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Urothelial Carcinoma

Clinical Updates From Madrid

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Systemic Therapy for BCG-Refractory, High-Risk, Non-CIS NMIBC

- Up to one-half of patients experience recurrence or become BCG-unresponsive[1]
- Radical cystectomy is current standard of care for BCG-unresponsive NMIBC; however, it is a complex surgery associated with high perioperative morbidity and QOL implications[2]
- Unmet need for alternative bladder-preserving treatments

Trial	KEYNOTE-057—Cohort B[3] NCT02625961	NCT02773849[4]	THOR-2—Cohort 1[5] NCT04172675
Phase	2 (single arm)	3 (single arm)	2
Intervention	IV pembrolizumab	Intravesical nadofaragene firadenovec-vncg	Erdafitinib 6 mg/d PO vs intravesical CT (2:1)
Population	BCG-unresponsive high-risk NMIBC with papillary tumors only (HG Ta or any-grade T1) at baseline, ECOG PS 0-2 (N = 132)	BCG-unresponsive NMIBC, ECOG PS 0-2 • CIS cohort: CIS with or without HG NMIBC Ta or T1 (n = 107) • HG Ta or T1 cohort: HG Ta or T1 w/o CIS (n = 50)	High-risk NMIBC (HG Ta or T1), select *FGFR*alt refusing/ineligible for radical cystectomy (N = 73)
Median follow-up	45.4 mo	20.2 mo for HG Ta or T1 cohort	13.4 mo
Efficacy outcomes	• 12-mo DFS, 43.5%[a] • Median high-risk NMIBC DFS: 7.7 mo • 12-mo OS: 96.2% (median NR) • Median PFS: 44.5 mo[b]	HG Ta or T1 cohort: • 12-mo HG RFS: 43.8% • Median HG RFS: 12.35 mo • 24-mo OS: 93.5%	• 12-mo RFS: 77% vs 41% • Median RFS: NR vs 11.6 mo (HR, 0.28)
Grade ≥ 3 trAE	14.4% (grade 3/4)	4%	31% vs 4%

[a]Primary endpoint. [b]To worsening of grade, stage, or death.

BCG, Bacillus Calmette-Guerin; CIS, carcinoma in situ; CT, chemotherapy; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *FGFR*alt, *FGFR* alteration(s); HG, high grade; HR, hazard ratio; IV, intravenous; NMIBC, non–muscle invasive bladder cancer; NR, not reached; OS, overall survival; PFS, progression-free survival; PO, oral; QOL; quality of life; RFS, recurrence-free survival; trAE, treatment-related adverse event.

1. Balar A et al. *Lancet Oncol*. 2021;22:919-930. 2. Claps F et al. *Int J Mol Sci*. 2023;24:12596. 3. Necchi A et al. ASCO GU 2023. Abstract LBA442. 4. Boorjian SA et al. *Lancet Oncol*. 2021;22:107-117.
5. Catto J et al. ESMO 2023. Abstract LBA102.

LBA102, THOR-2 Cohort 1: Results of Erdafitinib vs Intravesical Chemotherapy in Patients With High-Risk NMIBC With Select *FGFR*alt Who Received Prior BCG Treatment

