Tisotumab Vedotin in Combination With Carboplatin, Pembrolizumab, or Bevacizumab in Recurrent or Metastatic Cervical Cancer: Results From the innovaTV 205/GOG-3024/ENGOT-cx8 Study

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ABSTRACT

PURPOSE Tissue factor is highly expressed in cervical carcinoma and can be targeted by tisotumab vedotin (TV), an antibody-drug conjugate. This phase Ib/II study evaluated TV in combination with bevacizumab, pembrolizumab, or carboplatin for recurrent or metastatic cervical cancer (r/mCC).

METHODS This open-label, multicenter study (ClinicalTrials.gov identifier: NCT03786081) included dose-escalation arms that assessed dose-limiting toxicities (DLTs) and identified the recommended phase II dose (RP2D) of TV in combination with bevacizumab (arm A), pembrolizumab (arm B), or carboplatin (arm C). The dose-expansion arms evaluated TV antitumor activity and safety at RP2D in combination with carboplatin as first-line (1L) treatment (arm D) or with pembrolizumab as 1L (arm E) or second-/third-line (2L/3L) treatment (arm F). The primary end point of dose expansion was objective response rate (ORR).

RESULTS A total of 142 patients were enrolled. In dose escalation (n = 41), no DLTs were observed; the RP2D was TV 2 mg/kg plus bevacizumab 15 mg/kg on day 1 once every 3 weeks, pembrolizumab 200 mg on day 1 once every 3 weeks, or carboplatin AUC 5 on day 1 once every 3 weeks. In dose expansion (n = 101), the ORR was 54.5% (n/N, 18/33; 95% CI, 36.4 to 71.9) with 1L TV + carboplatin (arm D), 40.6% (n/N, 13/32; 95% CI, 23.7 to 59.4) with 1L TV + pembrolizumab (arm E), and 35.3% (12/34; 19.7 to 53.5) with 2L/3L TV + pembrolizumab (arm F). The median duration of response was 8.6 months, not reached, and 14.1 months, in arms D, E, and F, respectively. Grade ≥3 adverse events (≥15%) were anemia, diarrhea, nausea, and thrombocytopenia in arm D and anemia in arm F (none ≥15%, arm E).

CONCLUSION TV in combination with bevacizumab, carboplatin, or pembrolizumab demonstrated manageable safety and encouraging antitumor activity in treatment-naive and previously treated r/mCC.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Despite implementation of human papilloma virus vaccination and screening practices, some patients develop recurrent or metastatic cervical cancer (r/mCC), which is incurable.[1-3] Chemotherapy doublets + bevacizumab were standard of care (SOC) for first-line (1L) treatment of eligible patients with r/mCC on the basis of results of the phase III GOG 240 trial.[4,5] Current 1L SOC for patients with PD-L1–positive r/mCC is based on results of the KEYNOTE-826 study, which showed that the addition of pembrolizumab to a chemotherapy doublet with or without bevacizumab resulted in a superior overall survival (OS) benefit over the GOG240 regimen.[4,6,7] However, additional 1L treatment options are needed for patients with r/mCC. Furthermore, limited OS after disease progression on 1L regimens[8-10] marks the unmet need for new and effective treatment options in the second-line setting and beyond.

Tissue factor (TF) is expressed in many solid tumors, including cervical cancer.[11] Tisotumab vedotin (TV) is a

CONTEXT

Key Objective

Can treatment with tisotumab vedotin (TV) be safely and effectively combined with other anticancer therapies in cervical cancer, such as bevacizumab, carboplatin, or pembrolizumab, to improve treatment outcomes in patients with advanced cervical cancer?

Knowledge Generated

Combination treatment with TV + bevacizumab, or carboplatin, or pembrolizumab showed acceptable safety profiles and promising efficacy in pretreated patients during the dose escalation, supporting further evaluation of the selected recommended phase II dose in combination with current treatments (carboplatin or pembrolizumab) in earlier lines of treatment in the dose-expansion arms. First-line (1L) treatment with TV in combination with carboplatin and 1L or second-/third-line treatment with TV + pembrolizumab demonstrated encouraging and durable antitumor activity with tolerable and manageable safety profiles.

Relevance *(G.F. Fleming)*

While single-agent therapy with the antibody-drug conjugate TV is currently approved for pretreated recurrent or metastatic cervical cancer, these results lay the groundwork for future randomized explorations of combinations using this agent, potentially in an earlier line of therapy.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD.

TF-directed antibody-drug conjugate with a proposed multimodal mechanism of action that includes direct cytotoxicity, bystander effects, antibody-dependent cellular cytotoxicity and phagocytosis, and induction of immunogenic cell death.[12,13] TV monotherapy is approved in the United States for the treatment of adults with r/mCC who had disease progression on or after chemotherapy, on the basis of the clinically meaningful objective response rate (ORR) and duration of response (DOR) in the pivotal innovaTV 204/GOG-3023/ENGOT-cx6 study.[14,15] Combining TV with chemotherapy, bevacizumab, and/or immunotherapies could allow for enhanced antitumor effects. Here, we present results from the proof-of-concept arms of the innovaTV 205/GOG-3024/ENGOT-cx8 study, evaluating the safety and antitumor activity of TV in combination with bevacizumab, pembrolizumab, or carboplatin in patients with r/mCC.

METHODS

Study Design

innovaTV 205/GOG-3024/ENGOT-cx8 (ClinicalTrials.gov identifier: NCT03786081) is an open-label, multicenter phase Ib/II study in patients with recurrent or stage IVB cervical cancer. The study was performed according to ENGOT-GOG model C.[16] The objectives of the dose-escalation arms were to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of TV when combined with bevacizumab (arm A), pembrolizumab (arm B), or carboplatin (arm C; Data Supplement, Fig S1, online only). The dose-expansion arms included TV-doublet combinations, with either carboplatin in the 1L setting (arm D) or pembrolizumab in the 1L (arm E) or second-line/third-line (2L/3L) settings (arm F; Data Supplement, Fig S1).

The study was approved by an independent ethics committee/institutional review boards at each site and was conducted in accordance with good clinical practice and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Patients

Adults (18 years and older) with recurrent or stage IVB squamous carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix and measurable disease at baseline per RECIST v1.1 were enrolled.[17] Patients eligible for dose-escalation arms A-C had disease progression on or after, or were ineligible or intolerant to, SOC treatments (ie, ≥2L). Patients enrolled in dose-expansion arms D (1L TV + carboplatin) and E (1L TV + pembrolizumab) had not received previous systemic therapy for r/mCC. Patients in arm F (2L/3L TV + pembrolizumab) had disease progression during or after one or two previous lines of systemic therapy in the r/mCC setting. Previous treatment with anti–PD-1 or anti–PD-L1 therapy was not permitted for patients enrolled in arms B, E, and F. Key exclusion criteria were risk of clinically significant bleeding issues and active ocular surface disease. Full eligibility criteria are listed in the Data Supplement (Table S1). Patients were enrolled regardless of PD-L1 status or TF expression.

