ORIGINAL ARTICLE

Disitamab Vedotin plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer

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ABSTRACT

BACKGROUND

Human epidermal growth factor receptor 2 (HER2)–directed antibody–drug conjugate monotherapy has shown preliminary clinical efficacy in patients with chemotherapy-refractory HER2-positive locally advanced or metastatic urothelial cancer. Previous data showed promising antitumor activity and safety of HER2-specific disitamab vedotin as monotherapy and when combined with programmed cell death protein 1 (PD-1)–directed immunotherapy in this cancer.

METHODS

In this phase 3, multicenter, open-label, randomized trial, we assigned patients with previously untreated HER2-expressing (immunohistochemical score of 1+, 2+, or 3+) locally advanced or metastatic urothelial cancer in a 1:1 ratio to receive either disitamab vedotin plus PD-1–specific toripalimab every 2 weeks or chemotherapy (gemcitabine plus cisplatin or carboplatin) every 3 weeks. The dual primary end points were progression-free survival (assessed by blinded independent review) and overall survival. Secondary end points included objective response and safety. Here we report the prespecified progression-free survival analysis and interim overall survival analysis.

RESULTS

A total of 484 patients underwent randomization. The median follow-up was 18.2 months. Progression-free survival was significantly longer in the disitamab vedotin–toripalimab group than in the chemotherapy group (median, 13.1 vs. 6.5 months; hazard ratio for progression or death, 0.36; 95% confidence interval [CI], 0.28 to 0.46; P<0.001). Overall survival was also significantly longer in the disitamab vedotin–toripalimab group than in the chemotherapy group (median, 31.5 vs. 16.9 months; hazard ratio for death, 0.54; 95% CI, 0.41 to 0.73; P<0.001). The percentage of patients with an objective response was 76.1% (95% CI, 70.3 to 81.3) in the disitamab vedotin–toripalimab group and 50.2% (95% CI, 43.7 to 56.7) in the chemotherapy group. The safety profile of disitamab vedotin plus toripalimab was more favorable than that of chemotherapy; grade 3 or higher treatment-related adverse events occurred in 55.1% of patients who received disitamab vedotin plus toripalimab and 86.9% of those who received chemotherapy.

CONCLUSIONS

Disitamab vedotin–toripalimab led to a significantly greater improvement in outcomes than chemotherapy among patients with untreated HER2-expressing locally advanced or metastatic urothelial cancer. (Funded by RemeGen and others; RC48-C016 ClinicalTrials.gov number, NCT05302284; ChinaDrugTrials.org.cn number, CTR20220348.)

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*A complete list of the RC48-C016 trial investigators can be found in the Supplementary Appendix, available at NEJM.org.

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In recent years, human epidermal growth factor receptor 2 (HER2)–targeted therapy has expanded to include treatment of multiple solid tumors beyond breast cancer.[1] In addition to being present in breast cancer, HER2 is also highly prevalent in urothelial carcinoma, with 52 to 69.8% of persons with urothelial cancer having a score of at least 1+ on HER2 immunohistochemical (IHC) assay.[2-5] HER2 has emerged as a potential therapeutic target in the treatment of urothelial cancer.[1,6,7] However, tyrosine kinase inhibitors and monoclonal antibodies directed against HER2 have shown limited efficacy in this disease.[6,7] In contrast, HER2-targeted antibody–drug conjugate monotherapy has been established as an effective treatment option after chemotherapy for HER2-positive urothelial cancer and is approved in both China (disitamab vedotin is approved for persons with a HER2 IHC score of 2+ or 3+) and the United States (trastuzumab deruxtecan is approved for persons with a HER2 IHC score of 3+).[6,8,9] The Food and Drug Administration (FDA) has granted disitamab vedotin a "breakthrough therapy" designation for treating HER2-positive locally advanced or metastatic urothelial cancer.

Combining antibody–drug conjugates with immunotherapy could leverage the synergistic antitumor effects for the treatment of advanced urothelial cancer, as has been the case with enfortumab vedotin (which is nectin-4–specific) and pembrolizumab — a regimen that was approved by the FDA and European Medicines Agency and is now standard care.[10-12] In addition, a phase 2 study showed encouraging efficacy of disitamab vedotin plus pembrolizumab as a first-line treatment in HER2-expressing locally advanced or metastatic urothelial cancer (75.0% of participants had a response).[13] Our previous phase 1b–2, dose-escalation and expansion study (RC48-C014), which evaluated treatment with disitamab vedotin plus toripalimab (a humanized anti–programmed cell death protein 1 [PD-1] monoclonal antibody approved in China, the United States, the European Union, and other countries) in patients with untreated or chemotherapy-refractory HER2-unselected locally advanced or metastatic urothelial cancer, showed that an overall response occurred in 73.2% of patients.[14] These findings indicated that patients with HER2-expressing locally advanced or metastatic urothelial cancer may benefit from disitamab vedotin (at a dose of 2.0 mg per kilogram of body weight) in combination with toripalimab.

We conducted a phase 3, multicenter, open-label, randomized trial (RC48-C016) that evaluated the efficacy and safety of disitamab vedotin plus toripalimab as compared with platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic urothelial cancer. Here, we report the results of the prespecified analysis of progression-free survival with a coincident interim analysis of overall survival.