THOR-2 Study Design

ClinicalTrials.gov ID: NCT04172675

Primary endpoint: RFS

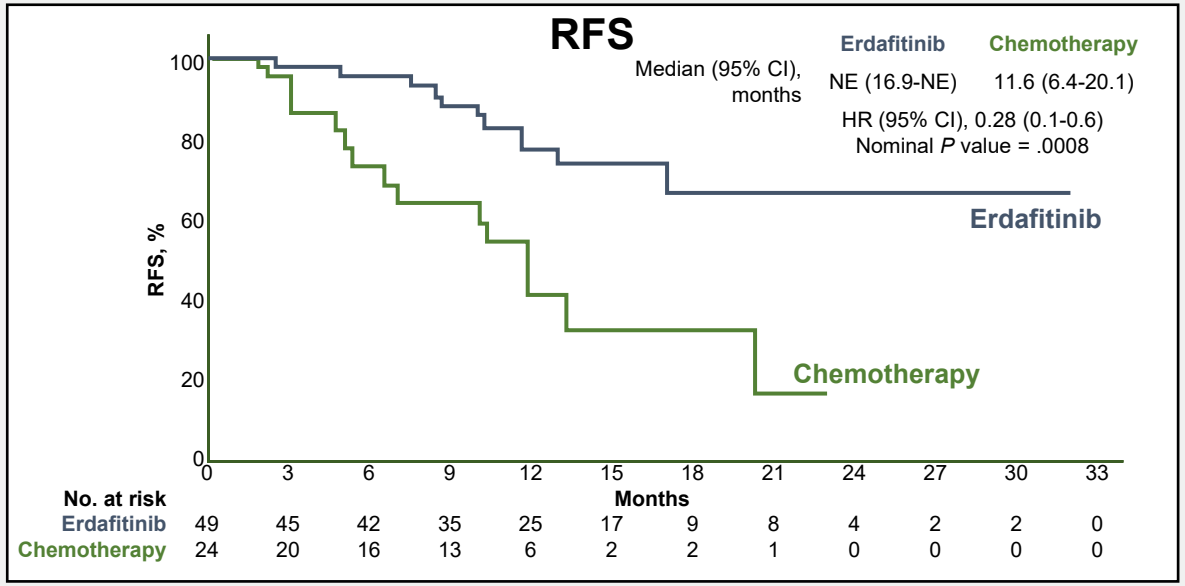
Screening for *FGFR* mutations or fusions in tumor tissue by central or local testing → Patients with NMIBC recurrence after BCG therapy → **Cohort 1**
- HR NMIBC
- Papillary disease only (no CIS)

→ R (2:1)
- **Erdafitinib** 6 mg/d
- **Investigator choice** Intravesical GEM **or** intravesical MMC/ hyperthermic MMC

N = 240

Stratification factors:
- Tumor type (Ta vs T1)
- Type of prior BCG therapy (BCG unresponsive vs BCG experienced)

Trial stopped early due to slow accrual; 73 patients were randomized



Patients with ≥1 AE, n (%)	Erdafitinib (n = 49)	
	Any grade	Grade ≥3
Any AEs of interest	49 (100)	—
Nail toxicity	38 (77.6)	3 (6.1)
Hyperphosphatemia	36 (73.5)	0
Eye toxicities (excluding central serous retinopathy)	29 (59.2)	2 (4.1)
Skin toxicity	25 (51.0)	0
Dry mouth	23 (46.9)	0
Stomatitis	20 (40.8)	5 (10.2)
Central serous retinopathy	19 (38.8)	2 (4.1)

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Erdafitinib in BCG-treated high-risk non-muscle-invasive bladder cancer

Clinical cutoff date: June 27, 2023.

AE, adverse event; BCG, Bacillus Calmette-Guerin; CIS, carcinoma in situ; *FGFR*alt, *FGFR* alteration(s); GEM, gemcitabine; HR, hazard ratio; MMC, mitomycin C; NE, not estimable; NMIBC, non–muscle invasive bladder cancer; RFS, recurrence-free survival.

1. Catto J et al. ESMO 2023. Abstract LBA102. 2. Catto J et al. *Ann Oncol*. 2023;S0923-7534(23)04015-2.

Summary of Phase 3 Data for First-Line Therapy for Locally Advanced or Metastatic UC Eligible for Platinum CT

Trial	JAVELIN Bladder 100[1,2] NCT02603432	KEYNOTE-A39/EV-302[3] NCT04223856	CheckMate 901[4,5] NCT03036098
Intervention	Platinum-based CT followed by avelumab + BSC or BSC alone (1:1)	Pembrolizumab + enfortumab vedotin vs gemcitabine-cisplatin/carboplatin (1:1)	Nivolumab + gemcitabine-cisplatin vs gemcitabine-cisplatin
Population	Advanced UC without progression after first-line platinum CT (N = 700)	Untreated locally advanced/metastatic UC, eligible for platinum CT, any PD-L1 status (N = 886)	Untreated unresectable or metastatic UC (N = 608) (1:1)
Median follow-up	38 mo	17.2 mo	33.6 mo
ORR	9.7% vs 1.4%	67.7% vs 44.4%	57.6% vs 43.1%
Median OS	23.8 vs 15 mo HR, 0.76 (95% CI, 0.63-0.91)[a]; *P* = .0036	31.5 vs 16.1 mo HR, 0.47 (95% CI, 0.38-0.58)[a]; *P* < .00001	21.7 vs 18.9 mo HR, 0.78 (95% CI, 0.63-0.96)[b]; *P* = .02
Median PFS	5.5 vs 2.1 mo HR, 0.54 (95% CI, 0.46-0.64); *P* < .0001	12.5 vs 6.3 mo HR, 0.45 (95% CI, 0.38-0.54)[a]; *P* < .00001	7.9 vs 7.6 mo HR, 0.72 (95% CI, 0.59-0.88)[b]; *P* = .001
Grade ≥3 trAE	19.5% in avelumab + BSC group	55.9% vs 69.5%	61.8% vs 51.7%

