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Tisotumab vedotin plus carboplatin or pembrolizumab in recurrent or metastatic cervical cancer: 5-year results from the innovaTV 205/ENGOT-cx8/GOG-3024 study☆

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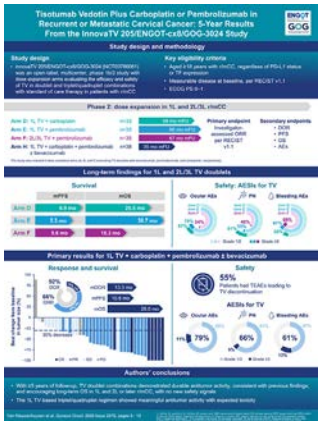
HIGHLIGHTS

- TV doublets demonstrated durable efficacy and encouraging 5-year overall survival.
- 1L TV + carboplatin + pembrolizumab ± bevacizumab yielded high response rates.
- TV-based combinations showed acceptable toxicity with no new safety signals.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. Treatment options for recurrent or metastatic cervical cancer (r/mCC) remain limited. We evaluated the efficacy and safety of tisotumab vedotin (TV)–based combinations with standard agents in first-line (1L) and previously treated (second-line or later [2L+]) settings in r/mCC.

Methods. innovaTV 205/ENGOT-cx8/GOG-3024 (NCT03786081) was a multicenter, open-label phase 1b/2 study, which included dose-expansion arms of 1L TV + carboplatin (arm D), 1L/2L+ TV + pembrolizumab (arms E/F), and 1L TV + carboplatin + pembrolizumab ± bevacizumab (arm H). The primary endpoint was investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors v1.1. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs).

Results. As of October 15, 2025, 139 patients were enrolled in dose-expansion arms D ($n = 33$), E (n = 33), F ($n = 35$), and H ($n = 38$). Confirmed ORR (median DOR) was 54.5% (8.6 months), 40.6% (not reached), 35.3% (18.2 months), and 65.8% (13.3 months) in arms D–F and H, respectively. Median PFS was 6.9, 5.3, 5.6, and 10.6 months; median OS was 25.5, 30.7, 15.3, and 28.0 months. Grade ≥ 3 AEs related to any treatment component occurred in 72.7%, 45.5%, 48.6%, and 86.8% of patients; AEs leading to TV discontinuation occurred in 24.2%, 24.2%, 34.3%, and 55.3% of patients in arms D–F and H, respectively.

Conclusion. With ≥ 5 years of follow-up, TV doublet combinations demonstrated durable activity consistent with previous findings and encouraging long-term OS in 1L and 2L+ r/mCC, with no new safety signals. The 1L TV-based triplet/quadruplet regimen showed meaningful antitumor activity with expected toxicity.

1. Introduction

Recurrent or metastatic cervical cancer (r/mCC) remains associated with a poor prognosis, with 5-year survival rates of <20%, underscoring an unmet need to improve outcomes [1,2]. Current first-line (1L) standard-of-care treatment for r/mCC includes chemotherapy-based regimens with bevacizumab and immunotherapy-based regimens as preferred approaches [3]. Pembrolizumab plus chemotherapy with or without bevacizumab is a preferred regimen in patients with programmed death-ligand 1 (PD-L1)–positive tumors, [3] based on results of the KEYNOTE-826 trial, which demonstrated clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) over chemotherapy alone [4]. Atezolizumab plus chemotherapy with or without bevacizumab is also a preferred regimen in r/mCC [3] based on results of the BEATcc study, which showed a meaningful survival benefit as 1L treatment for r/mCC, regardless of PD-L1 status [5,6]. Despite these advances, most patients experience progressive disease (PD) and require effective therapies for 1L and second-line or later (2L+) patient settings [2].

