteria met

Primary Endpoint: Overall survival

Secondary Endpoints: PFS, ORR, disease control rate, duration of response, safety, patient-reported outcomes.

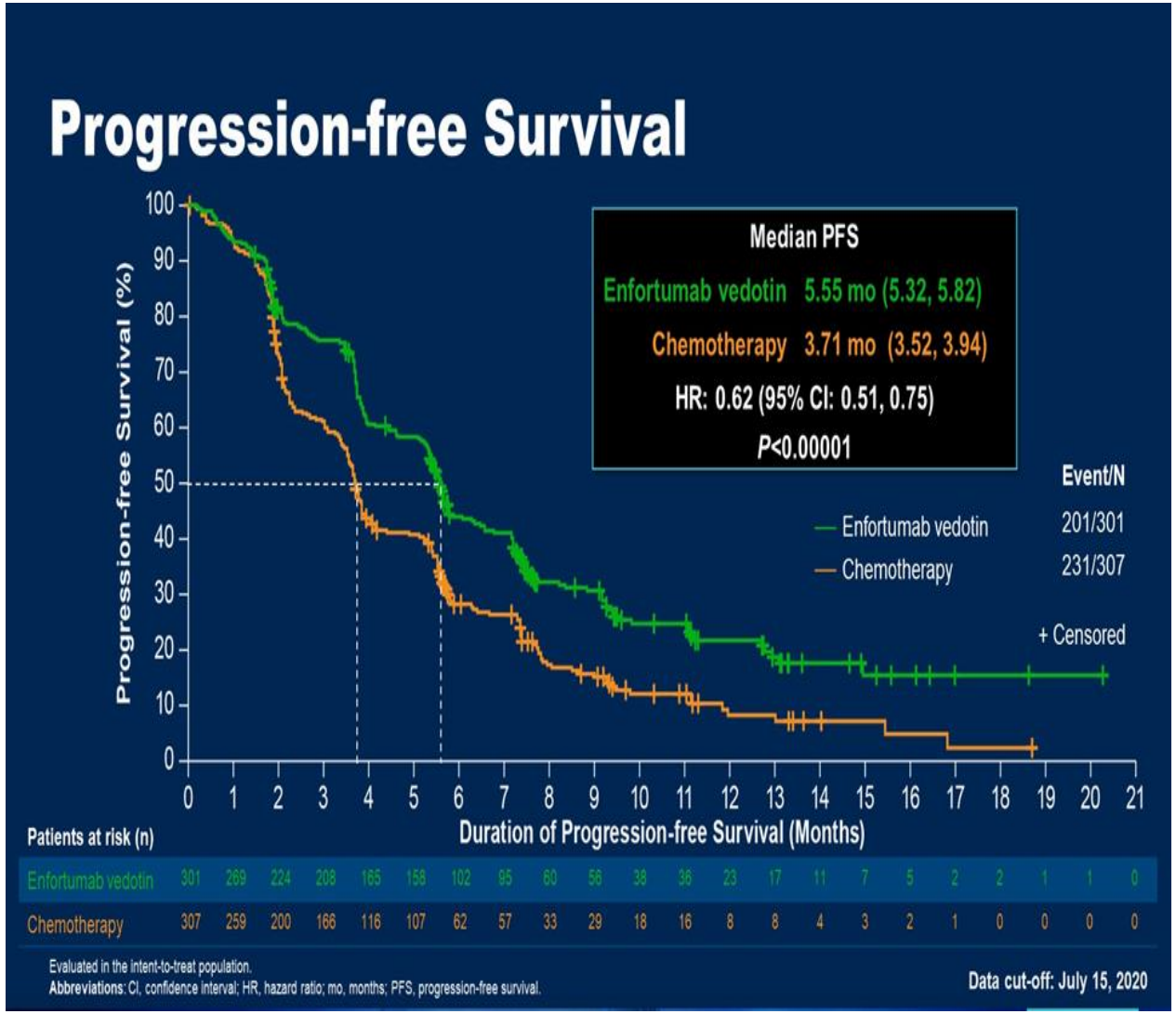
EV-301 Overall Survival

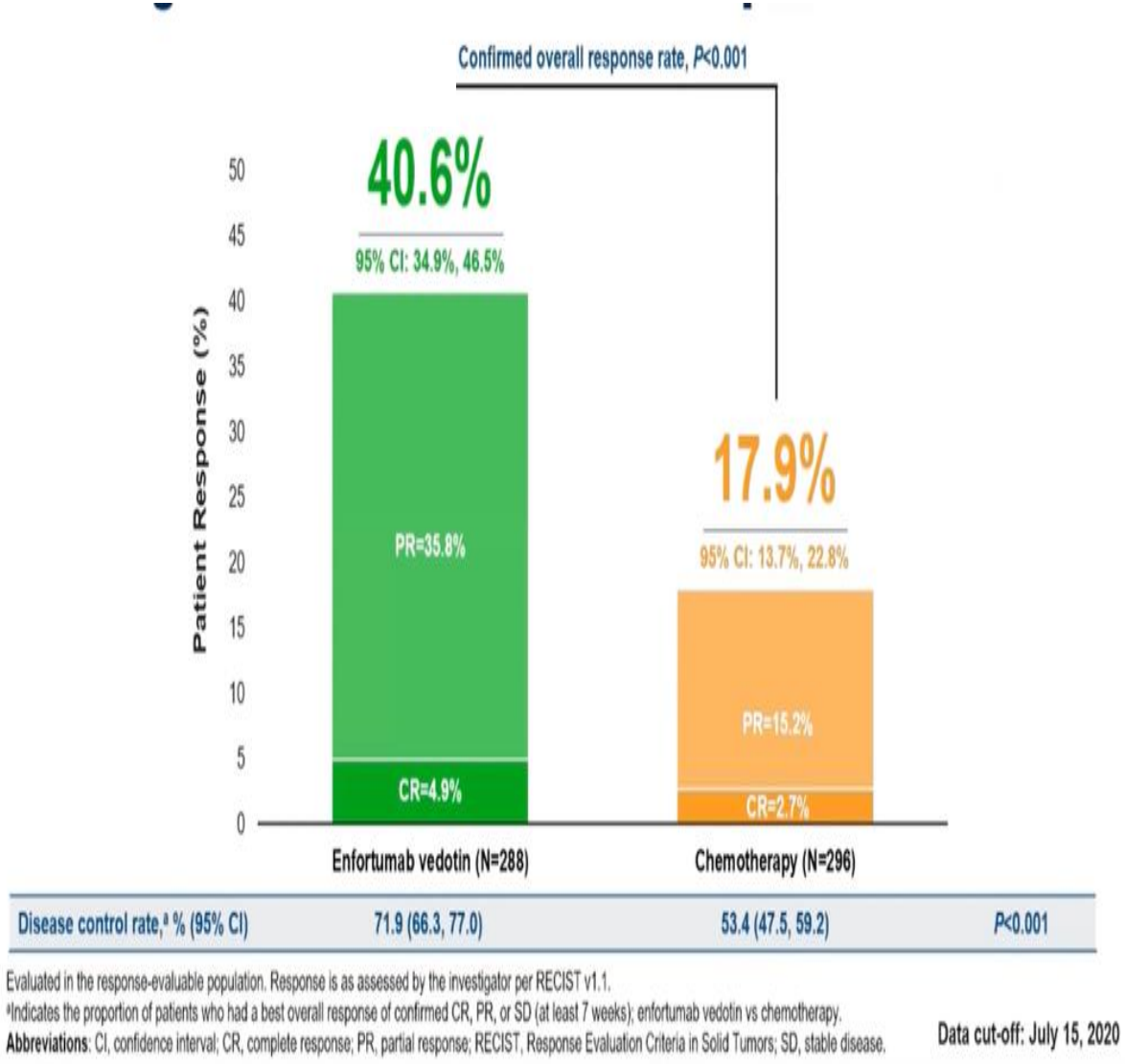


Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off: July 15, 2020

EV-301 Investigator-Assessed Overall Response





EV-301 Adverse Events

Treatment-Related Adverse Events

Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any adverse event	**94%**	**51%**	**92%**	**50%**
Alopecia	45%	0	36%	0
Peripheral sensory neuropathy	34%	3%	21%	2%
Pruritus	32%	1%	5%	0
Fatigue	31%	6%	23%	5%
Decreased appetite	31%	3%	23%	2%
Diarrhea	24%	3%	17%	2%
Dysgeusia	24%	0	7%	0
Nausea	23%	1%	22%	1%
Rash maculopapular	16%	7%	2%	0
Anemia	12%	3%	20%	8%
Neutrophil count decreased	10%	6%	17%	13%
Neutropenia	7%	5%	8%	6%
White blood cell decreased	5%	1%	11%	7%
Febrile neutropenia	1%	1%	6%	6%
Serious adverse events[a]	23%	-	23%	-
Leading to treatment withdrawal	14%	-	11%	-

TRAEs leading to death, excluding disease progression, occurred in 7 patients (2.4%) treated with EV and 3 (1.0%) treated with chemotherapy.

Powles T, et al. N Engl J Med 2021; Epub February 12, 2021.

EV-301 Adverse Events

Adverse Events of Special Interest

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.