[a]Primary endpoint. [b]Coprimary endpoints.

BSC, best supportive care; CT, chemotherapy; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death-ligand 1; trAE, treatment-related adverse events; UC, urothelial carcinoma.

1. Powles T et al. *N Engl J Med*. 2020;383:1218-1230. 2. Powles T et al. *J Clin Oncol.* 2023;41:3486-3492. 3. Powles T et al. ESMO 2023. Abstract LBA6. 4. Van Der Heijden M et al. ESMO 2023. Abstract LBA7. 5. van der Heijden MS et al. *N Engl J Med*. 2023. doi:10.1056/NEJMoa2309863.

Systemic Therapy for la/mUC (Post-Platinum CT)

Trial	CheckMate 275[1] NCT02387996	JAVELIN SOLID TUMOR[2] NCT01772004	KEYNOTE-045[3] NCT02256436	EV-301[4,5] NCT03474107	THOR[6] NCT03390504	TROPHY-U-01[7] NCT03547973
Phase	2 (single arm)	1/2 (single arm)	3	3	3	2
Intervention	Nivolumab	Avelumab	Pembrolizumab vs CT (1:1)	Enfortumab vedotin vs CT (1:1)	Erdafitinib vs pembrolizumab (1:1)	Sacituzumab govitecan
Population	Platinum-resistant la/mUC (N = 270)	mUC with PD after platinum CT (or cisplatin ineligible) (N = 249)	mUC with PD after platinum CT (N = 542)	la/mUC after platinum CT and with PD after PD-(L)1 inhibitor (N = 608)	la/mUC, *FGFR*alt, PD after ≥1 platinum CT, naive to PD-(L)1 therapy (N = 351)	la/mUC with PD after platinum CT and PD-(L)1 (N = 113)
Follow-up	33.7 mo (minimum)	2.7 years (median)	62.9 mo (median)	23.8 mo	33.2 mo (median)	9.1 mo
ORR	20.7%[a]	16.5%	21.9% vs 11.0%	41.3% vs 18.6%	40% vs 22%	27%[a]
Median DOR	20.3 mo	20.5 mo	29.7 vs 4.4 mo	7.4 vs 8.1 mo	4.3 vs 14.4 mo	7.2 mo
Median OS	8.6 mo	7.0 mo	10.1 vs 7.2 mo HR (95% CI), 0.71 (0.59-0.86)[d]	12.9 vs 8.9 mo HR (95% CI), 0.704 (0.58-0.85)[a]	10.9 vs 11.1 mo HR (95% CI), 1.18 (0.92-1.51)[a]	5.4 mo
Median PFS	1.9 mo	1.6 mo	2.1 vs 3.3 mo HR (95% CI), 0.95 (0.79-1.14)[d]	5.6 vs 3.7 mo HR (95% CI), 0.632 (0.53-0.76)	4.4 vs 2.7 mo HR (95% CI), 0.88 (0.70-1.10)	10.9 mo
trAE	25% (grade 3/4)[b]	11% (grade ≥ 3)	17% vs 50% (grade 3-5)	52% vs 50% (grade ≥ 3)	43% vs 12% (grade 3/4)[c]	94.7% (any grade); most common grade ≥ 3: cytopenia, diarrhea

[a]Primary endpoint. [b]Three grade 5 trAEs were observed. [c]trAEs leading to death occurred in 0 patients in the erdafitinib arm and 3 (2%) in the pembrolizumab arm. [d]Coprimary endpoints.