Tissue factor (TF) is highly expressed in many solid tumors, including r/mCC [7,8]. Tisotumab vedotin (TV), a TF-directed antibody–drug conjugate composed of a human monoclonal antibody covalently linked to a microtubule-disrupting payload, monomethyl auristatin E, is approved in several regions, including the United States, United Kingdom, European Union, and Japan, as monotherapy in the second-line (2L) or third-line (3L) setting for patients with r/mCC with PD on or after chemotherapy [9]. In the 2L/3L settings, TV monotherapy demonstrated significantly longer OS (hazard ratio: 0.70; 95% confidence interval [CI]: 0.54–0.89; $P = 0.004$) and PFS (hazard ratio: 0.67; 95% CI: 0.54–0.82; $P < 0.001$), as well as a significantly higher objective response rate (ORR; odds ratio: 4.0; 95% CI: 2.1–7.6; $P < 0.001$), compared with investigators' choice of chemotherapy in adults with r/mCC treated in the phase 3 innovaTV 301/ENGOT-cx12/GOG-3057 trial [10]. Treatment guidelines recommend TV monotherapy as a preferred therapy

option for previously treated r/mCC that has progressed on or after chemotherapy [3].

Given the ongoing unmet need in r/mCC, a strong rationale exists to evaluate TV in combination with other standard-of-care agents with proven activity against this disease. The phase 1b/2 innovaTV 205/ENGOT-cx8/GOG-3024 study was designed to evaluate the antitumor effects of TV in combination with chemotherapy, bevacizumab, and/or immunotherapy in r/mCC [11]. In the dose-expansion phase, TV doublets showed encouraging antitumor activity with a manageable safety profile in treatment-naive 1L r/mCC (TV plus pembrolizumab or carboplatin) and in previously treated r/mCC (TV plus pembrolizumab) through up to 2 years of follow-up [11].

Here, we present updated results from innovaTV 205/ENGOT-cx8/GOG-3024 with extended follow-up of up to 5.5 years, including OS and safety findings for TV doublets in the 1L and 2L+ settings. First results of the 1L combination of TV with carboplatin and pembrolizumab, with or without bevacizumab (arm H), are also reported.

2. Materials and methods

2.1. Study design and patients

Detailed methodology for innovaTV 205/ENGOT-cx8/GOG-3024 (ClinicalTrials.gov identifier: NCT03786081) have been published previously [11]. This open-label, multicenter, phase 2 study evaluated the efficacy and safety of TV in doublet and triplet/quadruplet combinations with carboplatin, pembrolizumab, and bevacizumab in patients with recurrent or stage IVB cervical cancer. The study was approved by an independent ethics committee/institutional review board and was conducted in accordance with good clinical practice and the principles of the Declaration of Helsinki. All patients provided written informed consent before study participation. The dose-expansion arms included TV-based doublets in the 1L setting (TV + carboplatin, arm D; TV + pembrolizumab, arm E) and in the 2L/3L setting (TV + pembrolizumab, arm F), as well as 1L TV triplet/quadruplet therapy (TV + carboplatin + pembrolizumab ± bevacizumab, arm H).

Eligible patients were aged ≥ 18 years with recurrent or stage IVB squamous carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix, regardless of PD-L1 status or TF expression. Patients were required to have measurable disease at baseline per Response Evaluation Criteria in Solid Tumors version 1.1 and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients enrolled in arms D, E, and H had not received prior systemic therapy for r/mCC, whereas patients in arm F had PD during or after one or two prior lines of systemic therapy for r/mCC. Key exclusion criteria across all arms included clinically significant bleeding risk, active ocular surface disease, clinically significant cardiovascular disease, prior treatment with a monomethyl auristatin E–derived drug, or treatment of any systemic anticancer therapy (including investigational agents) within 4 weeks of the first dose of trial treatment. Patients enrolled in arms E, F, and H could not have received prior anti–programmed cell death protein 1 or anti–PD-L1 therapy. Additional exclusion criteria in arm H related to bevacizumab included clinically significant bleeding or risks, uncontrolled hypertension, requirement for anticoagulation, history of thromboembolic events, recent (within 4 weeks) wound-healing complications, history of clinically significant fistula or gastrointestinal perforation, and others.