Treatments

Patients received treatment intravenously once every 3 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. Dose-escalation methods are given in detail in the Data Supplement. The MTD was defined as the dose below the lowest dose level that induced dose-limiting

toxicity (DLT) in at least one third of patients. Each patient received a minimum of two 21-day treatment cycles before the RP2D was defined. Patients in the dose-expansion arms received treatment with the RP2D identified during dose escalation. To prevent ocular adverse events (AEs), all patients received prophylactic eye care (Data Supplement).

End Points

The dose-escalation primary end point was the incidence of DLTs and AEs. The dose-expansion primary end point was investigator-assessed ORR per RECIST v1.1.[17] Secondary end points (dose escalation and dose expansion) included DOR, time to response (TTR), progression-free survival (PFS), OS, and AEs. Additional end points included immunogenicity and TF expression in tumor biopsies.

Assessments

AEs were monitored throughout treatment and at safety follow-up visits 30 days and 90 days after the last dose. Predefined AEs of special interest (AESIs) for TV included ocular, bleeding, and peripheral neuropathy AEs. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v5.0.

Tumor imaging by computed tomography (or contrast-enhanced magnetic resonance imaging when appropriate or indicated) was performed at screening, every 6 weeks for the first 31 weeks of treatment in arms A-C and F, or for the first 37 weeks in arms D-E, and every 12 weeks thereafter in all arms. Objective responses (complete response [CR] or partial response [PR]) were confirmed by repeat imaging assessment, performed ≥4 weeks after first indication of response. Stable disease (SD) criteria are summarized in the Data Supplement. Disease control rate (DCR) was the combined rate of CR or PR lasting ≥4 weeks after first CR/PR and SD lasting ≥5 weeks after the first dose. Clinical benefit rate (CBR) was the combined rate of CR or PR lasting ≥4 weeks after first CR/PR and SD lasting ≥10 weeks, where minimum duration for SD was calculated as the time from the start of treatment to the last SD.

Assessments of TV-directed antidrug antibodies (ADAs) in plasma and TF expression are described in the Data Supplement.

Statistical Analyses

The safety analysis population included all patients who received at least one dose of study treatment. Efficacy analyses were conducted on the full analysis set, which was the same as the safety population but excluded patients with protocol violations (Fig 1). ORRs were estimated with exact Clopper-Pearson two-sided 95% CIs. Time-to-event outcomes (DOR, TTR, PFS, OS) were analyzed using Kaplan-Meier methods. Data were analyzed using SAS software v9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Patients

A total of 142 patients were enrolled, including 41 patients in dose-escalation arms A-C between February 27, 2019, and October 6, 2020 (data cutoff January 25, 2022), and 101 patients in dose-expansion arms D-F from November 29, 2019, to December 15, 2020 (data cutoff June 20, 2022). In the dose-

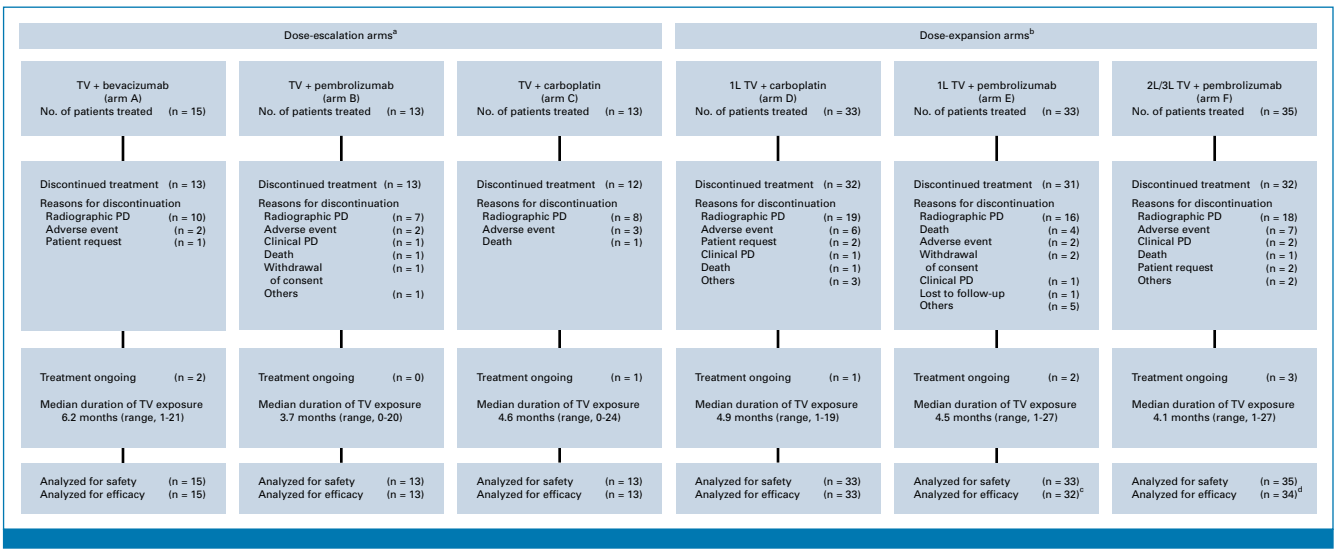

FIG 1. CONSORT diagram. [a]Data cutoff date for the dose-escalation arms was January 25, 2022. [b]Data cutoff date for the dose-expansion arms was June 20, 2022. [c]One patient received brentuximab and was not analyzed for efficacy. [d]One patient did not have measurable disease at baseline and was not analyzed for efficacy. 1L, first-line; 2L, second-line; 3L, third-line; PD, progressive disease; TV, tisotumab vedotin.