METHODS

PATIENTS

Eligible patients were at least 18 years of age; had histopathologically confirmed, unresectable, locally advanced or metastatic urothelial cancer for which they had not previously received systemic chemotherapy; and had no disease progression or recurrence within 12 months after receiving neoadjuvant or adjuvant treatment. Patients had to have a centrally confirmed HER2-expressing tumor (IHC score of 1+, 2+, or 3+), which was assessed with VENTANA anti-HER2/Neu (4B5) rabbit monoclonal antibody (Roche) and the ultraView Universal DAB Detection Kit (Roche)[15]; tumor specimens from primary or metastatic lesions were acceptable. Full eligibility criteria are listed in the protocol (available with the full text of this article at NEJM.org).

TRIAL OVERSIGHT

The first author conceptualized the trial design, and the primary investigators designed the trial in collaboration with the sponsor (RemeGen). The trial was approved by the ethics committee at each participating site and was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All the patients provided written informed consent before trial enrollment. Data were collected by the investigators and analyzed by employees of the sponsor. An independent data monitoring committee oversaw the trial safety and provided recommendations for the conduct of the trial on the basis of the interim analysis. The first three authors and the second-to-last author wrote the first draft of the manuscript. The sponsor was involved in the manuscript writing and the decision to submit the manuscript for publication. All the authors participated in writ-

ing the manuscript, approved the final version before submission for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL DESIGN AND TREATMENTS

In this phase 3, multicenter, open-label trial, eligible patients were randomly assigned in a 1:1 ratio to receive either disitamab vedotin plus toripalimab or chemotherapy (gemcitabine plus either cisplatin or carboplatin). Randomization was performed with the use of block randomization, with stratification according to eligibility for cisplatin treatment (eligible or ineligible), visceral metastases (present or absent), and HER2 expression (IHC score of 1+ or IHC score of 2+ or 3+). Enrollment of patients with an IHC score of 1+ was limited to up to 33% of the trial population. Patients assigned to the disitamab vedotin–toripalimab group received disitamab vedotin at a dose of 2.0 mg per kilogram of body weight and toripalimab at a dose of 3 mg per kilogram once every 2 weeks. Patients assigned to the chemotherapy group received gemcitabine at a dose of 1000 mg per square meter of body-surface area on days 1 and 8 of each 3-week cycle plus either cisplatin at a dose of 70 mg per square meter or carboplatin at a dose equivalent to an area under the concentration–time curve of 4.5 mg per milliliter per minute (as calculated with the use of the Calvert formula) intravenously on day 1 of each 3-week cycle. Split doses of cisplatin (administered on days 1 and 2 or on days 1, 2, and 3) were allowed according to clinical practice. Investigators assessed whether patients were eligible for cisplatin treatment according to Galsky criteria (a glomerular filtration rate of <60 ml per minute, grade ≥2 hearing loss, grade ≥2 peripheral neuropathy, an Eastern Cooperative Oncology Group performance-status score of ≥2 [scores range from 0 to 5, with higher scores indicating greater disability], or New York Heart Association class >II heart failure at enrollment).[16] Patients were monitored closely for adherence to the protocol-specified chemotherapy regimen.

Trial treatment was given until the occurrence of radiologically confirmed disease progression, unacceptable toxic effects, withdrawal of consent, other protocol-specified conditions, or completion of the maximum number of treatment cycles (6 cycles in the chemotherapy group and no set maximum number of cycles in the disitamab vedotin–toripalimab group), whichever occurred first. Patients who discontinued either disitamab vedotin or toripalimab were permitted to continue the other agent. Patients in the chemotherapy group were not allowed to cross over to receive disitamab vedotin plus toripalimab.

END POINTS AND ASSESSMENTS

The dual primary end points were progression-free survival (assessed by blinded independent review according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) and overall survival. Secondary end points were progression-free survival (assessed by the investigators), objective response (defined as the percentage of patients with a complete or partial response as assessed by both blinded independent review and the investigators), disease control (defined as the percentage of patients with a complete response, a partial response, or stable disease as assessed by both blinded independent review and the investigators), response duration (assessed by both blinded independent review and the investigators), and safety. Additional secondary end points including quality of life and pharmacokinetic and immunogenic characteristics were analyzed but are not reported here.

Tumors were assessed by both blinded independent review and the investigators (according to RECIST, version 1.1) with the use of computed tomography or magnetic resonance imaging at baseline and every 8 weeks until the occurrence of disease progression, death, withdrawal of informed consent, or trial termination, whichever occurred first. For each patient, the imaging modality used at baseline was used throughout the trial. Safety was continually monitored during the trial. The severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events, version 5.0.

STATISTICAL ANALYSIS

The sample size was determined with the aim of detecting superiority in either overall survival or progression-free survival. We assumed a median overall survival of 13.4 months and a median progression-free survival of 6.3 months[17] in the chemotherapy group and assumed a hazard ratio (disitimab vedotin plus toripalimab vs. chemotherapy) of 0.71 for overall survival and 0.68 for progression-free survival. The two-sided overall

alpha level was 0.05, which was split between progression-free survival (alpha level of 0.02) and overall survival (alpha level of 0.03) with the use of the Bonferroni method. Thus, to provide at least 80% power to detect superiority at an alpha level of 0.03 for overall survival and 0.02 for progression-free survival, we calculated that 452 patients were required to obtain 318 events for the analysis of overall survival and 278 events for the analysis of progression-free survival, considering an annual dropout rate of approximately 10% for both overall survival and progression-free survival.