2.2. Treatments

Patients received 1L TV 2.0 mg/kg in combination with carboplatin AUC 5 (arm D), 1L TV 2.0 mg/kg plus pembrolizumab 200 mg (arm E), or 2L/3L TV 2.0 mg/kg plus pembrolizumab 200 mg (arm F). In arm H, patients received 1L TV 2.0 mg/kg plus carboplatin AUC 5 and pembrolizumab 200 mg, with or without bevacizumab 15 mg/kg per investigator's choice. All study treatments were administered intravenously once every 3 weeks. Treatment with TV (in all arms) and bevacizumab (in arm H) were continued until PD, unacceptable toxicity, or withdrawal of consent. Treatment with carboplatin was continued until PD or unacceptable toxicity in arm D or for ≤ 6 cycles in arm H (could be continued beyond six cycles if the patient was deriving clinical benefit). Treatment with pembrolizumab was continued until PD or unacceptable toxicity in arms E, F, and H for ≤ 35 cycles or until the patient achieved a confirmed complete response (CR) after treatment for ≥ 8 cycles (patients could receive an additional two cycles beyond confirmation of CR). If any component of a combination was discontinued, the remaining agents could be continued at the investigator's discretion. All patients were required to receive prophylactic eye care, including corticosteroid and vasoconstrictor eye drops, lubricating eye drops, and cooling eye pads. Ocular examinations were performed at screening, on day 1 of cycle 1, day 1 of all subsequent cycles, as soon as possible after treatment discontinuation, and 30 days after the last dose.

2.3. Endpoints

The primary endpoint in the dose expansion arms was investigator-assessed ORR per Response Evaluation Criteria in Solid Tumors version 1.1. Secondary endpoints included duration of response (DOR), time to response (TTR), PFS, OS, and safety and tolerability. Other endpoints included anti-TV immunogenicity and pharmacodynamic biomarker analyses.

Tumor response was assessed locally by computed tomography or, where appropriate or indicated, contrast-enhanced magnetic resonance imaging. Imaging assessments were performed at screening, then every 6 weeks for the first 37 weeks in arms D and E and for the first 31 weeks in arm F, and every 9 weeks for the first 54 weeks in arm H. Thereafter, tumor imaging was performed every 12 weeks for all arms. Imaging continued until investigator-assessed PD, initiation of new anticancer treatment, withdrawal of consent, or death. Investigator-assessed objective responses (CR or partial response [PR]) were confirmed by repeat imaging assessment ≥ 4 weeks after the initial response was observed; subsequent tumor imaging was then performed at the regularly scheduled time points.

Adverse events (AEs) were monitored from the first dose of trial drug through safety follow-up visits at 30 days and 90 days after the last dose of trial drug. Adverse events of special interest (AESIs) for TV included ocular, bleeding, and peripheral neuropathy AEs. All AEs were assessed by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Ocular AEs were assessed by an ophthalmologist according to standard ophthalmological grading and the Common Terminology Criteria for Adverse Events grading system. Prophylactic premedication was not considered an intervention for AE grading.

Tumor biopsies collected at screening were analyzed for TF and PD-L1 expression (combined positive score). PD-L1 expression was analyzed by immunohistochemistry (central assessment using PD-L1 IHC 22C3 pharmDx [Agilent, Santa Clara, CA, USA]). Levels of TF expression were quantified by calculating a histology score that included staining expression and intensity.

2.4. Statistical analyses

Efficacy analyses were conducted on the full analysis set, which comprised all patients receiving ≥ 1 dose of trial treatment, except for two patients who were excluded (one patient received nonprotocol treatment and one patient did not have measurable disease at baseline, consistent with the prior report) [11]. The safety set

included all patients who received ≥ 1 dose of trial treatment. Demographic and baseline data, including disease characteristics, were summarized descriptively for the full analysis set. Categorical variables are presented as frequencies and percentages. Continuous variables are summarized using mean, standard deviation, median, minimum, and maximum.

ORRs were estimated with exact two-sided 95% CIs for each arm using the Clopper–Pearson method. Time-to-event endpoints (DOR, TTR, PFS, and OS) were analyzed using the Kaplan–Meier method, with the survival curve, median, and 95% CI reported for each treatment group. Data were analyzed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients and disposition

In total, 139 patients with r/mCC were enrolled in dose expansion arms D, E, F, and H, with 33, 33, and 35 patients in arms D, E, and F, respectively, and 38 patients enrolled in arm H (data cutoff: October 15, 2025). Median follow-up (range) was 58.0 months (0.8–65.5 months) in arm D, 66.4 months (0.5+ to 68.7 months) in arm E, 66.5 months (1.3+ to 68.3 months) in arm F, and 34.5 months (3.5+ to 41.2 months) in arm H.