CT, chemotherapy; DOR, duration of response; *FGFR*alt, *FGFR* alteration(s); la/mUC, locally advanced or metastatic urothelial carcinoma; mUC, metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD, disease progression; PD-(L)1, programmed cell death protein 1 or its ligand; PFS, progression-free survival; trAE, treatment-related adverse events; UC, urothelial carcinoma.

1. Galsky M et al. *Clin Cancer Res*. 2020;26(19):5120-5128. 2. Apolo AB et al. GU Cancers Symposium 2019. Abstract 425. 3. Balar AV et al. *Ann Oncol*. 2023;34:289-299. 4. Powles T et al. *N Engl J Med*. 2021;384:1125-1135. 5. Rosenberg J et al. ASCO 2022. Abstract 4516. 6. Siefker-Radtke AO et al. ESMO 2023. Abstract 2359O. 7. Tagawa S et al. *J Clin Oncol*. 2021;39:2474-2485.

2359O, Phase 3 THOR Study: Results of Erdafitinib vs Pembrolizumab in Pretreated Patients With Advanced or Metastatic UC With Select *FGFR*alt

Study Design

ClinicalTrials.gov ID: NCT03390504

Cohort 2

Key eligibility criteria
- Age ≥18 years
- Metastatic or unresectable UC
- Confirmed PD on 1 prior therapy
- Naive to anti-PD-(L)1 therapy
- Select *FGFR*alt (mutation/fusion)
- ECOG PS 0-2

1:1
N = 351

R

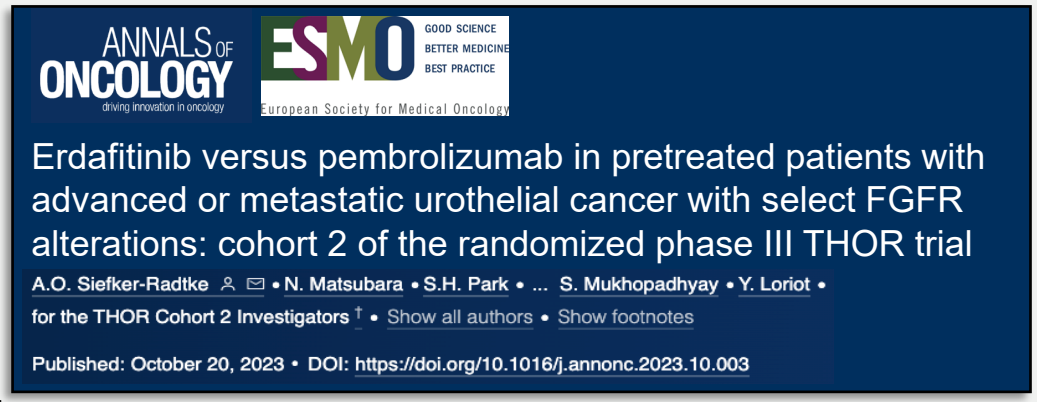
Erdafitinib
(n = 175)
Once-daily erdafitinib 8 mg with pharmacodynamically guided uptitration to 9 mg

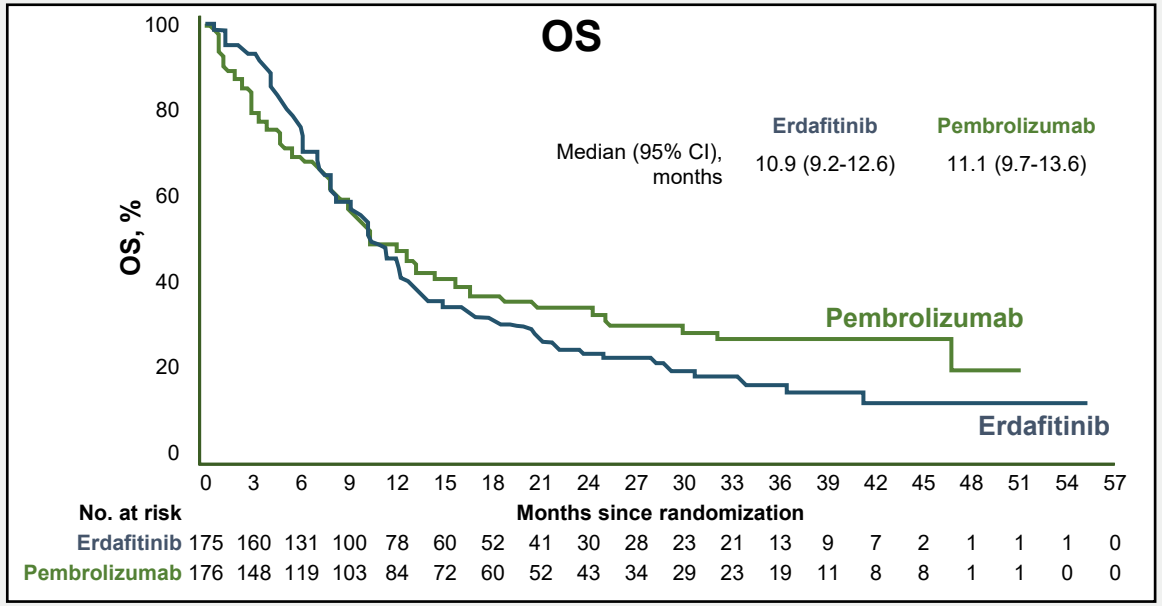
Pembrolizumab
(n = 176)
200 mg once every 3 weeks