One analysis of progression-free survival and two analyses of overall survival were planned. The interim analysis of overall survival was planned to be performed at the time of the analysis of progression-free survival, with approximately 183 of 318 targeted events for the analysis of overall survival (an overall survival information fraction of 57.5%). If the analysis of progression-free survival showed significance, the alpha level of 0.02 would be passed to overall survival. Similarly, if the interim analysis of overall survival showed significance, the alpha level of 0.03 would be passed to progression-free survival. More details are provided in the Supplementary Appendix (available at NEJM.org) and the statistical analysis plan (available with the protocol).

We performed the interim analysis at the data-cutoff date (March 31, 2025), after 275 blinded independent review–assessed events in the analysis of progression-free survival and 198 events in the analysis of overall survival had occurred (i.e., actual overall survival information fraction of 62%). The independent data monitoring committee confirmed that the results at the interim analysis of the dual primary end points were significant and that the superiority boundaries had been crossed (two-sided alpha level of 0.05 for progression-free survival and of 0.009 for overall survival; the latter was allocated with the use of the Lan–DeMets spending function).

The efficacy analyses included all the patients who underwent randomization, whether they received the assigned treatment or not (the intention-to-treat population). Progression-free survival and overall survival were compared between the groups with a stratified log-rank test (with stratification according to randomization stratification factors). The median progression-free survival and median overall survival were estimated with the Kaplan–Meier method. The hazard ratio was calculated with a stratified Cox proportional-hazards model. The percentage of patients with a response in each group was provided with the corresponding 95% Clopper–Pearson confidence interval. Among patients with an objective response, the duration of response was estimated with the Kaplan–Meier approach. All subgroup analyses were prespecified. The safety analyses included the patients who received any dose of the trial treatment and were performed with the use of descriptive statistics.

RESULTS

PATIENTS AND TREATMENT SUMMARY

Among the 811 patients who were screened, 765 had available HER2 test results, of whom 632 (82.6%) had a HER2 IHC score of 1+ or higher. A total of 484 patients underwent randomization to the disitamab vedotin–toripalimab group (243 patients) or the chemotherapy group (241 patients) (Fig. S1 in the Supplementary Appendix) at 72 sites in China. As of the data-cutoff date, the median follow-up time for overall survival was 18.2 months (95% confidence interval [CI], 16.6 to 19.3). A total of 148 patients with HER2 expression did not undergo randomization because they did not meet other inclusion criteria or met exclusion criteria unrelated to HER2 (137 patients), withdrew consent (7 patients), or had other reasons (4 patients).

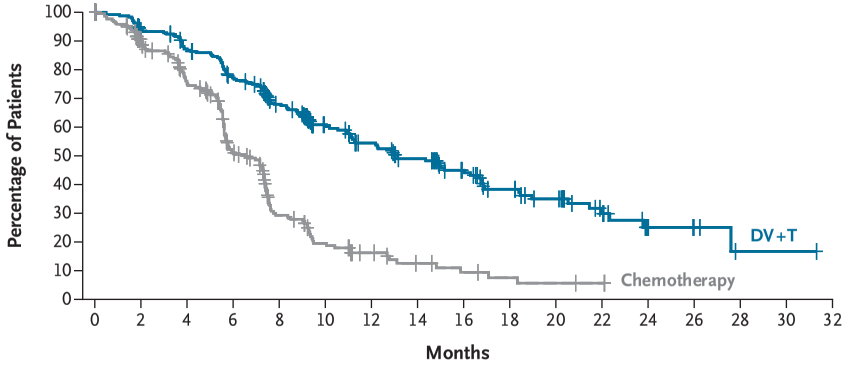
The baseline characteristics of the patients were generally balanced in the two groups (Table 1) and were representative of the overall Chinese population of patients with locally advanced or metastatic urothelial cancer (Table S1). Therefore, White and Black patients were underrepresented. The median age was 66.0 years (range, 39 to 84) in the disitamab vedotin–toripalimab group and 67.0 years (range, 33 to 85) in the chemotherapy group. The majority of the patients were men (72.4% in the disitamab vedotin–toripalimab group and 69.7% in the chemotherapy group) and had a HER2 IHC score of 2+ or 3+ (77.4% in the disitamab vedotin–toripalimab group and 78.0% in the chemotherapy group). The primary site of tumor origin was the upper urinary tract in 45.7% of the patients in the disitamab vedotin–toripalimab group and 50.6% of those in the chemotherapy group.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Disitamab Vedotin –Toripalimab (N=243)	Chemotherapy (N=241)
Median age (range) — yr	66.0 (39–84)	67.0 (33–85)
Age ≥65 yr — no. (%)	137 (56.4)	147 (61.0)
Sex — no. (%)†		
Male	176 (72.4)	168 (69.7)
Female	67 (27.6)	73 (30.3)
Asian race — no. (%)†	243 (100)	241 (100)
ECOG performance-status score — no. (%)‡		
0	61 (25.1)	65 (27.0)
1	182 (74.9)	176 (73.0)
Clinical stage of urothelial cancer — no. (%)		
III	10 (4.1)	8 (3.3)
IV	233 (95.9)	233 (96.7)
Primary site of origin of urothelial cancer — no. (%)		
Upper urinary tract	111 (45.7)	122 (50.6)
Lower urinary tract	130 (53.5)	119 (49.4)
Other	2 (0.8)	0
Visceral metastases — no. (%)		
Absent	119 (49.0)	115 (47.7)
Present	124 (51.0)	126 (52.3)
Lung	87 (35.8)	82 (34.0)
Liver	48 (19.8)	46 (19.1)
HER2 expression no. — (%)§		
IHC score 1+	55 (22.6)	53 (22.0)
IHC score 2+ or 3+	188 (77.4)	188 (78.0)
IHC score 2+	127 (52.3)	142 (58.9)
IHC score 3+	61 (25.1)	46 (19.1)
Cisplatin eligibility status — no. (%)		
Eligible	127 (52.3)	128 (53.1)
Ineligible	116 (47.7)	113 (46.9)
PD-L1 expression — no./total no. (%)¶		
Combined positive score <1	68/125 (54.4)	24/57 (42.1)
Combined positive score ≥1	57/125(45.6)	33/57 (57.9)