TABLE 1. Baseline Characteristics

Characteristic	Dose-Escalation Arms			Dose-Expansion Arms		
	TV + Bevacizumab (arm A; n = 15)	TV + Pembrolizumab (arm B; n = 13)	TV + Carboplatin (arm C; n = 13)	1L TV + Carboplatin (arm D; n = 33)	1L TV + Pembrolizumab (arm E; n = 33)	2L/3L TV + Pembrolizumab (arm F; n = 35)
Age, years, median (range)	46 (30-62)	45 (32-75)	52 (35-65)	51 (25-78)	47 (29-76)	47 (31-73)
Race, No. (%)						
White	11 (73.3)	11 (84.6)	10 (76.9)	25 (75.8)	31 (93.9)	27 (77.1)
Asian	0	0	0	1 (3.0)	2 (6.1)	2 (5.7)
Black or African American	0	0	1 (7.7)	0	0	0
Others or missing	4 (26.7)	2 (15.4)	2 (15.4)	7 (21.2)	0	6 (17.1)
Hispanic or Latino ethnicity, No. (%)	1 (6.7)	0	1 (7.7)	0	1 (3.0)	0
Cancer recurrence at screening, No. (%)	14 (93.3)	13 (100)	11 (84.6)	30 (90.9)	26 (78.8)	31 (88.6)
ECOG PS, No. (%)						
0	13 (86.7)	8 (61.5)	9 (69.2)	21 (63.6)	25 (75.8)	22 (62.9)
1	2 (13.3)	5 (38.5)	4 (30.8)	12 (36.4)	8 (24.2)	13 (37.1)
Histology, No. (%)						
Squamous	8 (53.3)	7 (53.8)	6 (46.2)	24 (72.7)	22 (66.7)	19 (54.3)
Adenocarcinoma	7 (46.7)	6 (46.2)	6 (46.2)	8 (24.2)	11 (33.3)	15 (42.9)
Adenosquamous	0	0	1 (7.7)	1 (3.0)	0	0
Other	0	0	0	0	0	1 (2.9)[a]
PD-L1–positive, No. (%)[b]	NA	NA	NA	NA	28 (96.6)	22 (81.5)
CPS score, median (range)	NA	NA	NA	NA	8.0 (0-100)	5.0 (0-100)
Previous radiotherapy, No. (%)	12 (80.0)	11 (84.6)	11 (84.6)	27 (81.8)	25 (75.8)	30 (85.7)
Previous chemoradiation, No. (%)	10 (66.7)	10 (76.9)	10 (76.9)	23 (69.7)	24 (72.7)	19 (54.3)
Previous lines of systemic treatment, No. (%)						
0	1 (6.7)	0	0	33 (100)	33 (100)	0
1	8 (53.3)	7 (53.8)	7 (53.8)	0	0	25 (71.4)
2	4 (26.7)	2 (15.4)	4 (30.8)	0	0	10 (28.6)
3	1 (6.7)	3 (23.1)	1 (7.7)	0	0	0
4	1 (6.7)	0	1 (7.7)	0	0	0
Missing	0	1 (7.7)	0	0	0	0
Previous bevacizumab, No. (%)	10 (66.7)	11 (84.6)	6 (46.2)	0	0	19 (54.3)
Bevacizumab + chemotherapy doublet as 1L therapy, No. (%)	10 (66.7)	9 (69.2)	6 (46.2)	0	0	19 (54.3)
Previous taxanes, No. (%)						
Paclitaxel	13 (86.7)	12 (92.3)	12 (92.3)	0	13 (39.4)	34 (97.1)
Paclitaxel albumin	1 (6.7)	0	1 (7.7)	0	0	0
Docetaxel	0	1 (7.7)	1 (7.7)	0	0	2 (5.7)

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not available; TV, tisotumab vedotin.
[a]The patient categorized as other histology had cervical mucinous carcinoma.
[b]PD-L1 prevalence is based on available biopsies. Positive means a CPS score of ≥1.

TABLE 2. Summary of Efficacy in the Dose-Expansion Arms

End Point	1L TV + Carboplatin (arm D; n = 33)	1L TV + Pembrolizumab (arm E; n = 32)	2L/3L TV + Pembrolizumab (arm F; n = 34)
Confirmed ORR, No. (%) (95% CI[a])	18 (54.5) (36.4 to 71.9)	13 (40.6) (23.7 to 59.4)	12 (35.3) (19.7 to 53.5)
Best overall response, No. (%)			
CR	5 (15.2)	5 (15.6)	4 (11.8)
PR	13 (39.4)	8 (25.0)	8 (23.5)
SD	12 (36.4)	13 (40.6)	13 (38.2)
PD	2 (6.1)	2 (6.3)	7 (20.6)
Not evaluable	1 (3.0)	4 (12.5)	2 (5.9)
DCR,[b] No. (%) (95% CI[a])	30 (90.9) (75.7 to 98.1)	26 (81.3) (63.6 to 92.8)	25 (73.5) (55.6 to 87.1)
CBR,[c] No. (%) (95% CI[a])	26 (78.8) (61.1 to 91.0)	23 (71.9) (53.3 to 86.3)	16 (47.1) (29.8 to 64.9)
Median time to response (range), months	1.4 (1.1-4.4)	1.4 (1.2-2.8)	1.4 (1.3-5.8)
Median DOR (95% CI), months	8.6 (4.2 to 11.5)	NR (NR to NR)	14.1 (4.2 to NR)
Median PFS (95% CI), months	6.9 (4.0 to 11.1)	5.3 (4.0 to 12.2)	5.6 (2.7 to 14.2)
Median OS (95% CI), months	NR (NR to NR)	NR (NR to NR)	15.3 (9.9 to NR)
Follow-up, months, median (range)	17.8 (1-26)	21.7 (1-29)	15.0 (1-29)

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TV, tisotumab vedotin.

[a]Exact 95% two-sided CI calculated using the Clopper-Pearson method.

[b]DCR was defined as CR or PR of ≥4 weeks after first CR/PR, and SD of ≥5 weeks after first dose.

[c]CBR was defined as CR or PR of ≥4 weeks after first CR/PR and SD with a minimum duration of ≥10 weeks, where minimum duration for SD is calculated as the time from the start of treatment to the last SD.

escalation arms, 61.0% of patients had previous 1L bevacizumab + platinum doublet chemotherapy, 73.2% had previous chemoradiotherapy, and 41.5% had ≥2 previous lines of treatment (Table 1). All 66 patients enrolled in dose-expansion arms D and E received study drug as 1L treatment for r/mCC; 71.2% had previous chemoradiotherapy. Of 35 patients in arm F (2L or 3L), 54.3% had previous chemoradiotherapy, 54.3% had received 1L bevacizumab + doublet chemotherapy, and 28.6% had received two previous lines of treatment.

Across dose-expansion and dose-escalation arms, nine patients (6.3%; two in arm A, one in arm C, one in arm D, two in arm E, and three in arm F) remained on study treatment and 133 (93.7%) had discontinued treatment, including 83 (58.5%) because of disease progression (radiographic or clinical) and 22 (15.5%) because of AEs (Fig 1). The median duration of TV exposure ranged from 3.7 to 6.2 months across arms (Fig 1).

Dose-Escalation Phase: Determination of RP2D

No DLTs were observed on the basis of Safety Data Monitoring Committee review. The MTD was not reached (NR) in any arm. AEs are summarized in the Data Supplement (Table S2). Grade 4 AEs considered related to any study treatment occurred in one patient in the TV + bevacizumab arm (arm A; rectal perforation), no patients in the TV + pembrolizumab arm (arm B), and four patients in the TV + carboplatin arm (arm C; thrombocytopenia [n = 2], hypomagnesemia [n = 1], and neutropenia, anemia, and thrombocytopenia combined [n = 1]). No fatal AEs related to any treatment were reported. Most AESIs were grade 1/2, and most events resolved or improved during the study (Data Supplement, Table S2). The most common bleeding AESI with TV + bevacizumab was epistaxis (66.7%; Data Supplement, Table S2). No clinically significant changes in clinical and coagulation laboratory results were observed. The RP2D was TV 2 mg/kg intravenously once every 3 weeks in combination with bevacizumab 15 mg/kg, pembrolizumab 200 mg, or carboplatin AUC 5 (each also administered once every 3 weeks).

Efficacy data and maximum change in target lesion size for the dose-escalation arms are provided in the Data Supplement (Table S3 and Fig S2, respectively).