Baseline demographic and disease characteristics for patients in arms D–F were published previously [11]. In arm H, the median age was 48 years (range: 32–74 years) and 29 (76.3%) patients had received prior chemoradiotherapy, radiotherapy, or systemic therapy for locally advanced disease (Table 1). The median (range) duration of TV exposure was 4.9 months (1.0–19.0 months) in arm D, 4.5 months (1.0–64.0 months) in arm E, 4.1 months (1.0–67.0 months) in arm F, and 6.6 months (1.0–27.0 months) in arm H. Patients in arm H received a median of 12.5 cycles (range: 2.0–47.0 cycles) of any combination of components and a median of 8.0 cycles (range: 2.0–33.0 cycles) of TV; 19 of 38 patients (50%) received bevacizumab treatment. At the data cutoff, 4 (2.9%) patients remained on study treatment (1 [3.0%] in arm E, 2 [5.7%] in arm F, and 1 [2.6%] in arm H) and 135 (97.1%) patients had discontinued treatment, including 86 (61.9%) patients due to radiographic or clinical PD or death and 24 (17.3%) patients due to AEs (**Fig. S1**).

Table 1
Baseline patient demographics and disease characteristics in arm H of innovaTV 205/ENGOT-cx8/GOG-3024.

Characteristic	1L TV + carboplatin + pembrolizumab ± bevacizumab* (arm H; *n* = 38)
Age, years, median (range)	48 (32–74)
ECOG PS, n (%)	
0	26 (68.4)
1	12 (31.6)
Histology, n (%)	
Squamous cell carcinoma	24 (63.2)
Adenocarcinoma	13 (34.2)
Other	1 (2.6)
PD-L1 positive (CPS ≥ 1%), n (%)†	32 (84.2)
Prior therapy, n (%)	
Chemoradiotherapy or radiotherapy with surgery	13 (34.2)
Chemoradiotherapy or radiotherapy only	15 (39.5)
Systemic therapy with surgery	1 (2.6)
Surgery only	3 (7.9)
None	6 (15.8)
Disease status at study entry, n (%)	
Metastatic	9 (23.7)
Persistent or recurrent with distant metastatic	20 (52.6)
Persistent or recurrent without distant metastatic	9 (23.7)
Metastatic disease at diagnosis, n (%)	
Yes	5 (13.2)
No	28 (73.7)
Not known/not applicable	5 (13.2)
Median time from initial diagnosis to start date of trial treatment, months (range)	12.5 (1.0–247.0)
Median time since primary radiotherapy, months	13.3
Median time since primary chemoradiotherapy, months	12.4

CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PS, performance status; TV, tisotumab vedotin.
* 19 patients (50%) received bevacizumab treatment on study.
† Central assessment using PD-L1 IHC 22C3 pharmDx (Agilent, Santa Clara, CA, USA).

3.2. Efficacy

1L TV + carboplatin (arm D). The investigator-assessed confirmed ORR was 54.5% (18 of 33 patients [95% CI: 36.4–71.9%]), with five patients achieving CR (15.2%) and 13 PR (39.4%) (Table 2). Median TTR was 1.4 months (range: 1.1–4.4 months) and median DOR was 8.6 months (95% CI: 4.2–11.5 months). One patient had an ongoing response at last assessment (**Fig. S2A**). Median PFS was 6.9 months (95% CI: 4.0–11.1 months) (**Fig. S2B**), and median OS was 25.5 months (95% CI: 12.4–36.6 months) (Fig. 1A).