* Percentages may not total 100 because of rounding.
† Sex and race were reported by the patient.
‡ Patients with a baseline Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 were eligible for the trial. Scores range from 0 to 5, with higher scores indicating greater disability.
§ Human epidermal growth factor receptor 2 (HER2) expression was assessed by immunohistochemical (IHC) analysis at a central laboratory. IHC scores range from 0 to 3+, with higher scores indicating higher expression.
¶ Programmed death ligand 1 (PD-L1) expression was assessed with the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). The combined positive score was defined as the total number of cells staining positive for PD-L1 divided by the total number of viable tumor cells, multiplied by 100. The PD-L1 test was included beginning with protocol version 4.0; a total of 182 patients provided samples for the PD-L1 expression test.

A Progression-free Survival



No. at Risk																
DV+T	243	220	201	174	141	98	81	68	51	37	29	16	7	4	1	1	0
Chemotherapy	241	181	143	86	42	25	15	9	6	4	3	2	0				

	No. of Events	Median Progression-free Survival (95% CI)
		mo
DV+T	126	13.1 (11.1–16.7)
Chemotherapy	149	6.5 (5.7–7.4)

Hazard ratio for disease progression or death, 0.36 (95% CI, 0.28–0.46)
P<0.001 by log-rank test

B Subgroup Analysis of Progression-free Survival

Subgroup	Total No. of Patients	No. of Patients		No. of Events		Median Progression-free Survival		Hazard Ratio for Disease Progression or Death (95% CI)
		DV+T	Chemotherapy	DV+T	Chemotherapy	DV+T	Chemotherapy	
						mo		
Overall	484	243	241	126	149	13.1	6.5	0.36 (0.28–0.46)
Eligibility for cisplatin treatment								
Yes	255	127	128	70	76	12.3	7.4	0.42 (0.30–0.59)
No	229	116	113	56	73	16.3	5.6	0.30 (0.21–0.44)
Visceral metastasis								
Yes	250	124	126	72	87	11.2	5.6	0.32 (0.23–0.45)
No	234	119	115	54	62	16.0	7.5	0.41 (0.28–0.61)
HER2 status								
IHC score 1+	108	55	53	33	31	12.3	6.5	0.42 (0.24–0.72)
IHC score 2+ or 3+	376	188	188	93	118	13.1	6.7	0.34 (0.26–0.46)
Age								
<65 yr	200	106	94	55	57	12.9	7.4	0.41 (0.27–0.62)
≥65 yr	284	137	147	71	92	14.4	5.9	0.30 (0.21–0.43)
Sex								
Male	344	176	168	92	102	13.0	7.2	0.38 (0.28–0.51)
Female	140	67	73	34	47	15.0	5.7	0.33 (0.20–0.54)
ECOG performance-status score								
0	126	61	65	28	35	14.9	7.3	0.33 (0.18–0.59)
1	358	182	176	98	114	13.0	5.9	0.38 (0.28–0.50)
Site of primary lesion								
Upper urinary tract	233	111	122	60	74	13.1	5.9	0.36 (0.25–0.53)
Lower urinary tract	249	130	119	65	75	13.0	7.2	0.37 (0.26–0.53)
PD-L1 status (CPS score)								
<1	92	68	24	32	15	15.2	7.5	0.21 (0.10–0.47)
≥1	90	57	33	24	23	16.9	6.1	0.19 (0.09–0.40)

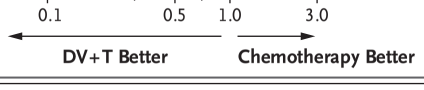


Figure 1 (facing page). Analysis of Progression-free Survival as Assessed by Blinded Independent Review.
Panel A shows the Kaplan–Meier curves of progression-free survival in the intention-to-treat population (all patients who underwent randomization). Tick marks denote censored data. Panel B shows a forest plot of the analyses of progression-free survival in all prespecified subgroups. Progression-free survival was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1. Immunohistochemical (IHC) scores range from 0 to 3+, with higher scores indicating higher expression. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. The combined positive score (CPS) was defined as the total number of cells staining positive for programmed death ligand 1 (PD-L1) divided by the total number of viable tumor cells, multiplied by 100. DV+T denotes disitimab vedotin plus toripalimab, and HER2 human epidermal growth factor receptor 2.

As of the data-cutoff date, 37.4% (91 of 243) of the patients in the disitamab vedotin–toripalimab group and none of the patients in the chemotherapy group were still receiving treatment. The median duration of treatment was 34.1 weeks (range, 2.0 to 143.6) with disitamab vedotin (median number of treatment cycles, 14; range, 1 to 66) and 35.0 weeks (range, 2.0 to 122.7) with toripalimab (median number of treatment cycles, 14; range, 1 to 54). In the chemotherapy group, 222 patients received the assigned treatment: 118 patients received cisplatin (41 received a split-dose regimen), and 104 patients who were ineligible for cisplatin received carboplatin. The median duration of treatment was 18.3 weeks (range, 3.0 to 35.0) with cisplatin (median number of treatment cycles, 6; range, 1 to 6), 18.4 weeks (range, 1.7 to 27.1) with carboplatin (median number of treatment cycles, 5; range, 1 to 6), and 19.4 weeks (range, 1.7 to 45.6) with gemcitabine (median number of treatment cycles, 6; range, 1 to 6) (Table S3).