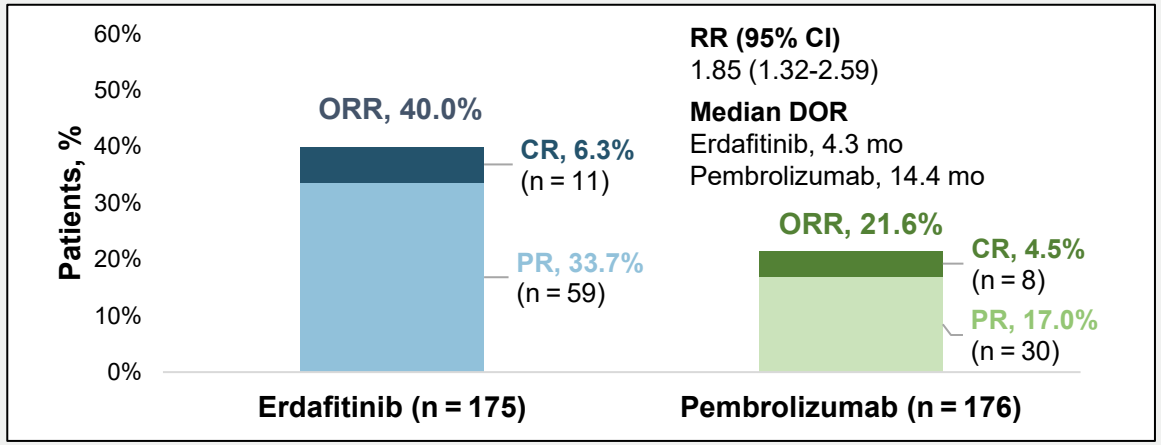
Primary endpoint
- OS

Secondary endpoints
- PFS
- ORR
- Safety

Stratification factors
- Region (North America vs EU vs ROW)
- ECOG PS (0/1 vs 2)
- Disease distribution (presence vs absence of visceral[a] metastases)







[a]Lung, liver, or bone.

CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EU, European Union; *FGFR*alt, *FGFR* alteration(s); ORR, overall response rate; OS, overall survival; PD, disease progression; PD-(L)1, programmed cell death protein 1 or its ligand; PFS, progression-free survival; PR, partial response; ROW, rest of world; RR, relative risk; UC, urothelial carcinoma.

1. Siefker-Radtke AO et al. ESMO 2023. Abstract 2359O. 2. Siefker-Radtke AO et al. *Ann Oncol.* 2023;S0923-7534(23)04021-8.

The Double ADC (DAD) Phase 1 Trial: SG + EV as ≥2L Therapy for Metastatic UC

Eligibility

Key inclusion criteria	Key exclusion criteria
• Metastatic or locally advanced predominant UC • Progression on platinum CT and immunotherapy **or** progression on 1 line and ineligible for cisplatin • Adequate organ function - ANC ≥1500/μL - Plt ≥100/μL - GFR ≥30 mL/min/1.73 m^2 - AST/ALT ≤2.5× ULN	• Small-cell carcinoma • Active CNS metastases • Ongoing toxicities grade ≥2 from prior therapy • Prior EV or SG therapy • Uncontrolled diabetes mellitus - A1C >8% or 7%-8% with diabetes symptoms