Dose-Expansion Phase: Efficacy

1L TV + Carboplatin (arm D)

For patients treated with TV + carboplatin in 1L (n = 33), the ORR was 54.5%, the DCR was 90.9%, and the CBR was 78.8% (Table 2). In the response-evaluable population (patients with ≥1 postbaseline imaging assessment or who died before first postbaseline assessment; n = 32), the ORR was 56.3%, the DCR was 93.8%, and the CBR was 81.3% (Data Supplement, Table S4). Maximum change in target lesion size is shown in Figure 2A. Responses were ongoing in two of 18

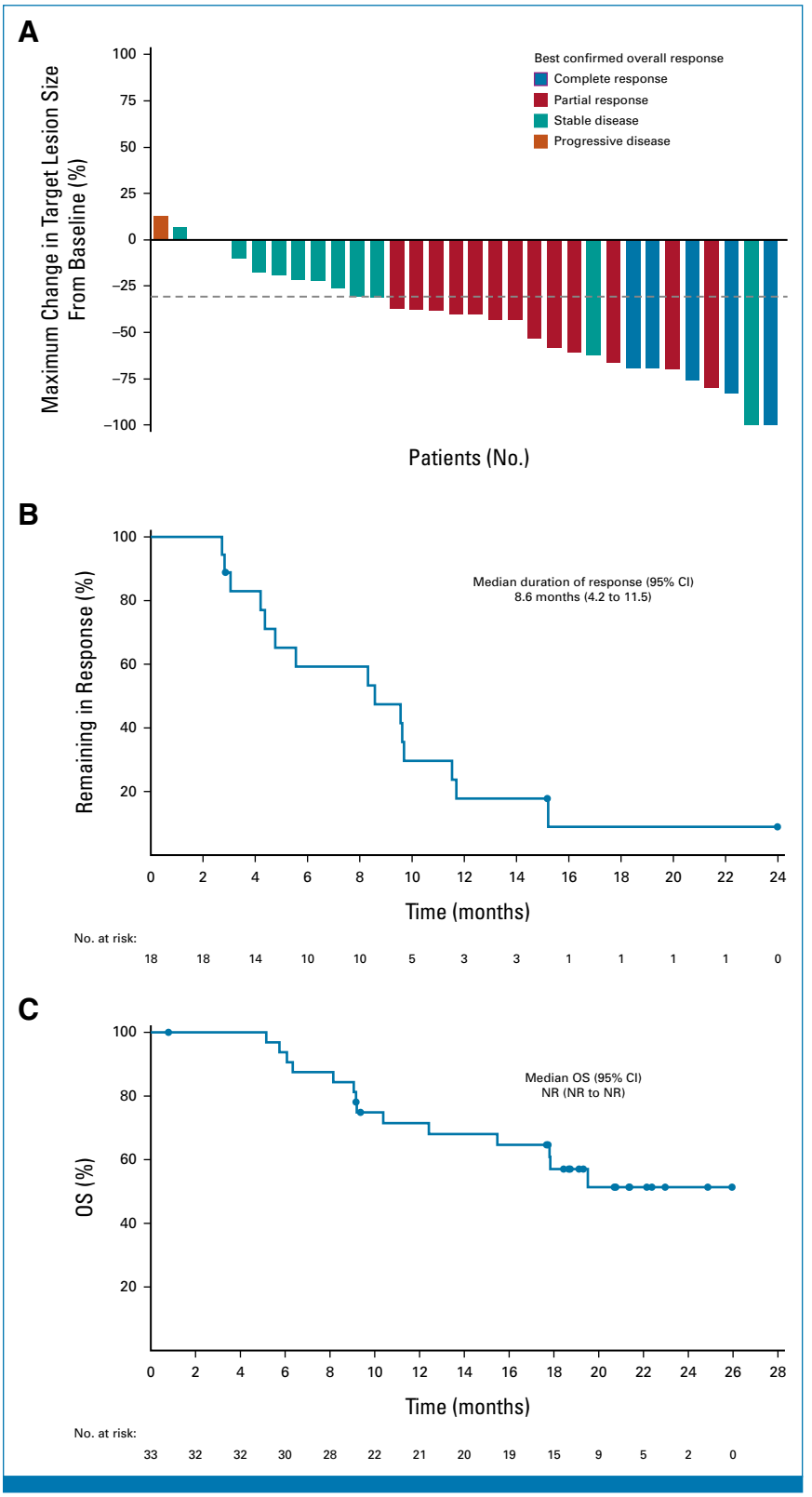

FIG 2. Efficacy outcomes in patients with r/mCC treated 1L with TV + carboplatin in the dose-expansion part (arm D). (A) Waterfall plot showing the maximum percentage change in target lesions. The dashed line indicates a 30% reduction from baseline. (B) Kaplan-Meier–estimated duration of response among the 18 patients with confirmed responses. (C) Kaplan-Meier–estimated overall survival. At data cutoff (June 20, 2022), the median follow-up was 17.8 months (range, 1-26). 1L, first-line; NR, not reached; OS, overall survival; r/mCC, recurrent or metastatic cervical cancer; TV, tisotumab vedotin.