DUAL PRIMARY END POINTS

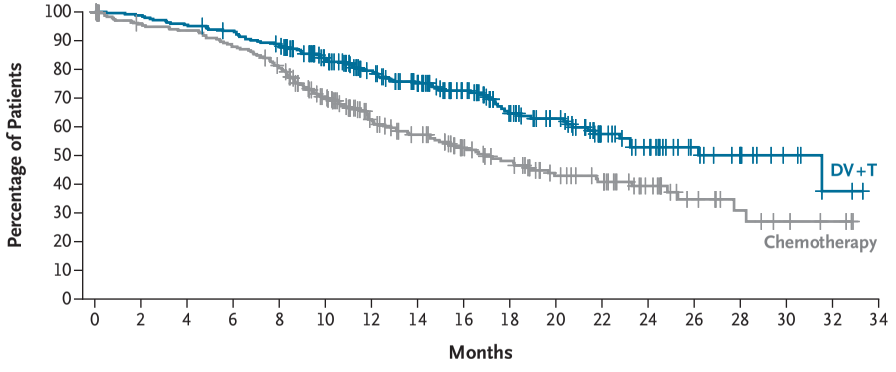
Progression-free survival was significantly longer in the disitamab vedotin–toripalimab group than the chemotherapy group (median progression-free survival, 13.1 months [95% CI, 11.1 to 16.7] vs. 6.5 months [95% CI, 5.7 to 7.4]; stratified hazard ratio for disease progression or death, 0.36 [95% CI, 0.28 to 0.46]; two-sided P<0.001), as assessed by blinded independent review (Fig. 1A). The estimated 12-month progression-free survival was 54.5% (95% CI, 47.3 to 61.1) in the disitamab vedotin–toripalimab group and 16.2% (95% CI, 10.7 to 22.8) in the chemotherapy group. The progression-free survival benefits appeared generally consistent across all the prespecified subgroups, including visceral metastases status, cisplatin eligibility status, and level of programmed death ligand 1 (PD-L1) expression (Fig. 1B and Fig. S2).

As of the data-cutoff date, treatment with disitamab vedotin plus toripalimab led to significantly longer overall survival than treatment with chemotherapy (median overall survival, 31.5 months [95% CI, 21.7 to not estimated] vs. 16.9 months [95% CI, 14.6 to 21.7]; stratified hazard ratio for death, 0.54 [95% CI, 0.41 to 0.73]; two-sided P<0.001) (Fig. 2A). The estimated 12-month overall survival was 79.5% (95% CI, 73.6 to 84.2) with disitamab vedotin plus toripalimab and 62.5% (95% CI, 55.6 to 68.6) with chemotherapy. The overall survival benefits across all prespecified subgroups are shown in Figure 2B and Figure S3, and the prespecified supplementary analysis for overall survival with different censoring rules is shown in Table S4 (hazard ratios range from 0.39 [95% CI, 0.28 to 0.55] to 0.55 [95% CI, 0.41 to 0.73]).

SECONDARY END POINTS

The investigator-assessed progression-free survival benefit with disitamab vedotin plus toripalimab was consistent with the blinded independent review–assessed results (Fig. S4). In the disitamab vedotin–toripalimab group, an objective response as assessed by blinded independent review occurred in 185 patients (76.1% [95% CI, 70.3 to 81.3]) — 11 had a complete response, and 174 had a partial response. In the chemotherapy group, an objective response as assessed by blinded independent review occurred in 121 patients (50.2% [95% CI, 43.7 to 56.7]) — 3 had a complete response, and 118 had a partial response. Consistent tumor responses were observed across all the prespecified subgroups (Fig. S5). The median duration of response was 14.6 months (95% CI, 11.3 to 18.7) in the disitamab vedotin–toripalimab group and 5.6 months (95% CI, 5.3 to 5.8) in the chemotherapy group. Investigator-assessed tumor responses were consistent with the blinded independent review results (Table 2).

A Overall Survival



	No. of Events	Median Overall Survival (95% CI)
		mo
DV+T	81	31.5 (21.7–NE)
Chemotherapy	117	16.9 (14.6–21.7)

Hazard ratio for death, 0.54
(95% CI, 0.41–0.73)
P<0.001 by log-rank test

No. at Risk																		
DV+T	243	240	232	225	213	176	149	127	102	78	64	41	31	19	12	6	2	0
Chemotherapy	241	220	215	202	183	148	109	93	73	61	45	38	24	13	8	5	3	0