1L TV + pembrolizumab (arm E). The investigator-assessed confirmed ORR was 40.6% (95% CI: 23.7–59.4%), with seven CRs (21.9%) and six PRs (18.8%) (Table 2). Median TTR was 1.4 months (range: 1.2–2.8 months) and median DOR was not reached (NR; 95% CI: 3.0–NR). Six of 13 responders had ongoing responses at the data cutoff, and one patient remained on treatment (**Fig. S3A**). Median PFS was 5.3 months (95% CI: 4.0–12.2 months) (**Fig. S3B**); median OS was 30.7 months (95% CI: 13.0–NR) (Fig. 1B).

2L or 3L TV + pembrolizumab (arm F). The investigator-assessed confirmed ORR was 35.3% (95% CI: 19.7–53.5%), including four CRs (11.8%) and eight PRs (23.5%) (Table 2). The median TTR was 1.4 months (range: 1.3–5.8 months), and median DOR was 18.2 months (95% CI: 4.2–NR). Of 12 responders, five had ongoing responses; two patients remained on treatment (**Fig. S4A**). Median PFS was 5.6 months (95% CI: 2.7–14.2 months) (**Fig. S4B**); median OS was 15.3 months (95% CI: 9.9–35.3 months) (Fig. 1C).

1L TV + carboplatin + pembrolizumab ± bevacizumab (arm H). Investigator-assessed confirmed ORR was 65.8% (95% CI: 48.6–80.4%), including seven CRs (18.4%) and 18 PRs (47.4%) (Table 2, Fig. 2A). Median TTR was 2.1 months (range: 1.4–4.2 months); median DOR was 13.3 months (95% CI: 6.1–NR). Eight patients had ongoing response, and one patient remained on treatment (Fig. 2B). Median PFS was 10.6 months (95% CI: 6.8–17.8 months), and the Kaplan–Meier-estimated PFS rate at 2 years was 29.3% (95% CI: 15.3–44.8%) (Fig. 2C). Median OS was 28.0 months (95% CI: 19.7–NR), and the estimated OS rate at 2 years was 62.4% (95% CI: 44.9–75.8%) (Fig. 2D).

3.3. Safety

The most commonly reported AEs across dose expansion arms D–F and H were nausea, diarrhea, anemia, alopecia, and fatigue (Table 3). AEs related to any trial treatment (any-grade in ≥ 20% of patients and grade ≥ 3 in ≥ 1 patient) are reported in **Table S1**. Grade ≥ 3 AEs related to any trial treatment were reported in 24 (72.7%), 15 (45.5%), 17 (48.6%), and 33 (86.8%) of patients in arms D, E, F, and H, respectively. In arm H, the most common treatment-related grade ≥ 3 AEs were anemia (39.5%), thrombocytopenia (15.8%), fatigue (13.2%), and neutropenia (13.2%).

AEs led to TV discontinuation in eight (24.2%) patients in arms D and E, 12 (34.3%) patients in arm F, and 21 (55.3%) patients in arm H; the most common AEs leading to TV discontinuation are noted in **Table S2**. Cumulative AE-related drug discontinuations by cycle for all treatment arms are shown in **Fig. S5**.

Table 2
Summary of efficacy in dose expansion arms D–F and H of innovaTV 205/ENGOT-cx8/GOG-3024.

Parameter	1L TV + carboplatin (arm D; $n = 33$)	1L TV + pembrolizumab (arm E; $n = 32$)	2L/3L TV + pembrolizumab (arm F; $n = 34$)	1L TV + carboplatin + pembrolizumab ± bevacizumab (arm H; n = 38)
Confirmed ORR, % (95% CI)	54.5 (36.4–71.9)	40.6 (23.7–59.4)	35.3 (19.7–53.5)	65.8 (48.6–80.4)
Best objective response, n (%)				
CR	5 (15.2)	7 (21.9)	4 (11.8)	7 (18.4)
PR	13 (39.4)	6 (18.8)	8 (23.5)	18 (47.4)
SD	12 (36.4)	13 (40.6)	13 (38.2)	10 (26.3)
PD	2 (6.1)	2 (6.3)	7 (20.6)	3 (7.9)
Not evaluable	1 (3.0)	4 (12.5)	2 (5.9)	0
Confirmed DCR,* % (95% CI)	90.9 (75.7–98.1)	81.3 (63.6–92.8)	73.5 (55.6–87.1)	92.1 (78.6–98.3)
Median DOR, months (95% CI)	8.6 (4.2–11.5)	NR (3.0–NR)	18.2 (4.2–NR)	13.3 (6.1–NR)
Median time to response, months (range)	1.4 (1.1–4.4)	1.4 (1.2–2.8)	1.4 (1.3–5.8)	2.1 (1.4–4.2)

