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Novel ADCs and combination therapy in urothelial carcinoma: latest updates from the 2023 ASCO-GU Cancers Symposium

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Abstract

Antibody–drug conjugates (ADCs) combine the cytotoxicity of small-molecule drugs with antibody targeting. Due to their precise and powerful effect, they have become a new hotspot and an important trend in the research and development of anti-tumor antibody drugs. Every year, exciting new developments and innovations in the treatment of urological tumors are introduced at the American Society of Clinical Oncology-Genitourinary (ASCO-GU) Cancers Symposium. In this article, we summarize some of the most impressive advances in new clinical trials and clinical data on ADCs in the 2023 ASCO-GU Cancers Symposium for the treatment of urothelial carcinoma.

Keywords ADCs, Enfortumab vedotin, Sacituzumab govitecan, Disitamab vedotin, Urothelial carcinoma

To the editor:

Each year, exciting developments in urological tumors are introduced at the American Society of Clinical Oncology-Genitourinary (ASCO-GU) Cancers Symposium. In this article, we review the impressive progress made in new clinical trials and data concerning antibody–drug conjugates (ADCs) for urothelial carcinoma treatment from the 2023 Symposium.

Enfortumab vedotin in urothelial carcinoma

Enfortumab vedotin (EV) is an ADCs formed by joining a humanized Nectin-4 targeted IgG1 monoclonal antibody, enfortumab, and a microtubule-disrupting agent, monomethyl auristatin E (MMAE), through a cleavable mc-val-cit-PABC linker. The EV-103 cohort K (NCT03288545) evaluated EV or EV + Pembrolizumab (Pembro) as a first-line therapy for cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (la/mUC). Patients were randomized 1:1 to receive EV monotherapy on days 1 and 8, or in combination with Pembro on day 1 of the 3-week cycles. EV monotherapy showed an objective response rate (ORR) of 45.2% (95% CI 33.5–57.3), while the EV + Pembro combination demonstrated an ORR of 64.5% (95% CI 52.7–75.1). Treatment-related adverse events (TRAEs) in the EV + Pembro arm included skin reactions (67.1%) and peripheral neuropathy (60.5%). TRAEs were observed in 68.4% of the patients. This led to the interruption of EV or Pembro, with 48.7% of patients requiring EV dose reduction [1]. This established the foundation for accelerated approval of EV

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+ Pembro by the US Food and Drug Administration (FDA), for cisplatin-ineligible mUC in April 2023.

Another ongoing phase 1 trial (NCT05014139) is studying intravesical EV infusion in high-risk, Bacillus Calmette-Guérin-unresponsive patients with non-muscle-invasive bladder cancer [2].

Sacituzumab govitecan in urothelial carcinoma

Sacituzumab govitecan (SG) is an ADC composed of an anti-Trop-2 antibody, sacituzumab, and a topoisomerase I inhibitor, SN-38, bound through the hydrolyzable linker CL2A. The ongoing phase 2 trial TROPHY-U-01, evaluated SG monotherapy and combination therapy in patients with la/mUC (NCT03547973). Cohort 1 demonstrated a 28% ORR (95% CI 20.2–37.6) in 113 patients with la/mUC, who had progressed after platinum-based chemotherapy and checkpoint inhibitor (CPI) treatment. Median overall survival (med-OS) was 10.9 months (95% CI 8.9–13.8), median progression-free survival (med-PFS) was 5.4 months (95% CI 3.5–6.9), and median duration of response (med-DOR) was 6.1 months (95% CI 4.7–9.7, $n=32$), leading to accelerated FDA approval for patients in cohort 1 [3]. Cohort 2 assessed SG monotherapy in patients with platinum-ineligible mUC who showed disease progression after CPI treatment [4]. Cohort 3 assessed combined SG and Pembro treatment in 41 patients with mUC, after platinum-based therapy, which supported the need for further evaluation of SG and CPI combination treatment in patients with mUC [5]. The common TRAEs in the cohort included febrile and non-febrile neutropenia, anemia, leukopenia, fatigue, and diarrhea. Anemia and fatigue appeared to be more SG-related, whereas diarrhea was more CPI-related. Cohort 5 evaluated SG + zimberelimab (ZIM) versus ZIM alone versus avelumab for switch maintenance in patients with mUC who received gemcitabine (GEM)/cisplatin without progressive disease [6]. In

Table 1 Characteristics of ADCs for the treatment of urothelial carcinoma

ADCs	Target	mAb	Linker	Payload	DAR
EV	Nectin-4	Enfortumab	vc-PABC linker	MMAE	3.8
SG	Trop2	Sacituzumab	CL2A	SN-38	7.6
RC48	HER2	Hertuzumab	vc-PABC linker	MMAE	4

ADCs Antibody–drug conjugates, *CL2A* A cleavable complicated PEG8- and triazole-containing PABC-peptide-mc linker, *DAR* Drug-to-antibody ratio, *EV* Enfortumab vedotin, *HER2* Human epidermal growth factor receptor 2, *MMAE* Monomethyl auristatin E, *RC48* Disitamab vedotin, *SG* Sacituzumab govitecan, *vc-PABC* Valyl-citrullinyl-p-aminobenzyloxycarbonyl