B Subgroup Analysis of Overall Survival

Subgroup	Total No. of Patients	No. of Patients		No. of Events		Median Overall Survival		Hazard Ratio for Death (95% CI)
		DV+T	Chemotherapy	DV+T	Chemotherapy	DV+T	Chemotherapy	
						mo		
Overall	484	243	241	81	117	31.5	16.9	0.54 (0.41–0.73)
Eligibility for cisplatin treatment								
Yes	255	127	128	42	59	26.2	18.9	0.55 (0.37–0.82)
No	229	116	113	39	58	NE	15.3	0.54 (0.36–0.81)
Visceral metastasis								
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No	234	119	115	30	41	NE	21.8	0.69 (0.43–1.10)
HER2 status								
IHC score 1+	108	55	53	21	31	26.2	16.1	0.55 (0.31–0.97)
IHC score 2+ or 3+	376	188	188	60	86	31.5	18.2	0.54 (0.39–0.76)
Age								
<65 yr	200	106	94	29	42	31.5	18.2	0.47 (0.28–0.76)
≥65 yr	284	137	147	52	75	23.2	16.5	0.62 (0.43–0.89)
Sex								
Male	344	176	168	61	83	31.5	16.1	0.53 (0.38–0.75)
Female	140	67	73	20	34	23.2	18.2	0.63 (0.36–1.12)
ECOG performance-status score								
0	126	61	65	12	23	NE	27.7	0.41 (0.19–0.87)
1	358	182	176	69	94	23.2	15.3	0.58 (0.42–0.79)
Site of primary lesion								
Upper urinary tract	233	111	122	37	58	31.5	16.9	0.53 (0.34–0.81)
Lower urinary tract	249	130	119	44	59	23.2	16.5	0.55 (0.37–0.82)
PD-L1 status (CPS score)								
<1	92	68	24	14	6	NE	28.3	0.43 (0.13–1.48)
≥1	90	57	33	9	14	NE	16.1	0.39 (0.16–0.97)

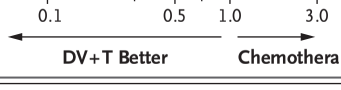

Figure 2 (facing page). Analysis of Overall Survival.
Panel A shows the Kaplan–Meier curves of overall survival in the intention-to-treat population. This interim analysis of overall survival was considered the final analysis because it reached the significance boundary. Panel B shows a forest plot of the analyses of overall survival in all prespecified subgroups. NE denotes not estimated.

SUBSEQUENT ANTICANCER TREATMENT

Fewer patients received subsequent anticancer therapies in the disitamab vedotin–toripalimab group (77 patients [31.7%]) than in the chemotherapy group (162 patients [67.2%]). Among the 243 patients in the disitamab vedotin–toripalimab group, 66 (27.2%) received subsequent systemic therapies, including pyrimidine analogues (50 patients [20.6%]), platinum-based agents (49 patients [20.2%]), and PD-1 or PD-L1 inhibitors (26 patients [10.7%]). In contrast, 156 of the 241 patients (64.7%) in the chemotherapy group received subsequent systemic therapies, most commonly PD-1 or PD-L1 inhibitors (121 patients [50.2%]) and anti-HER2 inhibitors (97 patients [40.2%]). Of the 241 patients in the chemotherapy group, 91 (37.8%) subsequently received disitamab vedotin–containing therapies and 72 (29.9%) received both disitamab vedotin and PD-1 or PD-L1 inhibitors (Table S5).

SAFETY

Treatment-related adverse events of any grade, as assessed by the investigator, occurred in 240 of the 243 patients (98.8%) in the disitamab vedotin–toripalimab group who received any dose of the trial treatment and in all 222 patients (100%) in the chemotherapy group who received any dose of the trial treatment (Table 3 and Table S6). The most frequent treatment-related adverse events of any grade across both groups were increased levels of aspartate aminotransferases (in 54.3% of the patients receiving disitamab vedotin plus toripalimab and in 22.1% of those receiving chemotherapy) and alanine aminotransferases (47.3% and 24.8%, respectively), anemia (46.9% and 90.1%), alopecia (40.7% and 10.4%), decreased appetite (30.9% and 40.1%), nausea (28.4% and 58.6%), decreased neutrophil count (22.2% and 85.1%), decreased white-cell count (21.4% and 86.9%), vomiting (20.2% and 43.2%), and decreased platelet count (9.9% and 77.5%). Treatment-related adverse events of grade 3 or higher occurred in 134 patients (55.1%) receiving disitamab vedotin plus toripalimab and in 193 patients (86.9%) receiving chemotherapy. The most frequent treatment-related adverse events of grade 3 or higher were increased gamma-glutamyltransferase (7.4%), hypokalemia (5.8%), and decreased neutrophil count (5.8%) among the patients receiving disitamab vedotin plus toripalimab and decreased neutrophil count (61.7%), decreased white-cell count (47.7%), decreased platelet count (45.9%), and anemia (45.5%) among those receiving chemotherapy. Serious treatment-related adverse events occurred in 28.4% of the patients in the disitamab vedotin–toripalimab group and in 40.5% of those in the chemotherapy group and are summarized in Table S7.

Among the patients in the disitamab vedotin–toripalimab group, hypoesthesia (any grade in 38.7% and grade ≥3 in 5.3%) and peripheral neuropathy (any grade in 21.8% and grade ≥3 in 4.1%) were the most frequently reported peripheral neurotoxic events, which are known toxic effects of disitamab vedotin. Most immune-related adverse events were grade 1 or 2 (Table S8).

Treatment-related adverse events led to discontinuation of any treatment in 12.3% of the patients receiving disitamab vedotin plus toripalimab and in 10.4% of the patients receiving chemotherapy. The most common treatment-related adverse events resulting in discontinuation of disitamab vedotin or toripalimab (or both) were peripheral neuropathy (1.6%) and immune-mediated lung disease (1.6%). The most common treatment-related adverse events leading to discontinuation of chemotherapy were thrombocytopenia (4.1%) and anemia (1.8%) (Table S9). Dose reductions resulting from treatment-related adverse events occurred more frequently with chemotherapy (49.5% of patients) than with disitamab vedotin plus toripalimab (32.5% of patients). Treatment-related adverse events that resulted in death were reported in 3 patients (1.2%) receiving disitamab vedotin plus toripalimab (1 patient had acute respiratory failure, 1 had interstitial lung disease, and 1 had pneumonia) and in 3 patients (1.4%) receiving chemotherapy (1 patient had cardiac arrest and 2 patients had both decreased platelet count and anemia).