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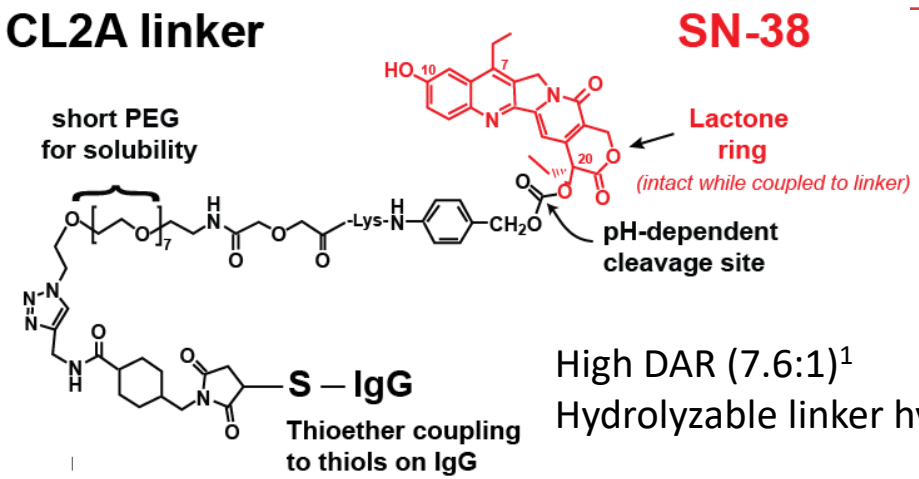
Sacituzumab govitecan



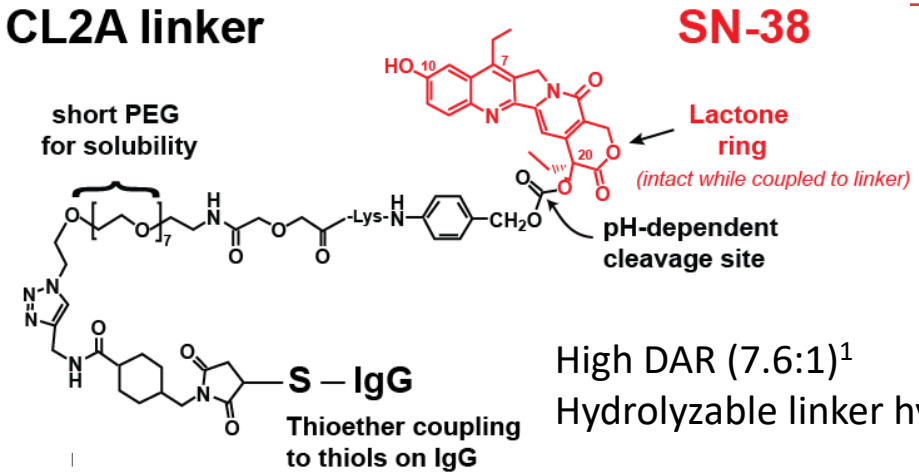
High DAR (7.6:1)[1]

Hydrolyzable linker hydrolysis[2]

1. Cardillo TM, et al. Bioconjug Chem 2015; 26:919-31
2. Govindan SV, et al. Mol Cancer Ther 2013; 12:968-78

Tagawa S, et al. Ann Oncol (2017) 28 (suppl_5):v295-v329
Tagawa S, et al. J Clin Oncol 37, no. 7_suppl (March 1, 2019) 354-354

Sacituzumab govitecan



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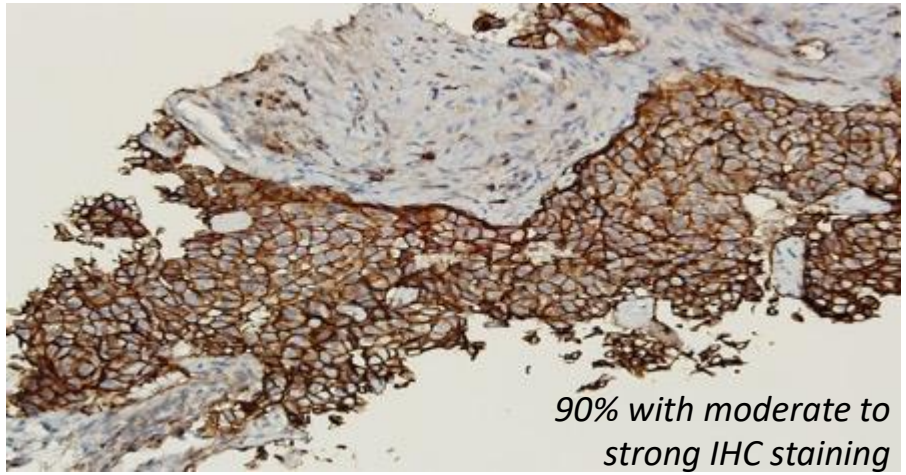

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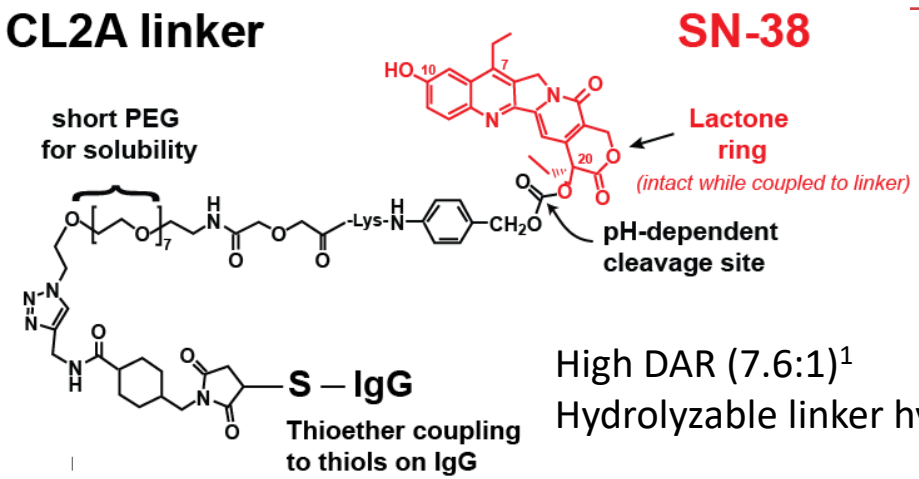

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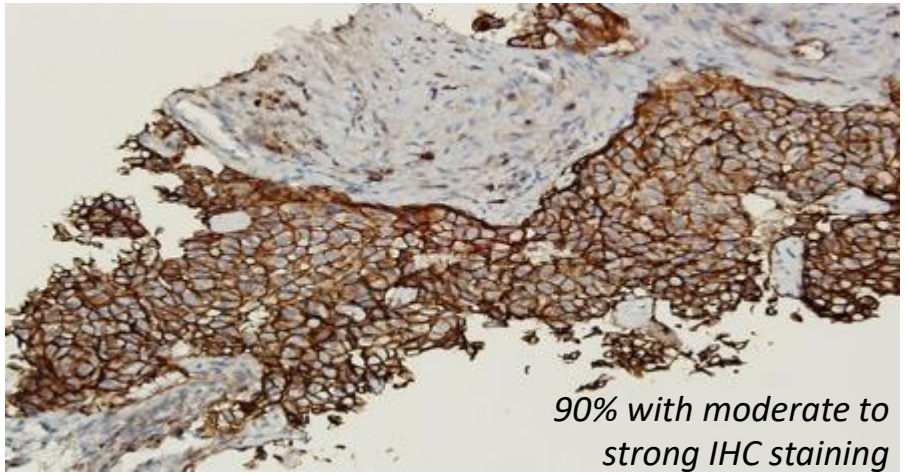

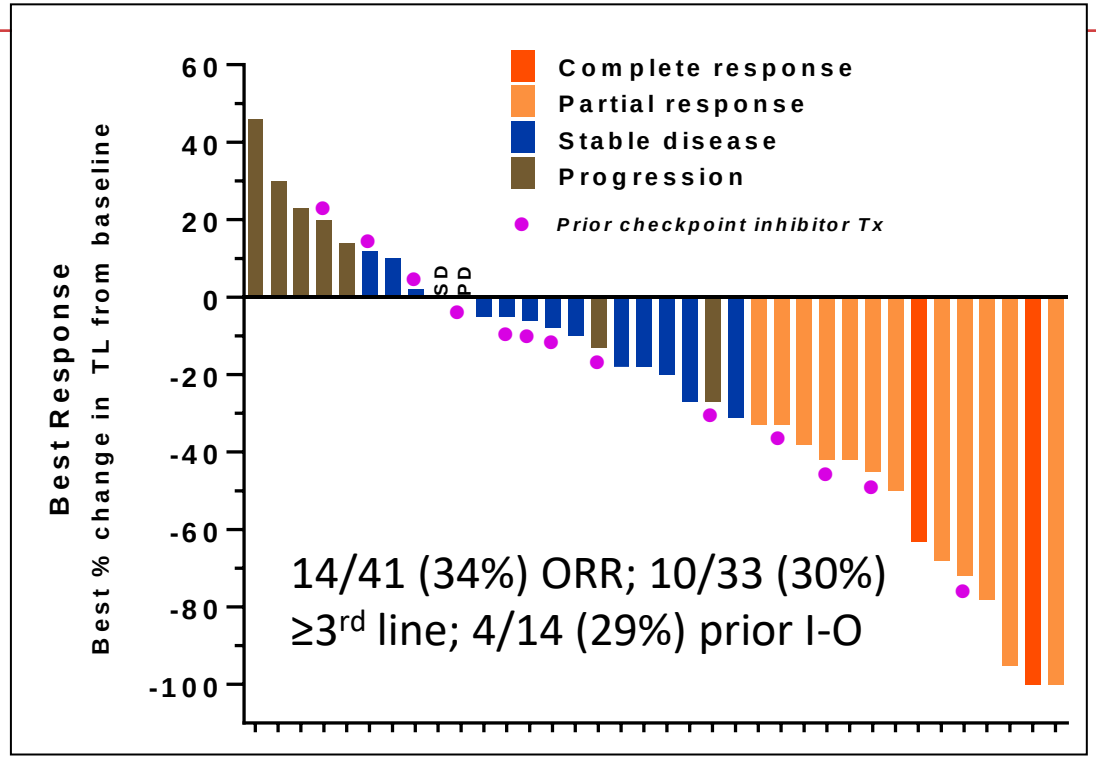

- Final 14/45 (31%) ORR
- Median PFS 7.3 months
- Median OS 18.9 months

1. Cardillo TM, et al. Bioconjug Chem 2015; 26:919-31
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TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC

TROPHY U-01

Cohort 1* (~100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies
→ SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 2 (~40 patients): patients with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies
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Cohort 3[a] (up to 61 patients): mUC CPI naïve patients who progressed after prior platinum-based therapies
→ SG 10 mg/kg Days 1 and 8, every 21 days; Pembrolizumab 200 mg day 1 every 21 days

Cohort 4 (up to 60 patients): mUC platinum-naïve patients
→ SG Days 1 and 8, every 21 days; Cisplatin[b]

Cohort 5 (up to 60 patients): mUC platinum-naïve patients
→ SG Days 1 and 8, every 21 days; Cisplatin[c] Avelumab 800 mg every 2 weeks

Continue treatment in the absence of unacceptable toxicity or disease progression

Continue until a maximum of 6 cycles has been completed,[d] disease progression, lack of clinical benefit, toxicity, or withdrawal of consent

→ **Maintenance avelumab (800 mg every 2 weeks) with SG (Days 1 and 8 every 21 days) for those without disease progression**

Primary Endpoint:
Objective response rate per RECIST 1.1 criteria

Key Secondary Endpoints:
Safety/tolerability, DOR, PFS, OS

Key Inclusion Criteria: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

***Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor[1]**

[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

ASCO Genitourinary Cancers Symposium

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TROPHY-U-01 Cohort 1 Response and Reduction in Tumor Size

Endpoint	Cohort 1 (N=113)
ORR, n (%) [95% CI]	**31 (27) [19, 37]**
CR, n (%)	6 (5)
PR, n (%)	25 (22)
Median duration of response, mos [95% CI] (Range)	**5.9** [4.70, 8.60] (1.4–11.7)
Median time to onset of response, mos (Range)	1.6 (1.2–5.5)

[a]Assessments were per Blinded Independent Review Assessment, RECIST 1.1.
CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; TTR, time to response.

Tagawa ST, et al. J Clin Oncol 2021; 39:2474-85.

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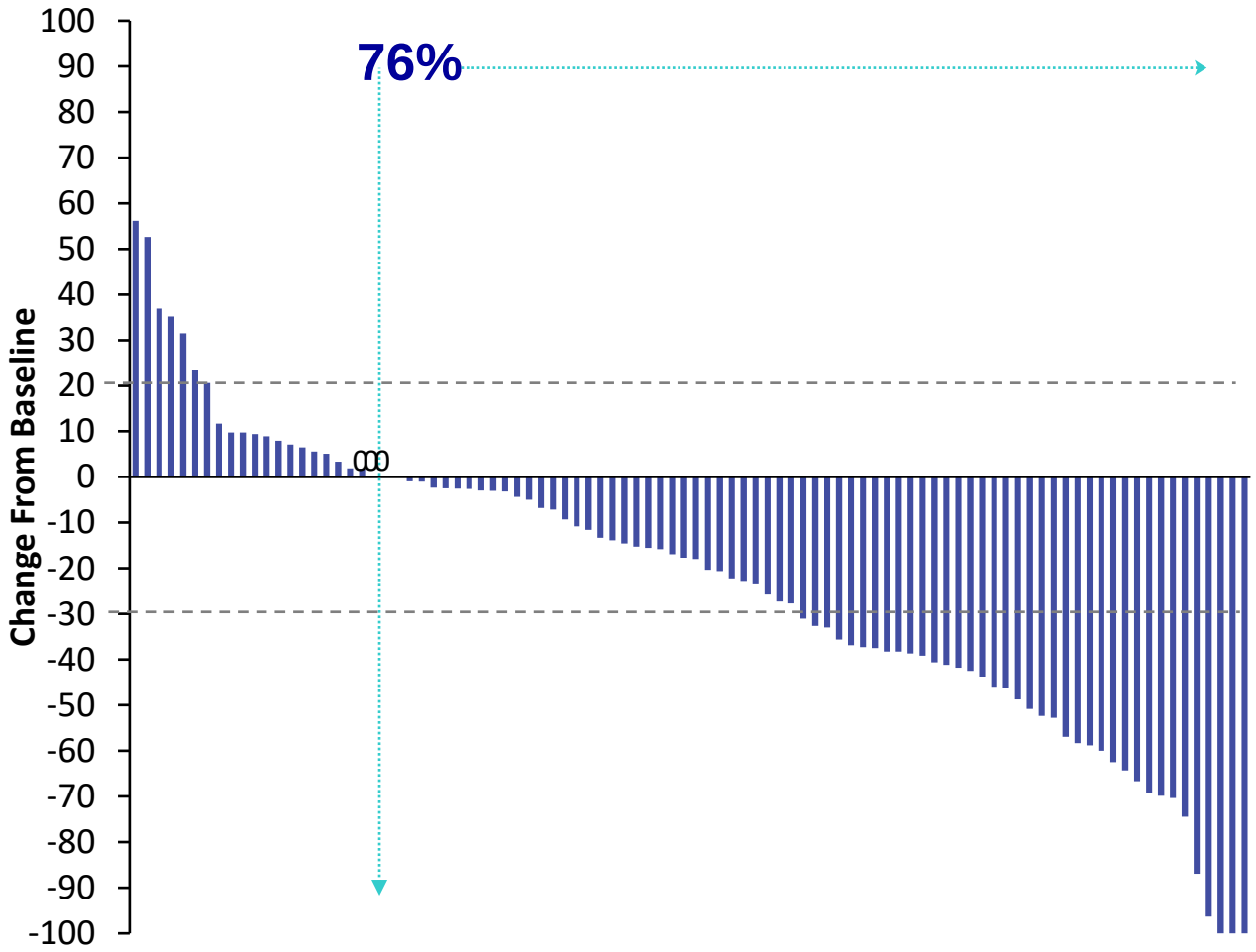
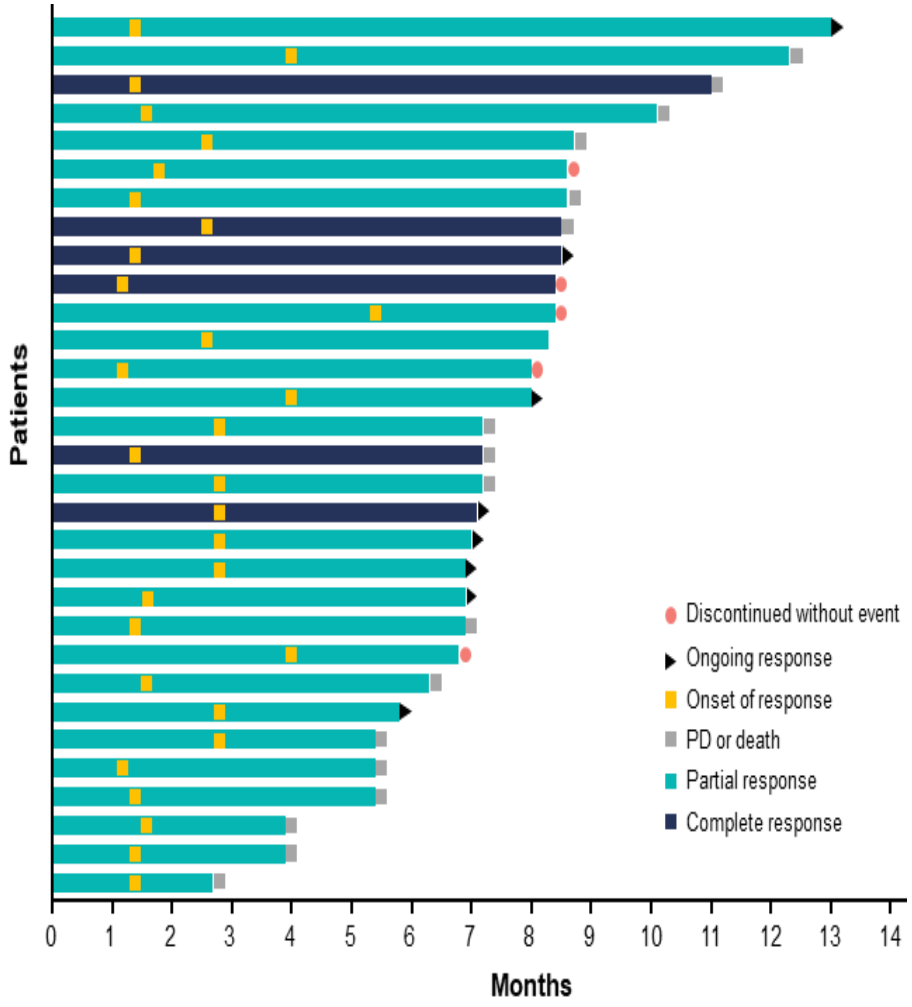