1L, first-line; 2L, second-line; 3L, third-line; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TV, tisotumab vedotin.
* Defined as confirmed CR or PR ≥ 4 weeks after first CR/PR and SD ≥ 5 weeks after first dose.

3.4. AESIs

For TV AESIs, any-grade ocular AEs were observed in 66.7%, 69.7%, 54.3%, and 78.9% of patients in arms D, E, F, and H, respectively (grade 3: 9.1%, 9.1%, 2.9%, and 10.5%; no grade ≥ 4), with median time to onset of 34, 24, 12, and 35 days, respectively (**Tables S3 and S4**). The most common ocular AEs were dry eye and conjunctivitis. Ocular AEs fully resolved/partially resolved or improved in 50.0%/36.4%, 39.1%/56.5%, 63.2%/36.8%, and 33.3%/53.3% of patients with events in arms D, E, F and H, with median time to resolution of 21, 16, 22, and 34 days, respectively.

Any-grade peripheral neuropathy AEs occurred in 60.6%, 54.5%, 40.0%, and 65.8% (grade 3: 12.1%, 3.0%, 2.9%, and 5.3%) in arms D, E, F, and H, respectively; no grade ≥ 4 events were reported (**Tables S3 and S4**). Sensory neuropathy was the most common peripheral neuropathy AE in all arms (42.4%, 39.4%, 25.7%, and 55.3% in arms D, E, F, and H, respectively); peripheral motor neuropathy was reported in seven patients (18.4%) in arm H (grade 1: $n = 3$; grade 2: n = 3; grade 3: $n = 1$) and in ≤ 2 patients each in arms D, E, and F (all grade 1/2). Median time to onset of peripheral neuropathy events was 40, 86, 105, and 67 days in arms D, E, F, and H, respectively. Peripheral neuropathy fully resolved/partially resolved or improved in 10.0%/45.0%, 50.0%/11.1%, 0%/43.0%, and 8.0%/40.0% of patients with events in arms D, E, F, and H, respectively, with median time to resolution of 13, 78, 89, and 26 days, respectively.

Any-grade bleeding AEs were observed in 57.6% of patients in arm D, 66.7% in arm E, 68.6% in arm F, and 60.5% in arm H (grade 3: 6.1%, 3.0%, 5.7%, and 7.9%, respectively), with median time to onset of 9, 8, 10, and 12 days in arms D–F and H (**Tables S3 and S4**). The most common bleeding AEs were epistaxis, vaginal hemorrhage, and hematuria. Bleeding AEs fully resolved/partially resolved or improved in 53.0%/37.0%, 55.0%/18.2%, 79.2%/13.0%, and 65.2%/26.1% of patients with events in each arm; median time to resolution was 12, 44, 7, and 17 days, respectively. Grade 4 bleeding events related to any trial treatment occurred in one patient (2.9%) in arm F (hematuria [TV-related] and hemorrhagic cystitis [TV-related]) and two patients (5.3%) in arm H (arterial hemorrhage [TV-related]; gastric hemorrhage [TV- and bevacizumab-related]). One patient (3.0%) in arm E experienced a grade 5 bleeding AE (disseminated intravascular coagulation [TV- and pembrolizumab-related]). Grade 4/5 AEs related to any study treatment are presented in **Table S5**.

Drug-related severe hepatic disorders, which are considered AESIs for pembrolizumab, were reported in one patient each in arms E, F, and H (3.0%, 2.9%, and 2.6%, respectively).