Table 2. Summary of Objective Treatment Response.

Variable	Blinded Independent Review Assessment		Investigator Assessment	
	Disitamab Vedotin –Toripalimab (N=243)	Chemotherapy (N=241)	Disitamab Vedotin –Toripalimab (N=243)	Chemotherapy (N=241)
Best overall response — no. (%)				
Complete response	11 (4.5)	3 (1.2)	10 (4.1)	8 (3.3)
Partial response	174 (71.6)	118 (49.0)	164 (67.5)	112 (46.5)
Stable disease	37 (15.2)	66 (27.4)	48 (19.8)	58 (24.1)
Progressive disease	14 (5.8)	16 (6.6)	14 (5.8)	23 (9.5)
Not evaluable	7 (2.9)	38 (15.8)*	7 (2.9)	40 (16.6)*
Objective response†				
Number of patients	185	121	174	120
Percentage of patients (95% CI)	76.1 (70.3–81.3)	50.2 (43.7–56.7)	71.6 (65.5–77.2)	49.8 (43.3–56.3)
Disease control rate				
Number of patients	222	187	222	178
Percentage of patients (95% CI)	91.4 (87.1–94.6)	77.6 (71.8–82.7)	91.4 (87.1–94.6)	73.9 (67.8–79.3)

* Nineteen patients in the chemotherapy group did not receive the assigned treatment after randomization and had no postbaseline tumor assessment.

† The between-group difference was 26.0 percentage points (95% CI, 17.6 to 34.1) in the blinded independent review assessment and 21.9 percentage points (95% CI, 13.3 to 30.2) in the investigator assessment.

DISCUSSION

Previous data indicated that 52 to 69.8% of patients with urothelial cancer have HER2 expression.[2-5] In our trial, 82.6% of the patients who underwent HER2 testing had a HER2 IHC score of 1+ or higher. This difference might be a result of potential selection bias for patients who had undergone testing before screening enrollment and of the growing implementation of routine HER2 testing in Chinese clinical practice.[18]

Among the patients with previously untreated HER2-expressing locally advanced or metastatic urothelial cancer, disitamab vedotin plus toripalimab provided significant benefits regarding progression-free survival and overall survival, as compared with chemotherapy. With respect to combinations of antibody–drug conjugates and PD-1 inhibitors that are transforming the treatment landscape for locally advanced or metastatic urothelial cancer, identifying predictive biomarkers is crucial to determine effective therapies by selecting patients most likely to benefit and guiding treatment sequencing.[8,19-21] Our trial defined a HER2-informed, precise first-line treatment using this combination of therapies.[22]

For patients with HER2-expressing locally advanced or metastatic urothelial cancer, the current first-line treatments include enfortumab vedotin plus pembrolizumab (median progression-free survival, 12.5 months; median overall survival 31.5 months; percentage of patients with a response, 67.7%) and nivolumab in combination with gemcitabine and cisplatin (median progression-free survival, 7.9 months; median overall survival, 21.7 months; percentage of patients with a response, 57.6%) on the basis of the EV-302 and CheckMate 901 trials, respectively.[10,23] In this context, disitamab vedotin plus toripalimab emerges as an alternative treatment option (median progression-free survival, 13.1 months; median overall survival, 31.5 months; percentage of patients with a response, 76.1%), with a lower risk of disease progression or death than chemotherapy. The Kaplan–Meier curves for both progression-free survival and overall survival had separated early at the first assessment and maintained higher survival percentages in the disitamab vedotin–toripalimab group than in the chemotherapy group at all subsequent time points. These efficacy benefits across all the prespecified subgroups, including cisplatin eligibility status and levels of HER2 expression, were consistent with the benefits in the intention-to-treat population. Disita-

Table 3. Treatment-Related Adverse Events in the Safety Population.*

Event	Disitamab Vedotin–Toripalimab (N=243)		Chemotherapy (N=222)†	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Any treatment-related adverse event	240 (98.8)	134 (55.1)	222 (100)	193 (86.9)
Aspartate aminotransferase level increased	132 (54.3)	12 (4.9)	49 (22.1)	2 (0.9)
Alanine aminotransferase level increased	115 (47.3)	9 (3.7)	55 (24.8)	3 (1.4)
Anemia	114 (46.9)	13 (5.3)	200 (90.1)	101 (45.5)
Alopecia	99 (40.7)	0	23 (10.4)	0
Hypoesthesia	94 (38.7)	13 (5.3)	5 (2.3)	0
Asthenia	92 (37.9)	10 (4.1)	82 (36.9)	7 (3.2)
Weight decreased	83 (34.2)	2 (0.8)	44 (19.8)	0
Hypertriglyceridemia	78 (32.1)	12 (4.9)	21 (9.5)	1 (0.5)
Decreased appetite	75 (30.9)	4 (1.6)	89 (40.1)	2 (0.9)
Nausea	69 (28.4)	1 (0.4)	130 (58.6)	1 (0.5)
Pruritus	60 (24.7)	3 (1.2)	15 (6.8)	0
Hypoalbuminemia	56 (23.0)	0	25 (11.3)	0
γ-Glutamyltransferase level increased	54 (22.2)	18 (7.4)	23 (10.4)	4 (1.8)
Neutrophil count decreased	54 (22.2)	14 (5.8)	189 (85.1)	137 (61.7)
Rash	54 (22.2)	2 (0.8)	23 (10.4)	1 (0.5)
Peripheral neuropathy	53 (21.8)	10 (4.1)	0	0
White-cell count decreased	52 (21.4)	9 (3.7)	193 (86.9)	106 (47.7)
Hyponatremia	51 (21.0)	10 (4.1)	37 (16.7)	4 (1.8)
Vomiting	49 (20.2)	7 (2.9)	96 (43.2)	1 (0.5)
Blood creatinine level increased	49 (20.2)	1 (0.4)	54 (24.3)	0
Lipase increased	45 (18.5)	13 (5.3)	9 (4.1)	1 (0.5)
Lymphocyte count decreased	35 (14.4)	12 (4.9)	63 (28.4)	26 (11.7)
Hypokalemia	34 (14.0)	14 (5.8)	19 (8.6)	2 (0.9)
Platelet count decreased	24 (9.9)	2 (0.8)	172 (77.5)	102 (45.9)