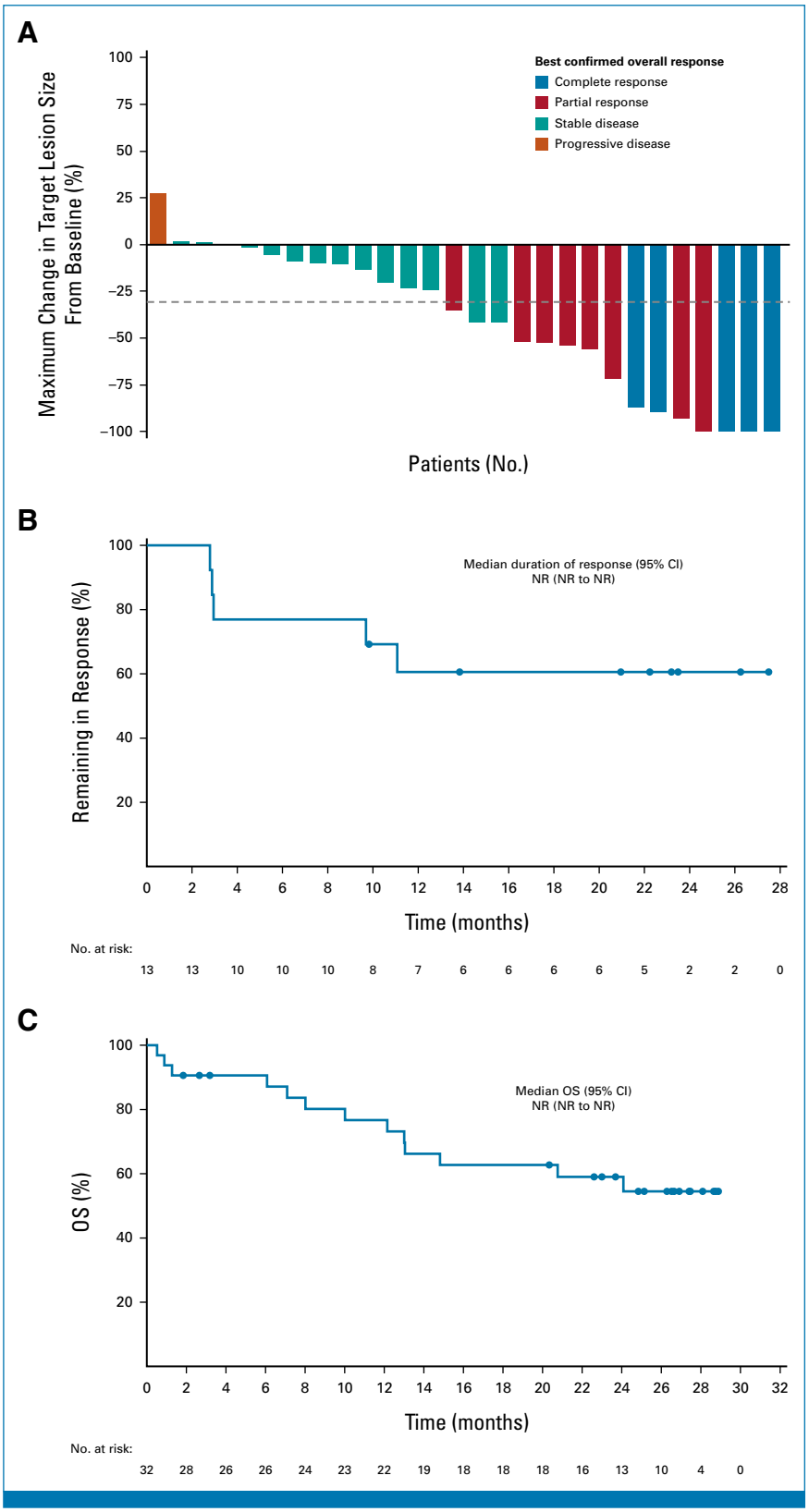

FIG 3. Efficacy outcomes in patients with r/mCC treated 1L with TV + pembrolizumab in the dose-expansion arm E. (A) Waterfall plot showing the maximum percentage change in target lesions. The dashed line indicates a 30% reduction from baseline. (B) Kaplan-Meier–estimated duration of response among the 13 patients with confirmed responses. (C) Kaplan-Meier–estimated overall survival. At data cutoff (June 20, 2022), the median follow-up was 21.7 months (range, 1-29). 1L, first-line; NR, not reached; OS, overall survival; r/mCC, recurrent or metastatic cervical cancer; TV, tisotumab vedotin.

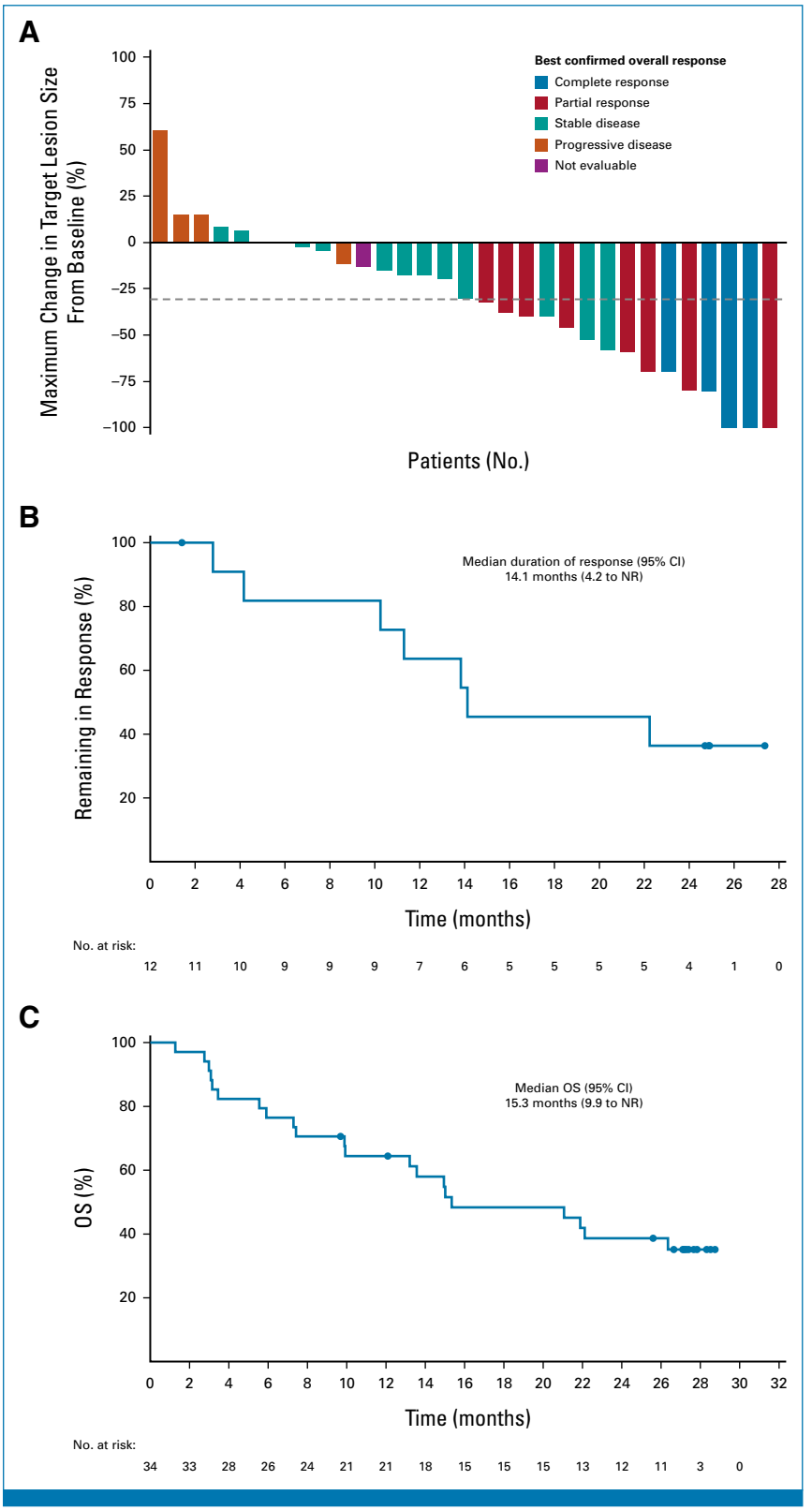

FIG 4. Efficacy outcomes in patients with r/mCC treated 2L or 3L with TV + pembrolizumab in the dose-expansion arm F. (A) Waterfall plot showing the maximum percentage change in target lesions. The dashed line indicates a 30% reduction from baseline. (B) Kaplan-Meier–estimated duration of response among the 12 patients with confirmed responses. (C) Kaplan-Meier–estimated overall survival. At data cutoff (June 20, 2022), the median follow-up was 15.0 months (range, 1-29). 2L, second line; 3L, third line; NR, not reached; OS, overall survival; r/mCC, recurrent or metastatic cervical cancer; TV, tisotumab vedotin.