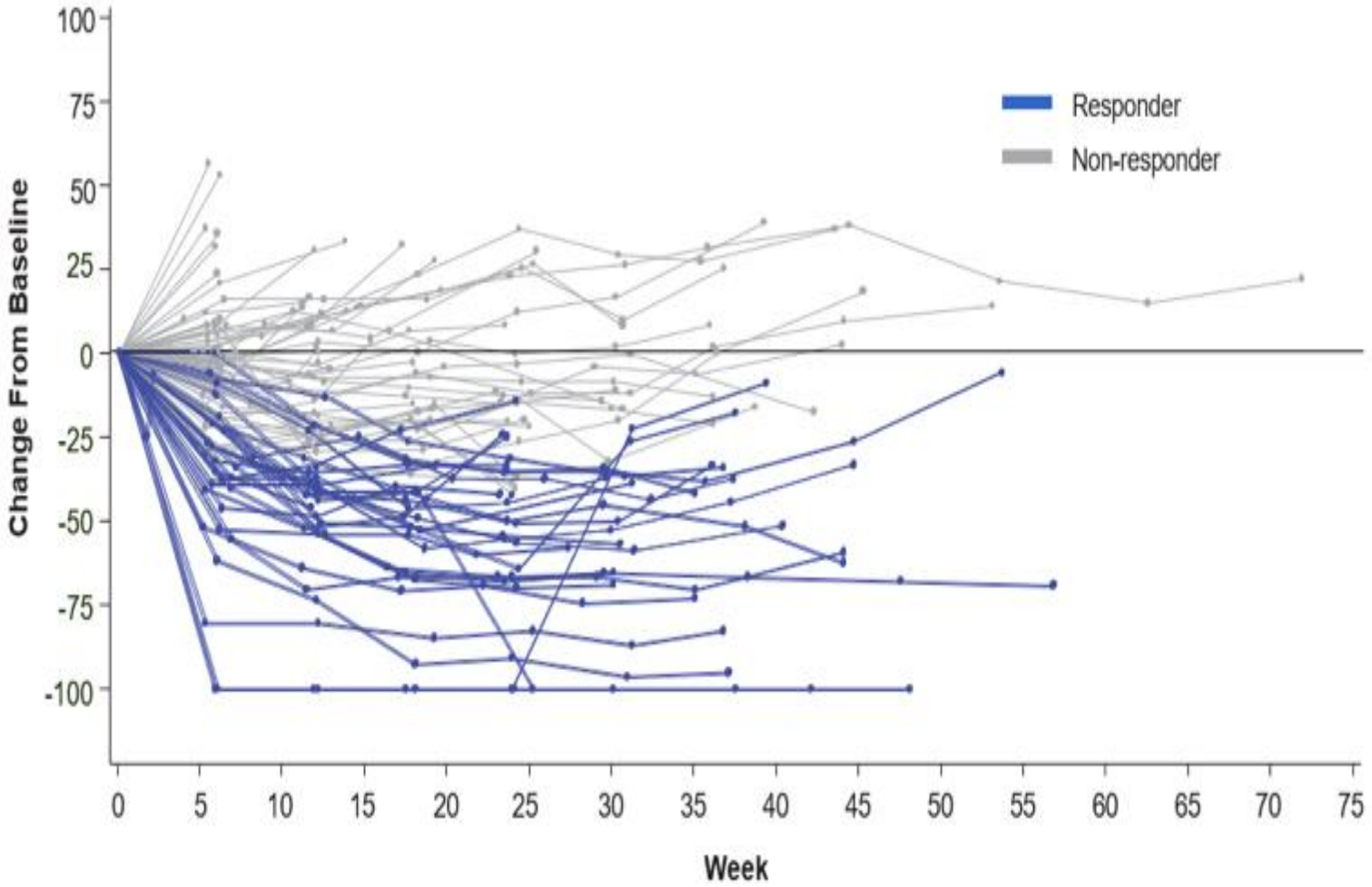
[a]Assessments were per Blinded Independent Review Assessment, RECIST 1.1.
CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; TTR, time to response.

[a]71/94 patients with at least one post-baseline target lesion measurement and accepted for central review. Fourteen patients had no post-treatment imaging, 1 patient lacked measurable lesions by central review, and 4 patients had poor image quality.

Tagawa ST, et al. J Clin Oncol 2021; 39:2474-85.

TROPHY-U-01 Cohort 1 Durability of Response





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TROPHY-U-01 Cohort 1 Treatment-Related Adverse Events ≥20% any grade or ≥5% Grade ≥3 (n=113)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	**Neutropenia**	**46**	**22**	**12**
	Leukopenia	26	12	5
	Anemia	34	14	0
	Lymphopenia	12	5	2
	Febrile neutropenia	**10**	**7**	**3**
Gastrointestinal	**Diarrhea[b]**	**65**	**9**	**1**
	Nausea	**58**	**4**	**0**
	Vomiting	28	1	0
General disorders & administrative site conditions	**Fatigue**	**50**	**4**	**0**
Skin & subcutaneous tissue	**Alopecia**	**47**	**0**	**0**
Metabolism & nutrition	Decreased appetite	36	3	0
Infections & infestations	Urinary tract infection	8	6	0

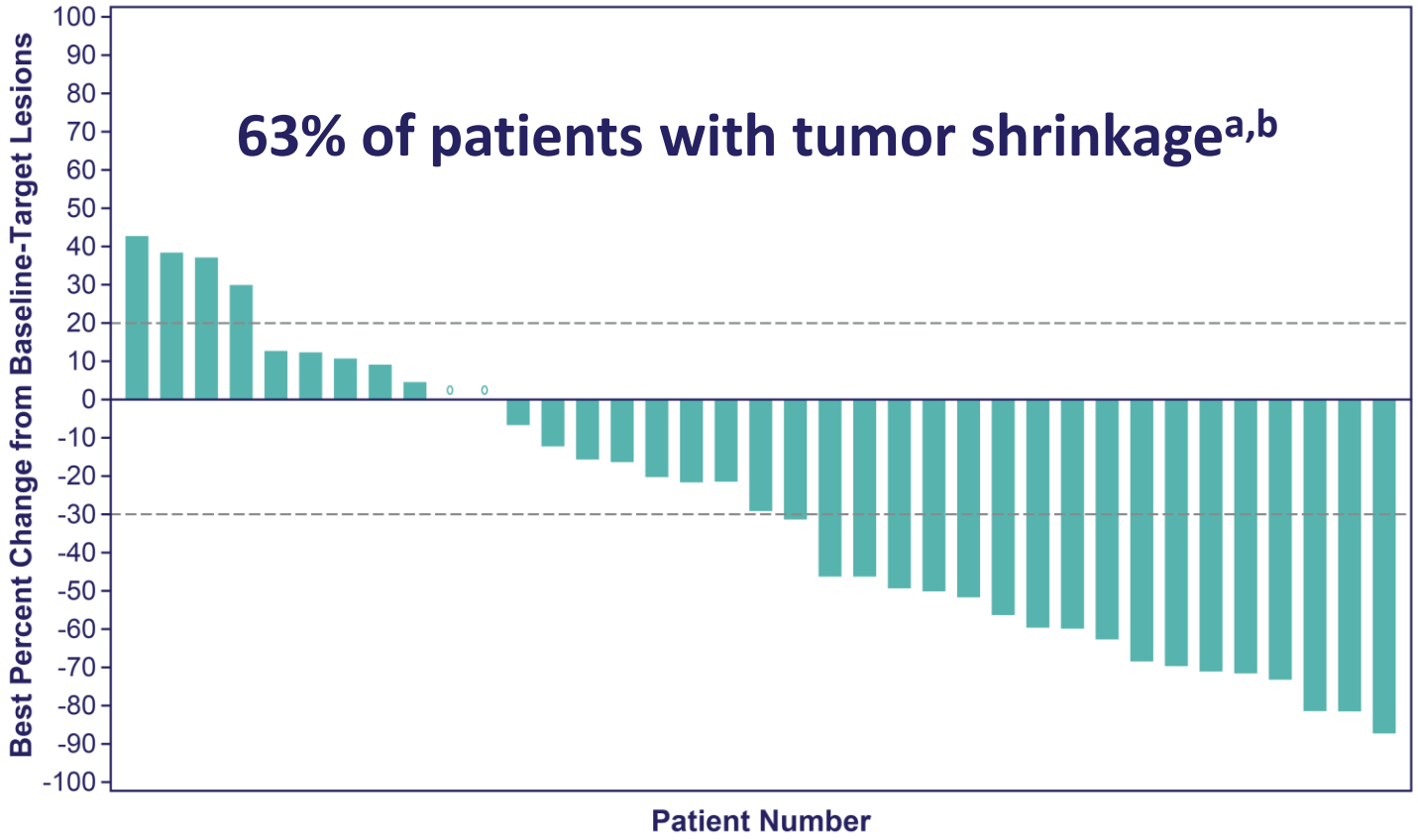
- 7 (6%) pts discontinued due to TRAEs
  - 3 discontinued due to neutropenia or its complications
- 30% G-CSF usage
- 1 treatment-related death (sepsis due to febrile neutropenia)

Median treatment cycles: 6 (range: 1–22); worst grade CTCAE reported

Tagawa ST, et al. J Clin Oncol 2021; 39:2474-85.