* The safety population included all patients who received any dose of the trial treatment. Treatment-related adverse events were related to any trial treatment as assessed by the investigator. Treatment-related adverse events of any grade that occurred in at least 20% of the patients in either group and those of grade 3 or higher that occurred in at least 5% of the patients in either group are shown.
† Nineteen patients in the chemotherapy group did not receive the assigned treatment after randomization and were excluded from the safety population.

mab vedotin plus toripalimab is a new treatment option for patients with HER2-expressing urothelial cancer, particularly those at risk of severe skin toxic effects from enfortumab vedotin. However, cross-trial comparison is challenging owing to differences in trial populations and designs, and the definitive superiority of any regimen cannot yet be established.

Previous trials of disitamab vedotin monotherapy for urothelial cancer showed a correlation between clinical efficacy and HER2 expression levels, with a response occurring in 50.5% of patients with a HER2 IHC score of 2+ or 3+, 46.2% of those with a HER2 IHC score of 1+, and 0% of those with a HER2 IHC score of 0.[8,24] Similarly, the early-phase RC48-C014 trial evaluating disitamab vedotin plus toripalimab in patients with HER2-expressing or HER2-negative disease further supported the association between higher HER2 expression and improved efficacy, with a

response occurring in 76.3% and 33.3% of patients with a HER2 IHC score of 1+ and 0, respectively.[14] The results of the HER2 subgroup analysis in our trial were consistent with the previous findings, supporting disitamab vedotin plus toripalimab as a valuable treatment in a biomarker-selected population.

The safety profile of disitamab vedotin plus toripalimab was consistent with the historical data of disitamab vedotin alone and toripalimab alone and with a previous phase 1b–2 study evaluating the drug combination in locally advanced or metastatic urothelial cancer.[14] The disitamab vedotin–toripalimab group had a higher incidence of aminotransferase elevation and peripheral neurotoxic effects (mostly grade 1 or 2) than the chemotherapy group. These events are well-characterized adverse effects of disitamab vedotin with established guidelines for effective clinical management. The incidence of peripheral neurotoxic events observed with disitamab vedotin plus toripalimab was similar to that of disitamab vedotin alone, with fewer grade 3 or higher events observed with the drug combination than with disitamab vedotin as monotherapy.[8] Disitamab vedotin plus toripalimab resulted in fewer grade 3 or higher adverse events than chemotherapy, particularly hematologic toxic effects including anemia (any grade, 46.9% vs. 90.1%; grade ≥3, 5.3% vs. 45.5%), decreased neutrophil count (any grade, 22.2% vs. 85.1%; grade ≥3, 5.8% vs. 61.7%), decreased white-cell count (any grade, 21.4% vs. 86.9%; grade ≥3, 3.7% vs. 47.7%), and decreased platelet count (any grade, 9.9% vs. 77.5%; grade ≥3, 0.8% vs. 45.9%). Other frequent adverse events were similar in the groups and were mostly grade 1 or 2, including metabolic and gastrointestinal toxic effects.

This trial had some limitations beyond its modest sample size. First, as a multicenter trial conducted solely in China, the generalizability of the findings to other populations remains uncertain. Second, the percentages of patients who had a complete response in the disitamab vedotin–toripalimab group and in the chemotherapy group were lower than those reported in contemporary trials, although cross-trial comparisons require cautious interpretation.[10,23,25] The phase 2 data of disitamab vedotin plus pembrolizumab in untreated HER2-expressing locally advanced or metastatic urothelial cancer showed a higher complete response of 35%.[13] The ongoing, international, phase 3 SGNDV-001 trial (ClinicalTrials.gov number, NCT05911295) investigating disitamab vedotin plus pembrolizumab may help address the above concerns. Third, maintenance therapy with avelumab was unavailable during the trial because it has not been approved in China. However, real-world data showed that only 20 to 40% of patients treated with platinum-based agents subsequently received maintenance therapy with avelumab,[26-28] whereas clinical trials showed even lower percentages (30.4% in the EV-302 trial and 10.5% in the CheckMate 901 trial).[10,23]

Our trial showed significantly greater progression-free survival and overall survival with disitamab vedotin plus toripalimab than with chemotherapy in patients with untreated HER2-expressing locally advanced or metastatic urothelial cancer.

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