3.5. Subsequent systemic therapy

Subsequent systemic therapy after discontinuation is presented in Table 4 (arm D, $n = 22$; arm E, $n = 17$; arm F, $n = 18$; arm H, $n = 20$). Across all arms, the most commonly reported poststudy treatments were chemotherapy (43.9%), immunotherapy (16.6%), bevacizumab (12.2%), an investigational agent (3.6%), a small molecule or tyrosine kinase inhibitor (3.6%), and an antibody–drug conjugate (2.9%).

4. Discussion

With follow-up durations among the longest reported in r/mCC, [4,12] this updated analysis of the innovaTV 205/ENGOT-cx8/GOG-3024 study showed meaningful long-term clinical benefit with TV and carboplatin or pembrolizumab doublets in patients with r/mCC in the 1L and 2L/3L treatment settings. At >5 years of follow-up, this analysis confirmed the sustained therapeutic effect of TV combinations. Responses were maintained or improved in dose expansion arms D–F compared with previous 2-year analysis [11]; ORRs in the current analysis (54.5%, 40.6%, and 35.3% in arms D, E, and F, respectively) were consistent with those in the previous report, [11] and two PRs deepened to CRs with 1L TV + pembrolizumab in arm E. Median DOR remained unchanged since the prior report in arm D (8.6 months) and improved from 14.1 months to 18.2 months in arm F; median DOR was still NR in arm E. Median OS exceeded 2 years with 1L TV + carboplatin, ≥ 2.5 years with 1L TV + pembrolizumab, and ≥ 1 year with 2L/3L TV + pembrolizumab. To our knowledge, TV is the only antibody–drug conjugate to demonstrate compatibility with platinum-based chemotherapy agents, highlighting an encouraging novel treatment combination, particularly in the 2L/3L r/mCC setting.

Building on the feasibility of TV doublets, the combination of 1L TV + carboplatin + pembrolizumab ± bevacizumab was evaluated in arm H. This combination showed encouraging antitumor activity and a toxicity profile consistent with the known profile of each individual agent in patients with r/mCC in the 1L setting, despite the relative intensity associated with a triplet/quadruplet treatment regimen. The confirmed ORR was 65.8%, including seven (18.4%) patients with CRs, with a median DOR of 13.3 months. Survival outcomes were encouraging as median OS exceeded 2 years, with 2-year PFS and OS rates of 29.3% and 62.4%, respectively.

Although head-to-head clinical trial data are not available and cross-trial comparisons must be made with caution (particularly when comparing single-arm studies with randomized controlled studies), the efficacy observed with TV combinations compare favorably with historical data in patients with r/mCC. In pembrolizumab-containing TV combination arms (arms E, F, and H), a decline in Kaplan–Meier-estimated PFS was observed during the first year of treatment, then appeared to plateau at approximately 30%–40% for 1L therapy and 15% for 2L/3L therapy after the 12- to 16-month period (**Fig. S3B, Fig. S4B,** Fig. 2C). A similar result was observed in the KEYNOTE-826 trial of pembrolizumab plus chemotherapy in patients with persistent r/mCC, with