Table 2 Outcomes of ADCs treatment in urothelial carcinoma from ASCO-GU 2023

Drug	Indication	Agents	Pts	ORR (%)	OS	PFS	DOR	TRAEs	NCT	References
EV	la/mUC	EV + Pembro	76	64.5	–	–	–	Skin reactions, peripheral neuropathy	NCT03288545	[1]
		EV	73	45.2	–	–	–			
	NMIBC	EV	Trials in progress						NCT05014139	[2]
SG	la/mUC	Cohort 1 SG	113	28	10.9	5.4	6.1	Neutropenia, anemia,	NCT03547973	[3]
		Cohort 2 SG	38	32	13.5	5.6	5.6	Leukopenia, fatigue		[4]
		Cohort 3 SG + Pembro	41	41	12.7	5.3	11.1	Diarrhea, febrile		[5]
		Cohort 5 SG + ZIM versus ZIM versus avelumab	Trials in progress					Neutropenia		[6]
		Cohort 6 SG versus SG + CPI versus carboplatin/GEM	Trials in progress							[7]
	mUC	SG + IPI + NIVO	6	66.6	–	8.8	9.2	Anemia, neutropenia, Pruritus, fatigue, Diarrhea, lymphopenia, arthralgia	NCT04863885	[8]
RC48	HER2 + laUC/mUC		Trials in progress						NCT04879329	[10]

ADCs Antibody–drug conjugates, *CPI* Checkpoint inhibitor, *DOR* Duration of response, *EV* Enfortumab vedotin, *GEM* Gemcitabine, *HER2* Human epidermal growth factor receptor 2, *IPI* Ipilimumab, *la/mUC* Locally advanced/metastatic urothelial carcinoma, *NIVO* Nivolumab, *NMIBC* Non muscle-invasive bladder cancer, *ORR*Objective response rate, *OS* Overall survival, *Pembro* Pembrolizumab, *PFS* Progression-free survival, *Pts* Patients, *RC48* Disitamab vedotin, *SG* Sacituzumab govitecan, *TRAEs* Treatment-related adverse events, *ZIM* Zimberelimab

Cohort 6, we assessed SG monotherapy versus SG + CPI combinations (SG + ZIM, SG + ZIM + domvanalimab) versus carboplatin/GEM, followed by avelumab maintenance, in treatment-naive cisplatin-ineligible patients with la/mUC [7].

Another ongoing trial (NCT04863885) is investigating ipilimumab plus nivolumab combined with SG in cisplatin-ineligible patients with mUC. Phase 1 results: ORR was 66.6% in 6 patients, med-DOR was 9.2 months (95% CI 4.6–12.0), and med-PFS was 8.8 months (95% CI 3.8–NR). The TRAEs included anemia, neutropenia, pruritus, fatigue, diarrhea, lymphopenia, and arthralgia. A phase 2 trial with biomarker analysis is ongoing [8].

Disitamab vedotin in urothelial carcinoma

Disitamab vedotin (DV; RC48) is an ADC composed of a human epidermal growth factor receptor 2 (HER2)-targeted monoclonal antibody, hertuzumab, and MMAE via an mc-val-cit-PABC linker. The phase II trial RC48-C005 showed excellent anti-tumor activity and controllable safety of RC48 monotherapy in patients with HER2 + la/mUC after at least one systemic treatment failure [9]. RC48G001 (NCT04879329) is a phase 2 trial assessing RC48's safety, tolerance, and pharmacokinetics in HER2 + patients with la/mUC, with or without Pembro [10].

Overall, the ASCO-GU2023 Cancer Symposium has shown significant progress in the clinical trials of la/mUC. There is promising data on EV, SG and RC48, both as single and combination therapies, as summarized in Tables 1 and 2.

Abbreviations

ADC	Antibody–drug conjugate
ASCO-GU	American Society of Clinical Oncology-Genitourinary
CPI	Checkpoint inhibitor
DAR	Drug-to-antibody ratio
DOM	Domvanalimab
DOR	Duration of response
DV; RC48	Disitamab vedotin
EV	Enfortumab vedotin
FDA	Food and Drug Administration
GEM	Gemcitabine
HER2	Human epidermal growth factor receptor 2
IPI	Ipilimumab
La/mUC	Locally advanced/metastatic urothelial carcinoma
MMAE	Monomethyl auristatin E
NIVO	Nivolumab
NMIBC	Non-muscle-invasive bladder cancer
ORR	Objective response rate
OS	Overall survival
Pembro	Pembrolizumab
PFS	Progression-free survival
Pts	Patients
SG	Sacituzumab govitecan
TRAEs	Treatment-related adverse events
Vc-PABC	Valyl-citrullinyl-p-aminobenzyloxycarbonyl
ZIM	Zimberelimab

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