TABLE 3. AEs Reported in ≥20% of Patients and Grade ≥3 AEs Reported in ≥5% of Patients in Dose-Expansion Arms D, E, or F

1L TV + Carboplatin (arm D)	n = 33, No. (%)
All grades	
≥1 AE	33 (100)
Nausea	26 (78.8)
Anemia	19 (57.6)
Fatigue	19 (57.6)
Alopecia	18 (54.5)
Diarrhea	15 (45.5)
Dry eye	15 (45.5)
Epistaxis	15 (45.5)
Neutropenia	15 (45.5)
Peripheral sensory neuropathy	14 (42.4)
Constipation	13 (39.4)
Decreased appetite	12 (36.4)
Conjunctivitis	11 (33.3)
Vomiting	10 (30.3)
Decreased platelet count	8 (24.2)
Dysgeusia	8 (24.2)
Dyspnea	8 (24.2)
Hypomagnesemia	8 (24.2)
Abdominal pain	7 (21.2)
Arthralgia	7 (21.2)
Decreased WBC count	7 (21.2)
Thrombocytopenia	7 (21.2)
Grade ≥3 AEs	
≥1 AE	26 (78.8)
Anemia	13 (39.4)
Diarrhea	5 (15.2)
Decreased platelet count	5 (15.2)
Nausea	5 (15.2)
Neutropenia	4 (12.1)
Thrombocytopenia	4 (12.1)
Decreased lymphocyte count	3 (9.1)
Decreased neutrophil count	3 (9.1)
Decreased WBC count	3 (9.1)
Fatigue	3 (9.1)
Asthenia	2 (6.1)
Decreased appetite	2 (6.1)
Febrile neutropenia	2 (6.1)
General physical health deterioration	2 (6.1)
Muscular weakness	2 (6.1)
Ulcerative keratitis	2 (6.1)
Urinary tract infection	2 (6.1)

1L TV + Pembrolizumab (arm E)	n = 33, No. (%)
All grades	
≥1 AE	33 (100)
Alopecia	20 (60.6)
Diarrhea	18 (54.5)
Epistaxis	16 (48.5)

(continued on following page)

TABLE 3. AEs Reported in ≥20% of Patients and Grade ≥3 AEs Reported in ≥5% of Patients in Dose-Expansion Arms D, E, or F (continued)

1L TV + Pembrolizumab (arm E)	n = 33, No. (%)
Conjunctivitis	16 (48.5)
Nausea	15 (45.5)
Dry eye	14 (42.4)
Constipation	13 (39.4)
Peripheral sensory neuropathy	13 (39.4)
Decreased appetite	12 (36.4)
Anemia	11 (33.3)
Fatigue	11 (33.3)
Pruritus	11 (33.3)
Pyrexia	11 (33.3)
Arthralgia	10 (30.3)
Abdominal pain	9 (27.3)
Asthenia	8 (24.2)
Dry mouth	7 (21.2)
Hot flush	7 (21.1)
Increased ALT	7 (21.2)
Myalgia	7 (21.2)
Nasal congestion	7 (21.2)
Vomiting	7 (21.2)
Weight decreased	7 (21.2)
Grade ≥3 AEs	
≥1 AE	22 (66.7)
Anemia	4 (12.1)
Asthenia	3 (9.1)
Hypokalemia	3 (9.1)
Acute kidney injury	2 (6.1)
Decreased WBC count	2 (6.1)
Dyspnea	2 (6.1)
Increased ALT	2 (6.1)
Neutropenia	2 (6.1)

2L or 3L TV + Pembrolizumab (arm F)	n = 35, No. (%)
All grades	
≥1 AE	35 (100)
Anemia	19 (54.3)
Diarrhea	19 (54.3)
Nausea	16 (45.7)
Fatigue	15 (42.9)
Epistaxis	13 (37.1)
Constipation	12 (34.3)
Alopecia	11 (31.4)
Decreased appetite	11 (31.4)
Vomiting	11 (31.4)
Hypomagnesemia	10 (28.6)
Arthralgia	9 (25.7)
Asthenia	9 (25.7)
Conjunctivitis	9 (25.7)
Dry eye	9 (25.7)
Hypokalemia	9 (25.7)

(continued on following page)

TABLE 3. AEs Reported in ≥20% of Patients and Grade ≥3 AEs Reported in ≥5% of Patients in Dose-Expansion Arms D, E, or F (continued)

2L or 3L TV + Pembrolizumab (arm F)	n = 35, No. (%)
Increased blood CPK	9 (25.7)
Peripheral sensory neuropathy	9 (25.7)
Urinary tract infection	9 (25.7)
Dyspnea	7 (20.0)
Increased AST	7 (20.0)
Increased blood alkaline phosphatase	7 (20.0)
Increased gamma-glutamyl transferase	7 (20.0)
Grade ≥3 AEs	
≥1 AE	26 (74.3)
Anemia	10 (28.6)
Intestinal obstruction	4 (11.4)
Weight decreased	4 (11.4)
Acute kidney injury	3 (8.6)
Asthenia	3 (8.6)
Fatigue	3 (8.6)
Urinary tract infection	3 (8.6)
Decreased neutrophil count	2 (5.7)
Diarrhea	2 (5.7)
Hypertension	2 (5.7)
Hypokalemia	2 (5.7)
Hypomagnesemia	2 (5.7)
Increased blood alkaline phosphatase	2 (5.7)
Neutropenia	2 (5.7)
Rash	2 (5.7)
Sepsis	2 (5.7)

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; AE, adverse event; CPK, creatine phosphokinase; TV, tisotumab vedotin.

responders at last assessment, one of whom remained on study treatment (Fig S3, Data Supplement). The median TTR was 1.4 months (range, 1.1-4.4). The median DOR was 8.6 months (95% CI, 4.2 to 11.5; Fig 2B). With a median follow-up of 17.8 months, the median PFS was 6.9 months (95% CI, 4.0 to 11.1; Data Supplement, Fig S4). The 1-year PFS rate was 28.1% (95% CI, 13.1 to 45.4). The 2-year PFS rate was 5.4% (95% CI, 0.4 to 20.8). Median OS was NR at data cutoff (14 patients [42.4%] had died; Fig 2C).

1L TV + Pembrolizumab (arm E)

For treatment-naive patients who received TV + pembrolizumab (n = 32), the ORR was 40.6%, the DCR was 81.3%, and the CBR was 71.9% (Table 2; Fig 3A). In response-evaluable patients (n = 31), the ORR was 41.9%, the DCR was 83.9%, and the CBR was 74.2% (Data Supplement, Table S4). Seven of 13 responders had ongoing response at last assessment, two of whom remained on study treatment (Data Supplement, Fig S5). The median TTR was 1.4 months (range, 1.2-2.8); median DOR was NR (Fig 3B). With a median follow-up of 21.7 months, the median PFS was 5.3 months (95% CI, 4.0 to 12.2); the PFS rate was 37.1% (95% CI, 19.9 to 54.5) at 1 year and 28.9% (95% CI, 13.4 to 46.4) at 2 years (Data Supplement, Fig S6). Median OS was NR (13 deaths [40.6%]; Fig 3C).

2L or 3L TV + Pembrolizumab (arm F)

Among patients who received 2L or 3L treatment with TV + pembrolizumab (n = 34), the ORR was 35.3%, the DCR was 73.5%, and the CBR was 47.1% (Table 2; Fig 4A). In response-evaluable patients (n = 32), the ORR was 37.5%, the DCR was 78.1%, and the CBR was 50.0% (Data Supplement, Table S4). Responses were maintained in four of 12 responders at last assessment, three of whom remained on study treatment (Data Supplement, Fig S7). The median TTR was 1.4 months (range, 1.3-5.8). The median DOR was 14.1 months (95% CI, 4.2 to NR; Fig 4B). With a median follow-up of 15.0 months, the median PFS was 5.6 months (95% CI, 2.7 to 14.2; Data Supplement, Fig S8). The 1- and 2-year PFS rates were 34.5% (95% CI, 17.9 to 51.8) and 15.3% (95% CI, 4.9 to 31.2), respectively. The median OS was 15.3 months (95% CI, 9.9 to NR; 21 deaths [61.8%]; Fig 4C). The ORR was similar in patients with (33.3% [6 of 18]; 95% CI, 13.3 to 59.0) and without previous bevacizumab treatment (37.5% [6 of 16]; 95% CI, 15.2 to 64.6).