Primary endpoint: feasibility and toxicities of SG + EV by estimation of combination MTDs by assessing **DLTs during cycle 1 of therapy**

Secondary endpoints: ORR, PFS, OS

- MTD: 10 mg/kg + 1.25 mg/kg EV
- RP2D: 8 mg/kg SG + 1.25 mg/kg EV, days 1 and 8 of 21-day cycle, with GCSF support

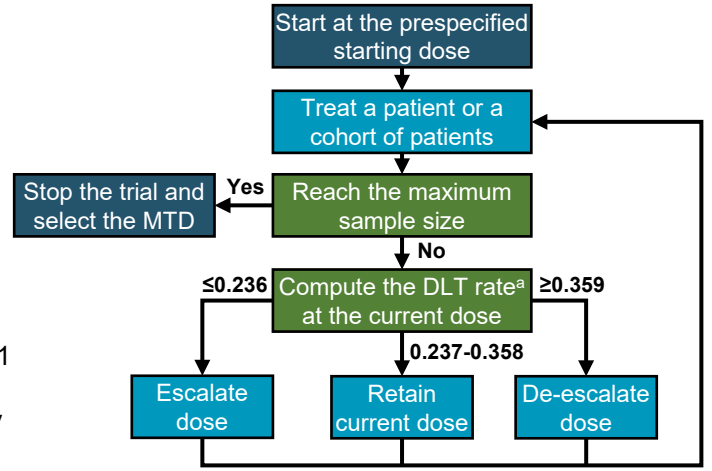
- Toxicities as expected with single agents
- Most common toxicities: diarrhea, anemia, neutropenia
- One case of grade 5 pneumonitis

Bayesian Optimal Internal Design (BOIN)

ClinicalTrials.gov ID: NCT04724018

	Starting dose, mg/kg	
	SG	EV
DL1	8	1
DL2	8	1.25
DL3	10	1.25
DL4	6	1
Both drugs given on days 1 and 8 of a 21-day cycle		

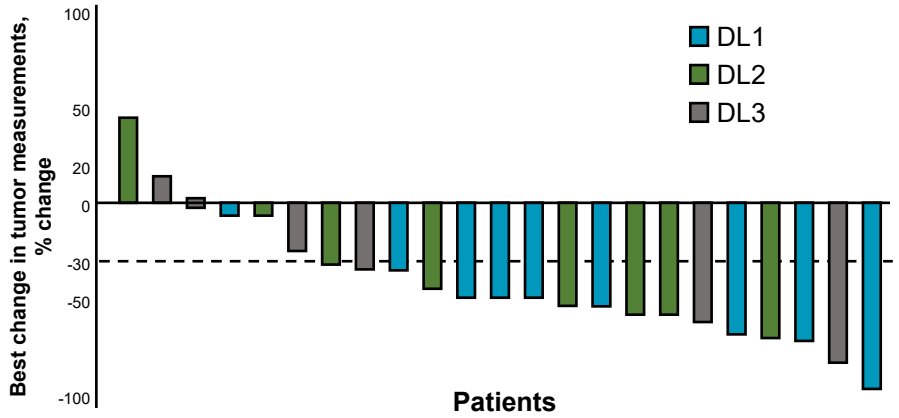
- Patients had to receive both drugs on day 1 of each cycle to continue
- Either therapy could be held independently on day 8 based on toxicity



[a]DLT rate = (total number of patients who experienced DLT at the current dose) / (total number of patients treated at the current dose).

Yuan Y et al. *Clin Cancer Res.* 2016;22(17):4291-301.

20 out of 23 patients with any degree of shrinkage in target lesions



2L, second line; A1C, glycosylated hemoglobin; ADC, antibody-drug conjugate; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; CT, chemotherapy; DL, dose level; DLT, dose-limiting toxicity; EV, enfortumab vedotin; GCSF, granulocyte-colony stimulating factor; GFR, glomerular filtration rate; MTD, maximum tolerable dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Plt, platelet count; RP2D, recommended phase 2 dose; SG, sacituzumab govitecan; UC, urothelial carcinoma; ULN, upper limit of normal.

1. McGregor B et al. ESMO 2023. Abstract 2360O. 2. McGregor B et al. *Ann Oncol*. 2023;S0923-7534(23)04012-7.