Overall Response and Best % Change From Baseline in Tumor Size (Cohort 3: Pembro + SG)

- 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

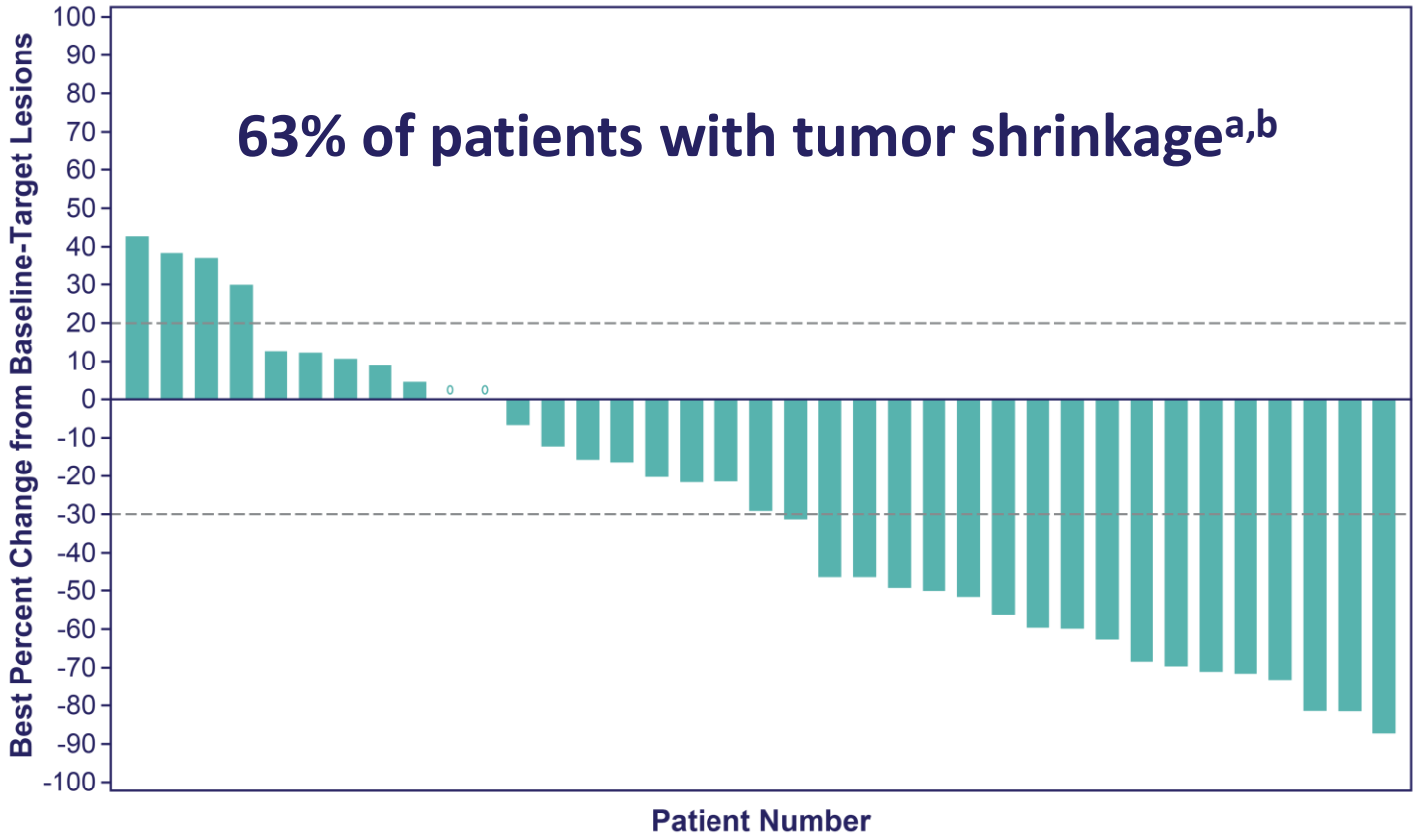


	Cohort 3[a] (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	**14 (34) [20.1-50.6]**
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	*4 (10)*
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR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

[a]Responses assessed by investigator in the intent-to-treat population. [b]Patients without post-baseline assessments are not shown here.
CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Overall Response and Best % Change From Baseline in Tumor Size (Cohort 3: Pembro + SG)

- 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



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Most Common Treatment-Related Adverse Events for All Patients (Cohort 3: Pembro + SG)

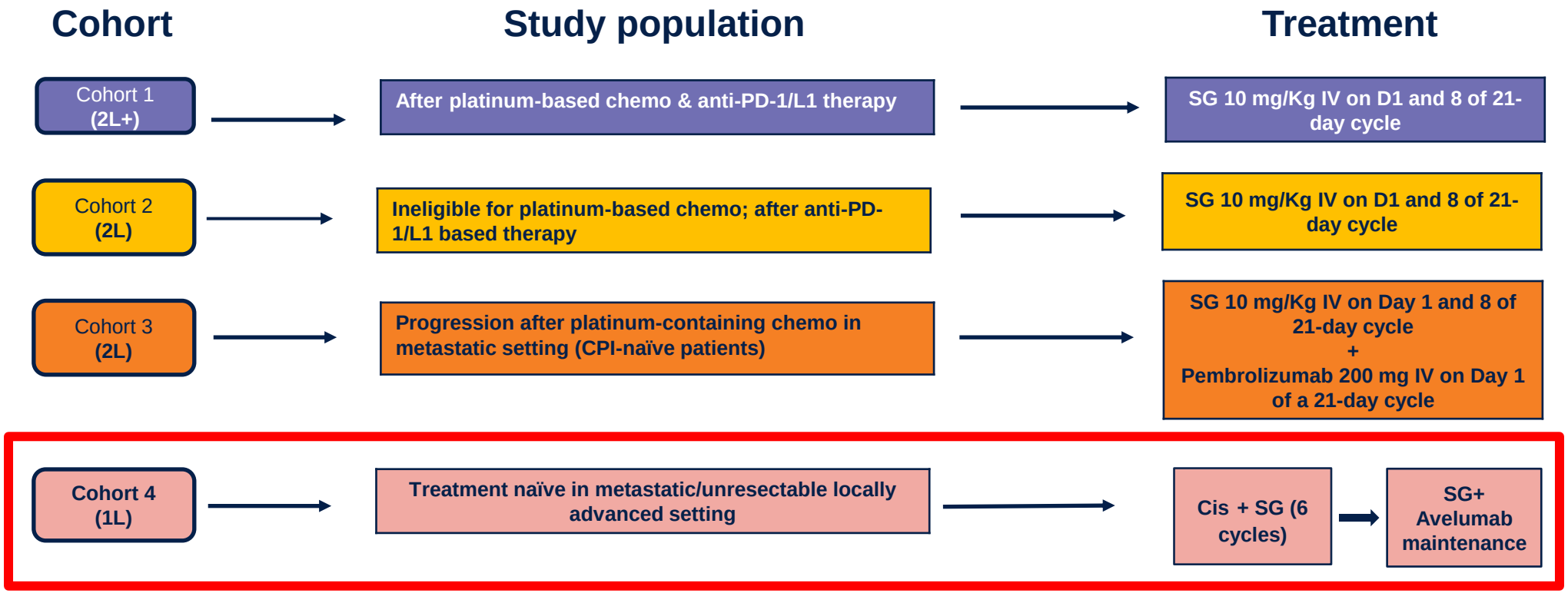
TROPHY U-01

	Cohort 3 (N=41)
TRAEs Occurring in >20% of Patients, n (%)	All Grade
Diarrhea	29 (71)
Nausea	22 (54)
Vomiting	10 (24)
Neutropenia	18 (44)
Anemia	17 (41)
Leukopenia	12 (29)
Fatigue	12 (29)
Asthenia	16 (39)
Alopecia	14 (34)
Decreased appetite	11 (27)
Pruritus	9 (22)

- Treatment-related Gr 3-4 AEs in 59% of patients
- 16 (39%) patients had SG dose reduction due to TRAE
- No treatment-related death occurred
- 10 (25%) patients received steroids for iRAE[a]
  - Topical: 6 (15%) patients
  - Oral: 4 (10%) patients
    - diarrhea (2 patients)
    - pruritus (1 patient)
    - rash maculopapular (1 patient)
- 12 (29%) patients received G-CSF
- Gr ≥3 febrile neutropenia, 4 (10%) without prior G-CSF

G-CSF, granulocyte colony stimulating factor; iRAE, immune-related adverse event; Pembro, pembrolizumab; TEAE, treatment-emergent adverse event.