Dose-Expansion Phase: Safety

The most common AEs in the dose-expansion arms are listed in Table 3. Grade ≥3 AEs occurred in 78.8%, 66.7%, and 74.3% of patients in arms D, E, and F, respectively. AEs related to any study treatment are listed in the Data Supplement (Table S5). One treatment-related fatal AE (disseminated intravascular coagulation) occurred in arm E. The most common AEs leading to discontinuation of TV were ocular or peripheral neuropathy AEs (Data Supplement, Table S6).

Ocular AESIs were reported in 66.7%, 69.7%, and 54.3% of patients in arms D, E, and F, respectively (grade 3: 9.1%, 9.1%, and 2.9%, respectively; none grade ≥4; Data Supplement, Fig S9 and Table S7); the median time to onset was 33, 24, and 12 days, respectively. Ocular AEs resolved or improved in >85% of patients with events in each arm, with the median time to resolution of 21, 16, and 22 days in arms D, E, and F, respectively.

Peripheral neuropathy AESIs occurred in 60.6%, 51.5%, and 40.0% of patients in arms D, E, and F, respectively (grade 3: 12.1%, 3.0%, and 2.9%, respectively; none grade ≥4), with the median time to onset of 40, 85, and 105 days, respectively (Data Supplement, Fig S9 and Table S7). Peripheral neuropathy resolved or improved in >40% of patients with events in each arm, with the median time to resolution of 13, 43, and 49 days in arms D, E, and F, respectively.

Bleeding AESIs occurred in 57.6%, 66.7%, and 68.6% of patients in arms D, E, and F, respectively (grade ≥3: 6.1%, 6.1% [including 1 grade 5 disseminated intravascular coagulation], and 8.6%, respectively; Data Supplement, Fig S9); the median time to onset was 7-9 days. Bleeding AEs resolved or improved in >70% of patients with events in each arm, with the median time to resolution of 12, 34, and 7 days, respectively (Data Supplement, Table S7). Bleeding AEs related to TV treatment were reported in 42.4%, 54.5%, and 40.0% of patients in arms D, E, and F, respectively, most commonly grade 1/2 epistaxis (36.4%, 48.5%, and 25.7%, respectively). Thrombotic events are listed in the Data Supplement (Table S8); grade 3 thrombotic events included infusion site thrombosis (n = 1; 3.0%) in arm D, deep vein thrombosis (n = 1; 3.0%) in arm E, and pulmonary embolism (n = 1; 2.9%) in arm F.

Immune-related AEs in the pembrolizumab arms (arms E and F) are listed in the Data Supplement (Table S9). Immunogenicity results for TV ADAs are presented in the Data Supplement.

TF Expression

Membrane TF expression (≥1%) was confirmed for biopsy-evaluable patients in the dose-expansion arms (median [range] membrane H-score at baseline: arm D, 85.0 [2-290], n = 27; arm E, 120.0 [0-290], n = 30; arm F, 140.0 [14-285], n = 33). Tumor membrane H-scores for TF expression at baseline were not directly associated with response to treatment in arms D, E, or F (Data Supplement, Fig S10).

DISCUSSION

Doublet combination regimens of TV with bevacizumab, carboplatin, or pembrolizumab demonstrated acceptable safety and encouraging antitumor activity in patients with advanced r/mCC in the dose-escalation phase. Treatment history was similar to the real-world population,[10,18,19] with the majority of patients having previous 1L bevacizumab + platinum doublet chemotherapy or previous chemoradiotherapy. Across arms A, B, and C, most AEs were grade 1/2 and no DLTs occurred with the TV-doublet combinations. Observed safety profiles were generally consistent with those known for each individual agent.[4,15,20-23] The RP2D for TV in combination with bevacizumab, carboplatin, or pembrolizumab is the same as the approved dose for TV monotherapy.

Combining vascular endothelial growth factor angiogenesis inhibition (bevacizumab) with potential coagulation effects of TV via the TF target carries the potential for overlapping toxicities; however, data from this study suggest that there were no meaningful changes in coagulation parameters. For bevacizumab + TV, the bleeding AE rate was within the range of previous reports with TV monotherapy (57%-76%).[15,20,21] Our results confirm the feasibility of adding TV to bevacizumab.

In the dose-expansion phase, 1L treatment with TV + carboplatin demonstrated a tolerable safety profile and encouraging antitumor activity, with numerically higher observed ORR (54.5%; CR, 15.2%) than that observed with cisplatin or topotecan + paclitaxel without bevacizumab (ORR, 36%; CR, 8%) in GOG 240.[24] The CR rate observed with TV + carboplatin is comparable with that achieved with the current 1L SOC (12.9%-21.4%).[6] TV + carboplatin appeared to have a more favorable tolerability profile than that previously noted with cisplatin + paclitaxel in previous studies.[4,24,25] No grade 4 neutropenia was reported in patients receiving TV + carboplatin, whereas grade ≥4 neutropenia was reported in 26% of patients receiving cisplatin + paclitaxel in GOG 240.[4,24,25] Peripheral neuropathy AEs, which are common with cisplatin/carboplatin + paclitaxel (any grade, 62%-77%; grade 3, 5%-9%),[4,23] were reported in 60.6% of patients who received TV + carboplatin. The incidence of ocular AEs with TV + carboplatin (66.7%; grade 3, 9.1%) was comparable with that observed with TV monotherapy (53%[15]-65%[20]). The encouraging antitumor activity and tolerability of TV + carboplatin warrant further evaluation of this combination in the frontline setting.

Both pembrolizumab (in PD-L1$^+$ tumors) and TV are approved in the United States as monotherapies for patients with r/mCC in the 2L setting.[14,26] Pembrolizumab + chemotherapy showed improved OS versus chemotherapy alone in patients with PD-L1$^+$ r/mCC in the 1L setting.[6] There may be additive effects when combining TV and pembrolizumab.

Clinical data suggest that the combination delivers a clinically meaningful response rate and prolonged DOR compared with each drug as monotherapy.[15,22,27] The potential additive effects appear to be irrespective of previous therapy exposure. Additional research is needed to better understand the potential synergy. The immune-related AE profile with TV + pembrolizumab was comparable with that of pembrolizumab monotherapy in KEYNOTE-158 (n = 98).[22] The observed additive clinical benefit and favorable safety profile support further evaluation of TV in combination regimens that may improve clinical outcomes for patients with treatment-naive and previously treated r/mCC.

A limitation of our study is small sample sizes of the combination arms, which limit our ability to make definitive conclusions regarding the efficacy of these combinations. Larger studies are needed to assess optimal treatment sequencing. The six arms of patients included in this phase Ib/II trial enabled systematic and careful evaluation of the feasibility of incorporating TV into established combination regimens. While these doublet data are encouraging, further investigation is ongoing to continue potential development of TV as part of evolving 1L SOC.