TROPHY U-01: Sacituzumab Govitecan Multi-Cohort Trial in mUC



Cohorts 5 & 6 pending

Key Inclusion Criteria:

- **PS ECOG 0-1**
- **C1-C3: Creatinine clearance ≥30 mL/min; C4: Creatinine clearance ≥50 mL/min**
- **Adequate organ function & stable brain metastases**

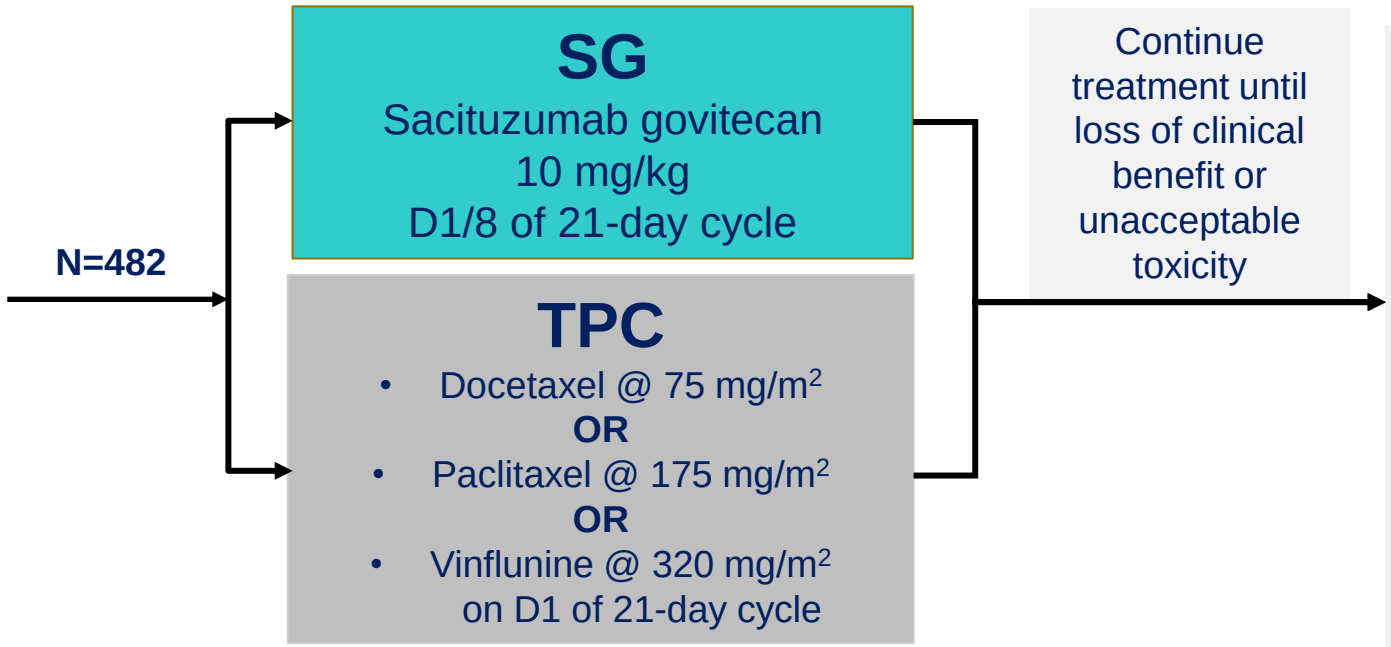
TROPiCS-04 Design

Study Population

- Locally advanced unresectable or mUC
- Upper/lower tract tumors
- Mixed histologic types are allowed if urothelial is predominant
- Progression after platinum-based **and** anti–PD-1/PD-L1 therapy

OR

- Platinum in neo/adj setting if progression within 12 months and subsequent CPI



Endpoint (EP)

Primary EP:

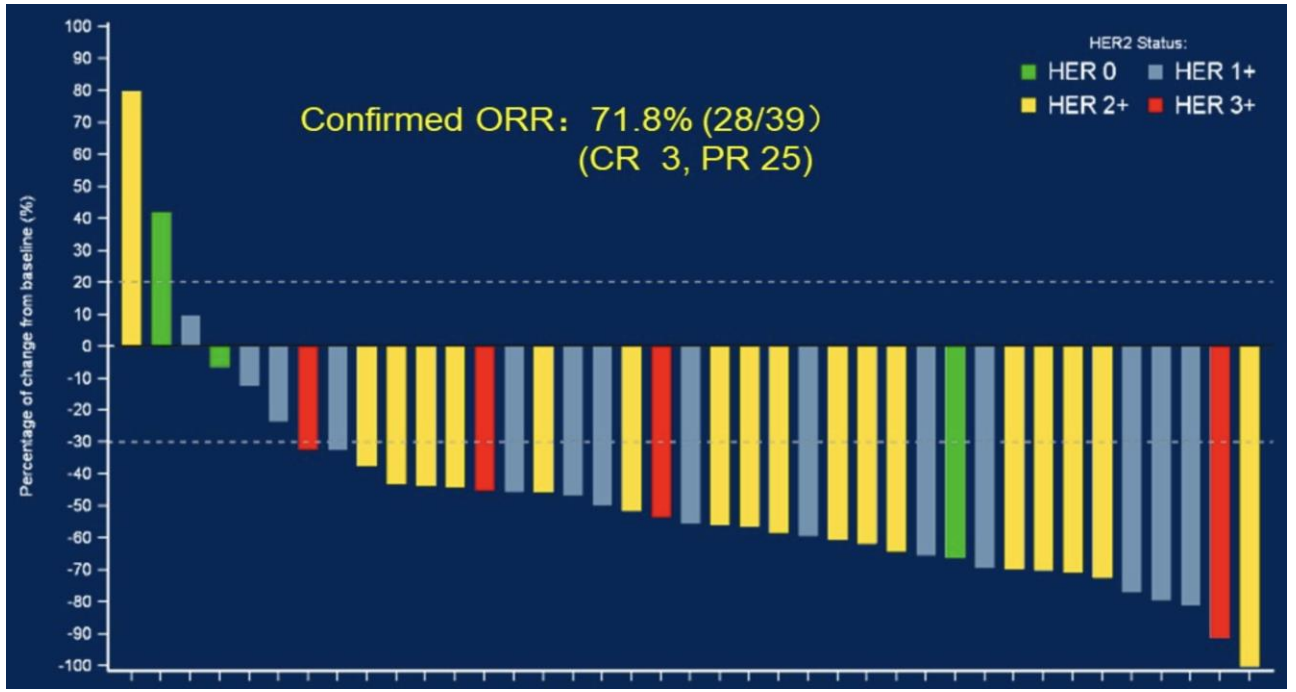
- OS

Secondary EP:

- PFS by PI assessment using RECIST 1.1
- ORR, DOR, and CBR by PI assessment using RECIST 1.1
- EORTC QLQ C30 score and EuroQOL EQ-5D-5L QOL score

Disitamab Vedotin with Anti-PD-1 (Toripalimab) in mUC

- Pts with locally advanced or metastatic UC
- 41 pts (25 treatment-naïve / 16 with 1+ lines of therapy)
  - 39 pts evaluable for response
- Confirmed ORR: 72% (28/39)
  - cORR in IHC 0 or 1+ pts: 9/17 (53%)
- Median PFS: 9.2 months
- Median OS: NR (86% 12-month OS)



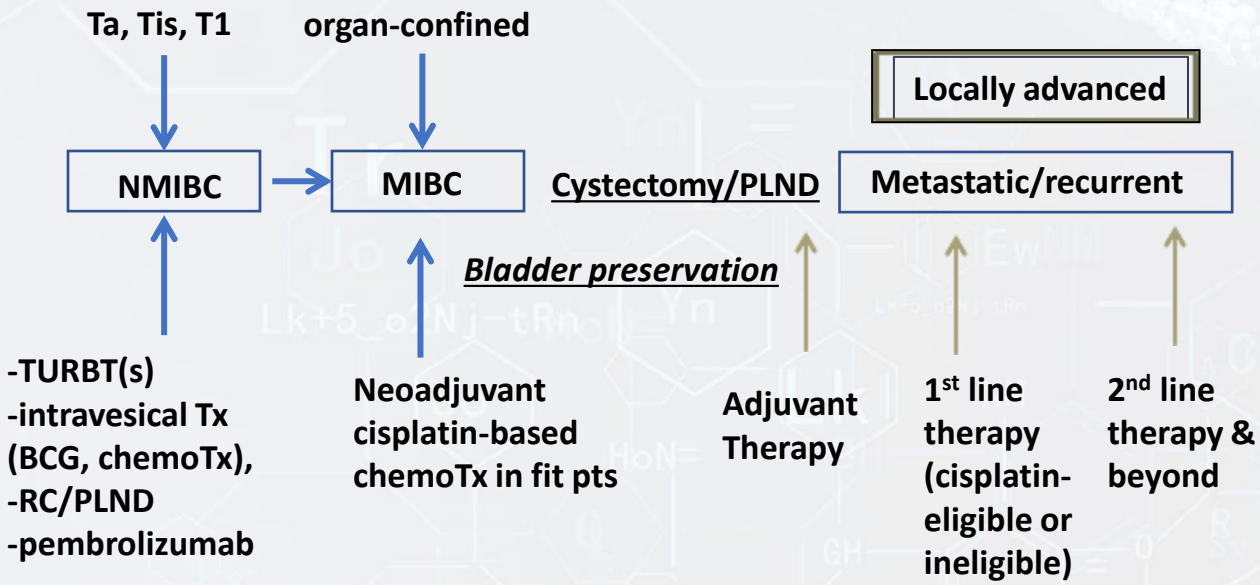
Promising results with DV trials in China led to a Breakthrough Therapy Designation by FDA
Phase II & III registrational trials (post-platinum monotherapy & combo with anti-PD-1) pending

Differences Among the ADC/IO Combinations

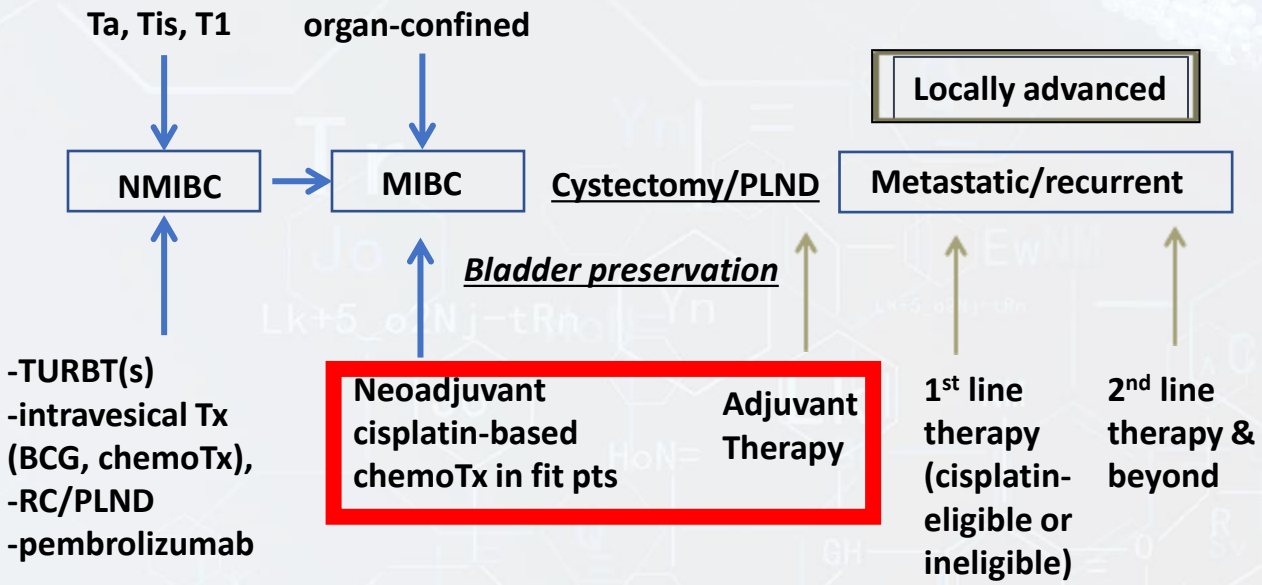
Regimen	Payload	N	Population	HER2	ORR
Enfortumab vedotin + Pembrolizumab	MMAE (tubulin)	43	Cis-ineligible, tx naive	All	73%
Disitimab vedotin + Toripalimab	MMAE (tubulin)	39	60% tx naive	All	72%
Trastuzumab deruxtecan + Nivolumab	Dxd (Topo I)	26	Progressed despite prior platinum	2+ or 3+	36%
Sacitizumab govitecan + Pembrolizumab	SN38 (Topo I)	41	Progressed despite prior platinum	All	34%

Slide Courtesy of Matt Galsky and ASCO

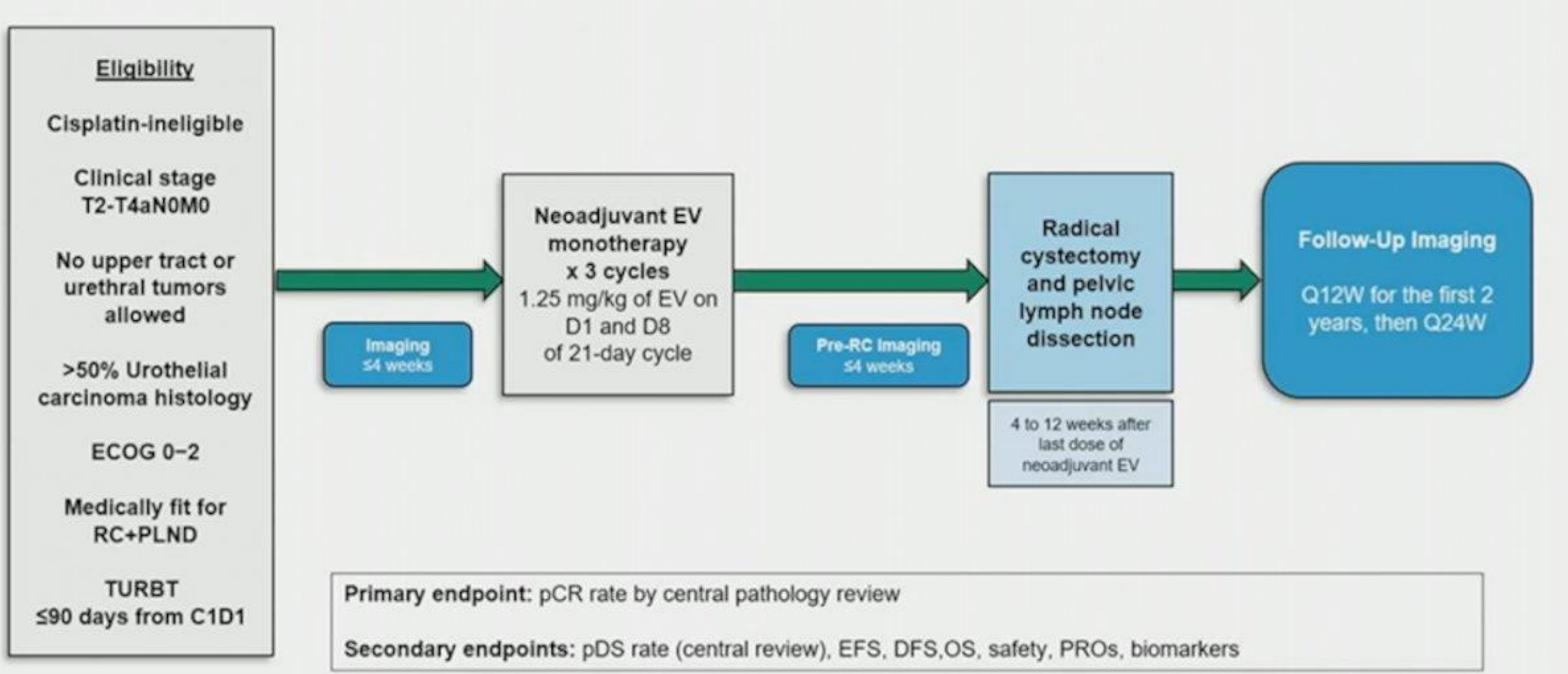
Disease / treatment settings



Disease / treatment settings



EV-103 cohort H (neoadjuvant setting)

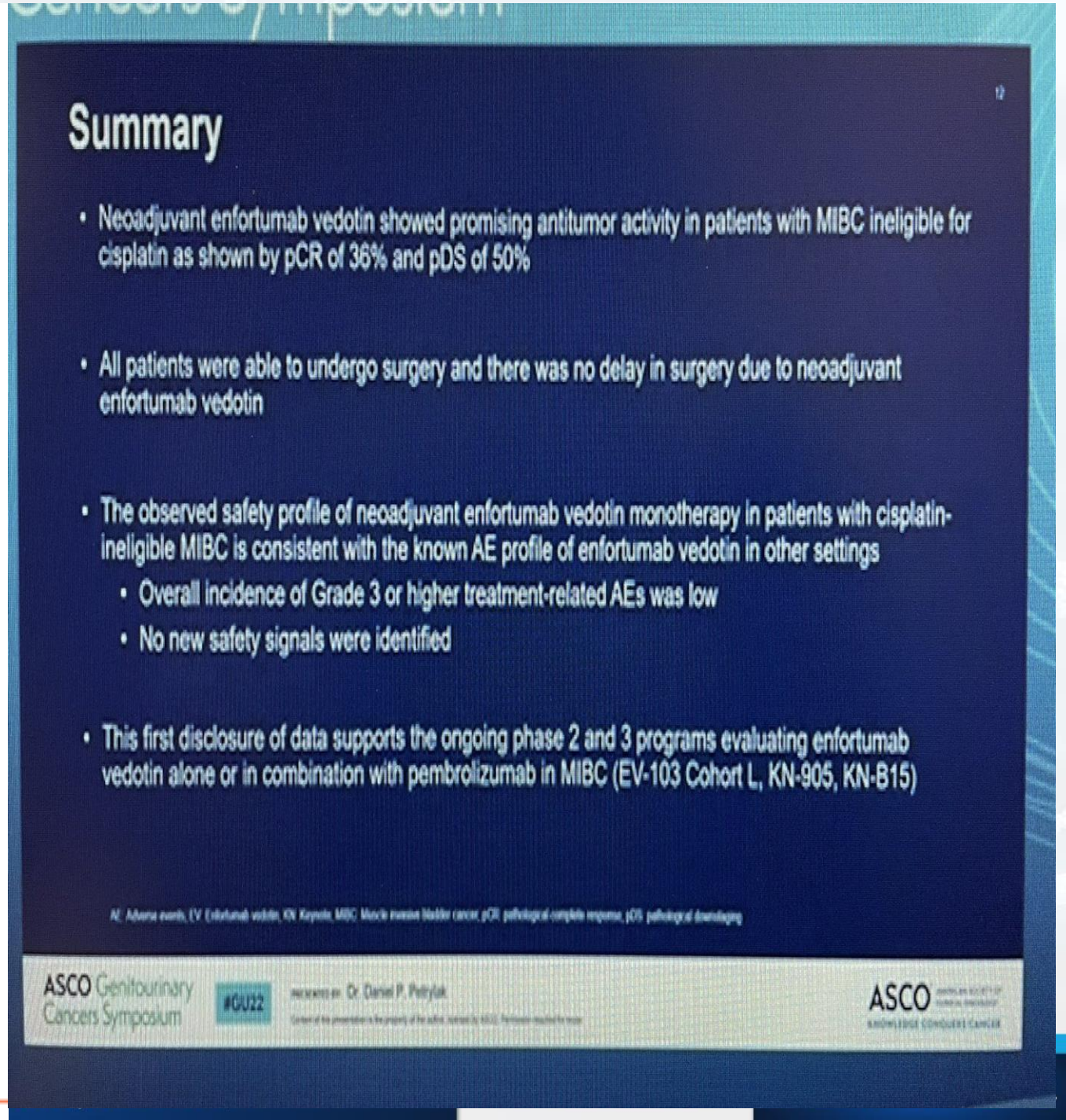


EV-103 Cohort H: Rates of pCR and Pathologic Downstaging by Central Pathology Review

Pathologic Response, n (%) (95% CI)	Cohort H (N = 22)
Primary endpoint: pCR*	8 (36.4) (17.2-59.3)
Pathologic downstaging rate†	11 (50.0) (28.2-71.8)

Defined as: *Absence of any viable tumor tissue (ypT0 and N0). †Presence of ypT0, ypTis, ypTa, ypT1, and N0.