In conclusion, TV demonstrated acceptable safety and promising antitumor activity when administered in combination with bevacizumab, pembrolizumab, or carboplatin, supporting additional studies combining TV with individual backbone treatments for patients with r/mCC. Furthermore, TV in combination with carboplatin or pembrolizumab in the 1L setting showed durable antitumor activity and tolerable safety, supporting ongoing evaluation of triplet/quadruplet combinations of TV + carboplatin + pembrolizumab with or without bevacizumab as 1L treatment of r/mCC in an additional dose-expansion arm (arm H).

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Deidentified individual participant data collected during the trial will not be available upon request for further analyses by external independent researchers. Aggregated clinical trial data from the trial are provided via publicly accessible study registries/databases as required by law. For more information, please contact clinicaltrials@genmab.com.

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Speakers' Bureau: Roche/Genentech, AstraZeneca, Merck, Tesaro, Clovis Oncology, Eisai, Genmab
Research Funding: AbbVie (Inst), Genentech/Roche (Inst), Morphotek (Inst), Merck (Inst), Regeneron (Inst)
Travel, Accommodations, Expenses: Roche/Genentech

Kristine Madsen
Travel, Accommodations, Expenses: GlaxoSmithKline

Fatih Köse
Honoraria: Roche (Inst), AstraZeneca (Inst), MSD/Merck (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Pfizer (Inst), Takeda (Inst), Deva (Inst), Nobelpharma (Inst), Astellas Pharma (Inst), Janssen (Inst)
Consulting or Advisory Role: Roche, AstraZeneca, MSD/Merck, GlaxoSmithKline, Novartis, Pfizer, Takeda, Deva, Nobelpharma, Astellas Pharma, Janssen

Amanda L. Jackson
Consulting or Advisory Role: Ethicon, Seagen, Sutro Biopharma, AstraZeneca

Ingrid A. Boere
Consulting or Advisory Role: Tesaro/GSK (Inst), AstraZeneca (Inst)
Research Funding: GlaxoSmithKline (Inst)

Giovanni Scambia
Consulting or Advisory Role: Clovis Oncology, AstraZeneca, PharmaMar, Roche, Tesaro
Speakers' Bureau: Clovis Oncology, MSD

Leslie M. Randall
Honoraria: BluPrint Oncology, PER, Curio Science
Consulting or Advisory Role: AstraZeneca, Clovis Oncology, GOG Foundation, Merck, Mersana, Rubius Therapeutics, Myriad Genetics, Genentech/Roche, Seagen, Eisai, Novocure, AADi, On Target Laboratories, Immunogen
Speakers' Bureau: Genmab/Seagen
Research Funding: Genentech/Roche (Inst), On Target Laboratories (Inst), Pfizer (Inst), Aivita Biomedical (Inst), Tesaro (Inst), AstraZeneca (Inst), Merck (Inst), Akeso Biopharma (Inst), GEICO (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Seagen, Genmab, GOG Foundation

Jean-François Baurain
Consulting or Advisory Role: MSD Oncology (Inst), BMS (Inst), Novartis (Inst), Pierre Fabre (Inst), Sanofi/Regeneron (Inst), GlaxoSmithKline (Inst), AstraZeneca (Inst), Sun Pharma (Inst)

Hannelore G. Denys
Consulting or Advisory Role: Pfizer (Inst), Roche (Inst), PharmaMar (Inst), AstraZeneca (Inst), Lilly (Inst), Novartis (Inst), Amgen (Inst), GlaxoSmithKline (Inst), MSD (Inst), Seagen (Inst), Gilead Sciences (Inst)
Research Funding: Gilead Sciences (Inst)
Travel, Accommodations, Expenses: Pfizer (Inst), Roche (Inst), PharmaMar (Inst), Teva (Inst), AstraZeneca (Inst), Gilead Sciences (Inst)

Nelleke Ottevanger
Consulting or Advisory Role: AstraZeneca (Inst), GlaxoSmithKline (Inst), Nykode Therapeutics (Inst)

Frédéric Forget
Travel, Accommodations, Expenses: Ipsen, Teva

Camilla Mondrup Andreassen
Employment: Genmab
Stock and Other Ownership Interests: Genmab, Scandion Oncology, Novo Nordisk, Bavarian Nordic, 3M, AbbVie, Colgate Palmolive, Coloplast, Demant, Expres2ion Biotechnologies, Lundbeck, Johnson & Johnson/Janssen, Teva, Unilever

Michael J. Chisamore
Employment: Merck
Stock and Other Ownership Interests: Merck

Leonardo Viana Nicacio
Employment: Seagen
Stock and Other Ownership Interests: Florence Healthcare, Seagen
Honoraria: Seagen
Travel, Accommodations, Expenses: Seagen

Ibrahima Soumaoro
Employment: Genmab
Stock and Other Ownership Interests: Genmab, Bristol Myers Squibb
Travel, Accommodations, Expenses: Genmab, Bristol Myers Squibb

Bradley J. Monk
Leadership: US Oncology
Honoraria: Agenus, Akeso Biopharma, Amgen, Aravive, AstraZeneca, Clovis Oncology, Eisai, Genmab/Seattle Genetics, ImmunoGen, Iovance Biotherapeutics, Merck, Mersana, Pfizer, Puma Biotechnology, Regeneron, Roche/Genentech, Tesaro/GSK, Vascular Biogenics, GOG Foundation, Elevar Therapeutics, Novocure, Gradalis, Karyopharm Therapeutics, Bayer, EMD Serono/Merck, Sorrento Therapeutics, US Oncology, Myriad Pharmaceuticals, Novartis, OncoC4, Pieris Pharmaceuticals, Acrivon Therapeutics, Adaptimmune, HenRui, Laekna Health Care, Panavance Therapeutics, Verastem, Zentalis
Consulting or Advisory Role: Agenus, Akeso Biopharma, Amgen, Aravive, AstraZeneca, Clovis Oncology, Eisai, Genmab/Seattle Genetics, GOG Foundation, ImmunoGen, Iovance Biotherapeutics, Merck, Mersana, Myriad Pharmaceuticals, Pfizer, Puma Biotechnology, Regeneron, Roche/Genentech, Tesaro/GSK, Vascular Biogenics, Gradalis, Karyopharm Therapeutics, Sorrento Therapeutics, Novocure, Bayer, Elevar Therapeutics, EMD Serono/Merck, Gradalis, US Oncology, Novartis, Pieris Pharmaceuticals, OncoC4, Adaptimmune, HenRui, Laekna Health Care, Panavance Therapeutics, Verastem, Zentalis
Speakers' Bureau: Roche/Genentech, AstraZeneca, Clovis Oncology, Eisai, Tesaro/GSK, Merck
Research Funding: Novartis (Inst), Amgen (Inst), Genentech (Inst), Lilly (Inst), Janssen (Inst), Array BioPharma (Inst), Tesaro (Inst), Morphotek (Inst), Pfizer (Inst), Advaxis (Inst), AstraZeneca (Inst), Immunogen (Inst), Regeneron (Inst), Nucana (Inst)

No other potential conflicts of interest were reported.