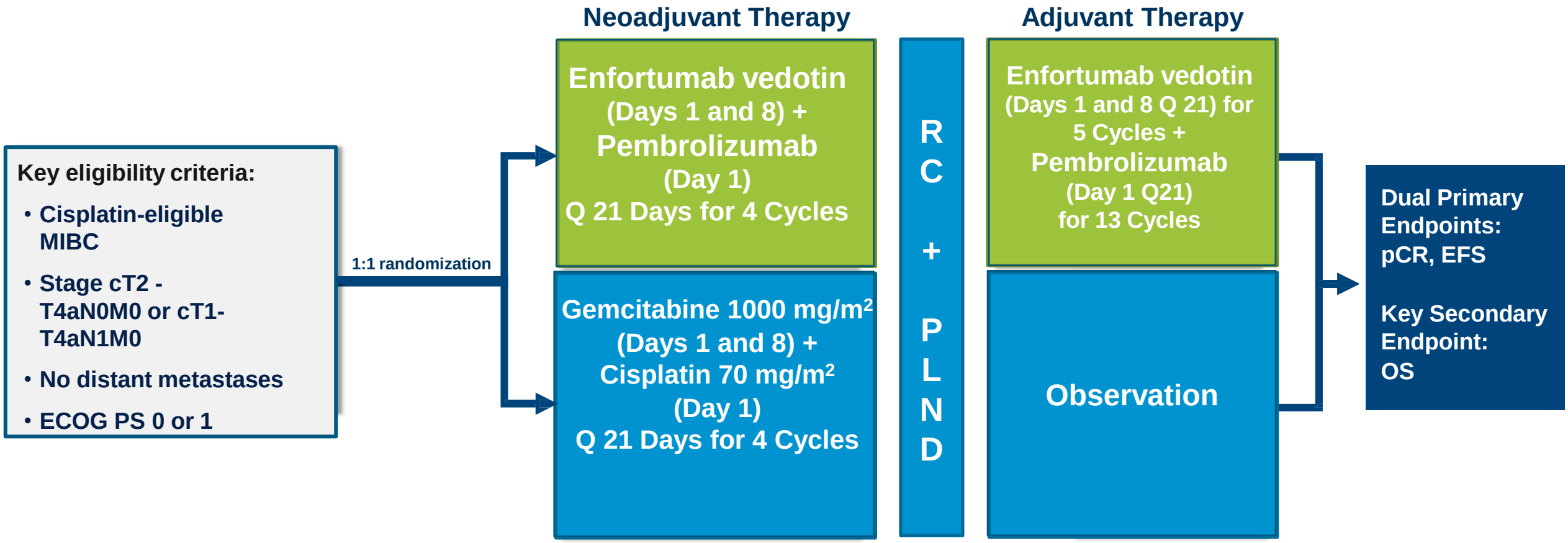
- Antitumor activity observed with neoadjuvant enfortumab vedotin



Petrylak. ASCO GU 2022. Abstr 435.

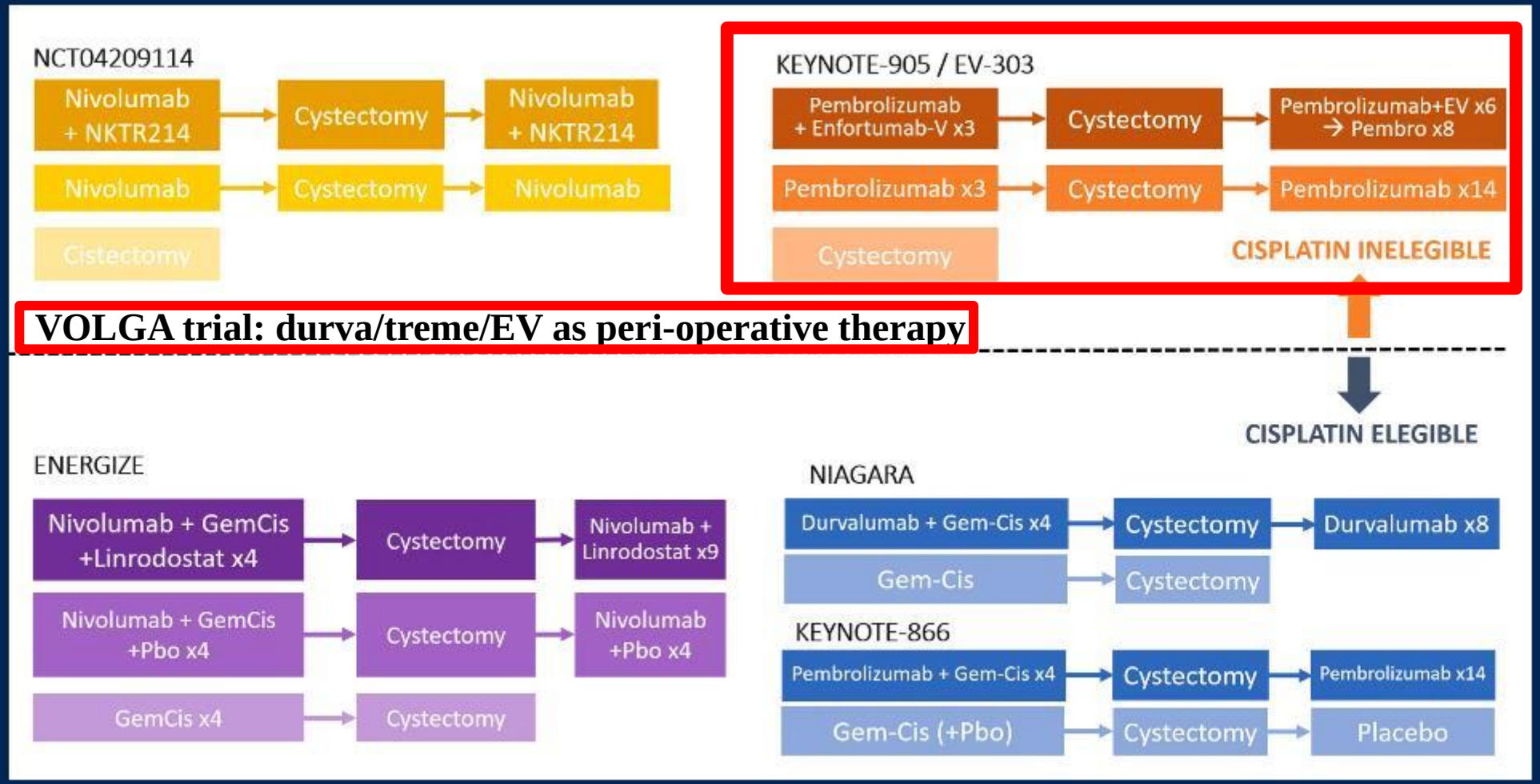
Slide credit: clinicaloptions.com

Enfortumab Vedotin for Perioperative Treatment: KEYNOTE-B15 / EV-304 Study



RC = Radical Cystectomy; PLND = Pelvic lymph node dissection

Phase III neoadjuvant IO trials



Rey-C´ardenas et al. Cancer Treatment Reviews, 2021.

Rafee Talukder

Neoadjuvant trial for cisplatin-unfit pts with variant histology MIBC

Accrual target: 18 pts

Key Eligibility

- Muscle Invasive Bladder Cancer (cT2-T4aN0-N1M0 or cT1-4aN1M0)
- Candidates for radical cystectomy
- Variant histology as defined in eligibility criteria
- Cisplatin-ineligible or refuses cisplatin

Sacituzumab Govitecan

10mg/kg on days 1 & 8
Every 21 days x 3 cycles

Maximal TURBT → Radical Cystectomy & Pelvic Lymph Node Dissection

Endpoints

Primary:

- Pathologic complete response rate

Secondary:

- Toxicity
- Two-year recurrence free survival
- Translational studies with tissue, blood, urine, stool

Thank you ☺
Patient & families!

Collaborators, sponsors, institutions, foundations, colleagues, research, admin & clinical staff: TEAMS!

@PGrivasMDPhD