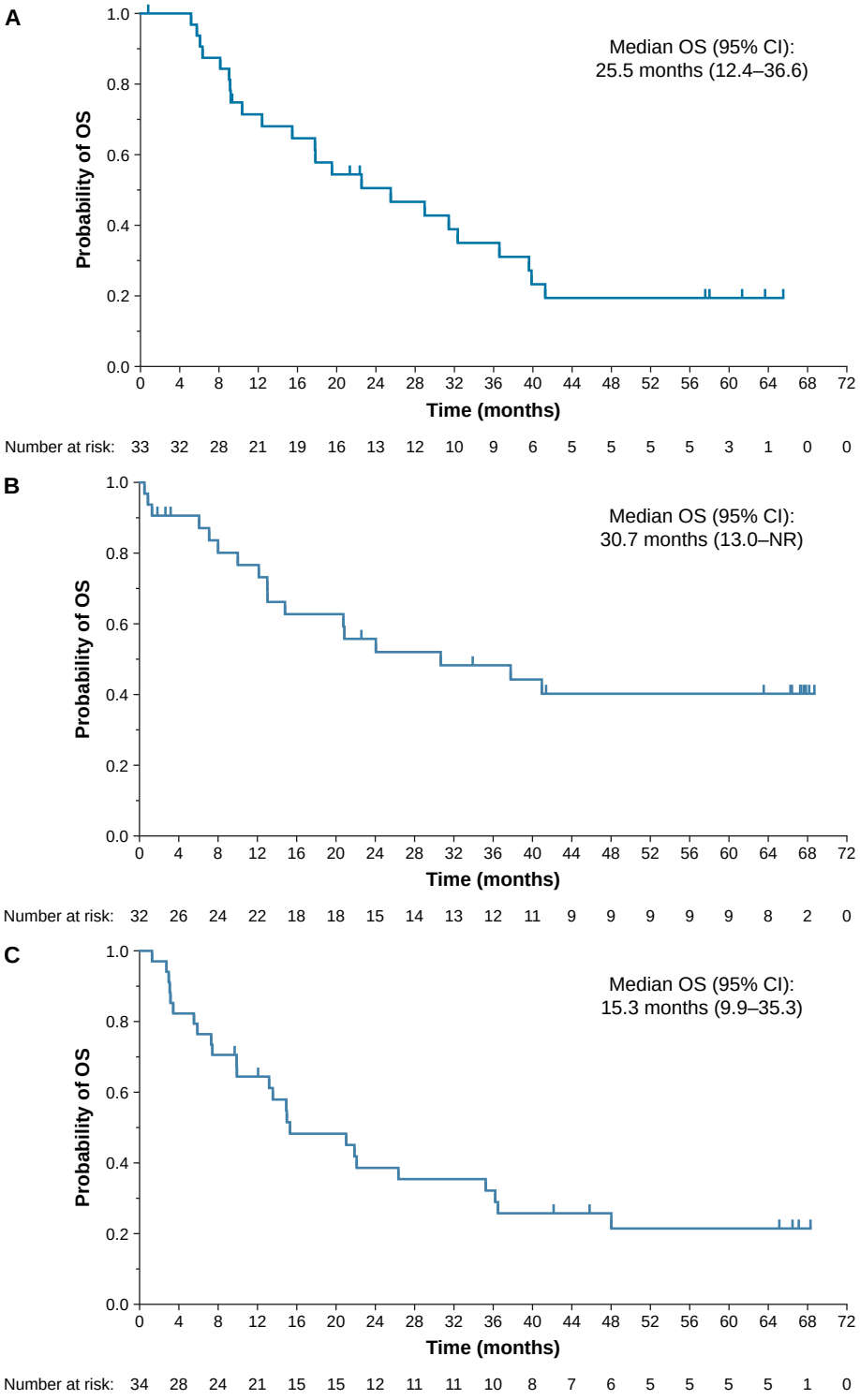

Fig. 1. Kaplan-Meier estimated OS in patients with r/mCC treated with (**A**) 1L TV + carboplatin (arm D), (**B**) 1L TV + pembrolizumab (arm E), and (**C**) 2L/3L TV + pembrolizumab (arm F). 1L, first-line; 2L, second-line; 3L, third-line; mOS, median overall survival; NR, not reached; OS, overall survival; r/mCC, recurrent or metastatic cervical cancer; TV, tisotumab vedotin.

PFS stabilizing at approximately 35%–40% after the first year of treatment, regardless of PD-L1 status [4,13]. Overall, the proportion of long-term responders observed with TV-pembrolizumab combinations (30%–40% in 1L and 15%–20% in the later lines) is encouraging. In addition, median OS observed with TV combinations in this proof-of-concept study (25.5, 30.7, 15.3, and 28.0 months in arms D, E, F, and H, respectively) aligns with or exceeds historical phase 3 data from other standard-of-care regimens in the 1L setting (17.5 months with paclitaxel/cisplatin + bevacizumab in the GOG-240 trial [14] and 24.4 months with pembrolizumab/platinum chemotherapy and bevacizumab in KEYNOTE-826) [4,13]. Further, ORRs and DORs observed with TV-based triplet/quadruplet therapy in arm H are comparable to those observed in the intention-to-treat population of KEYNOTE-826 (ORR, 65.8% and 65.9%; median DOR, 13.3 months and 18.0 months,

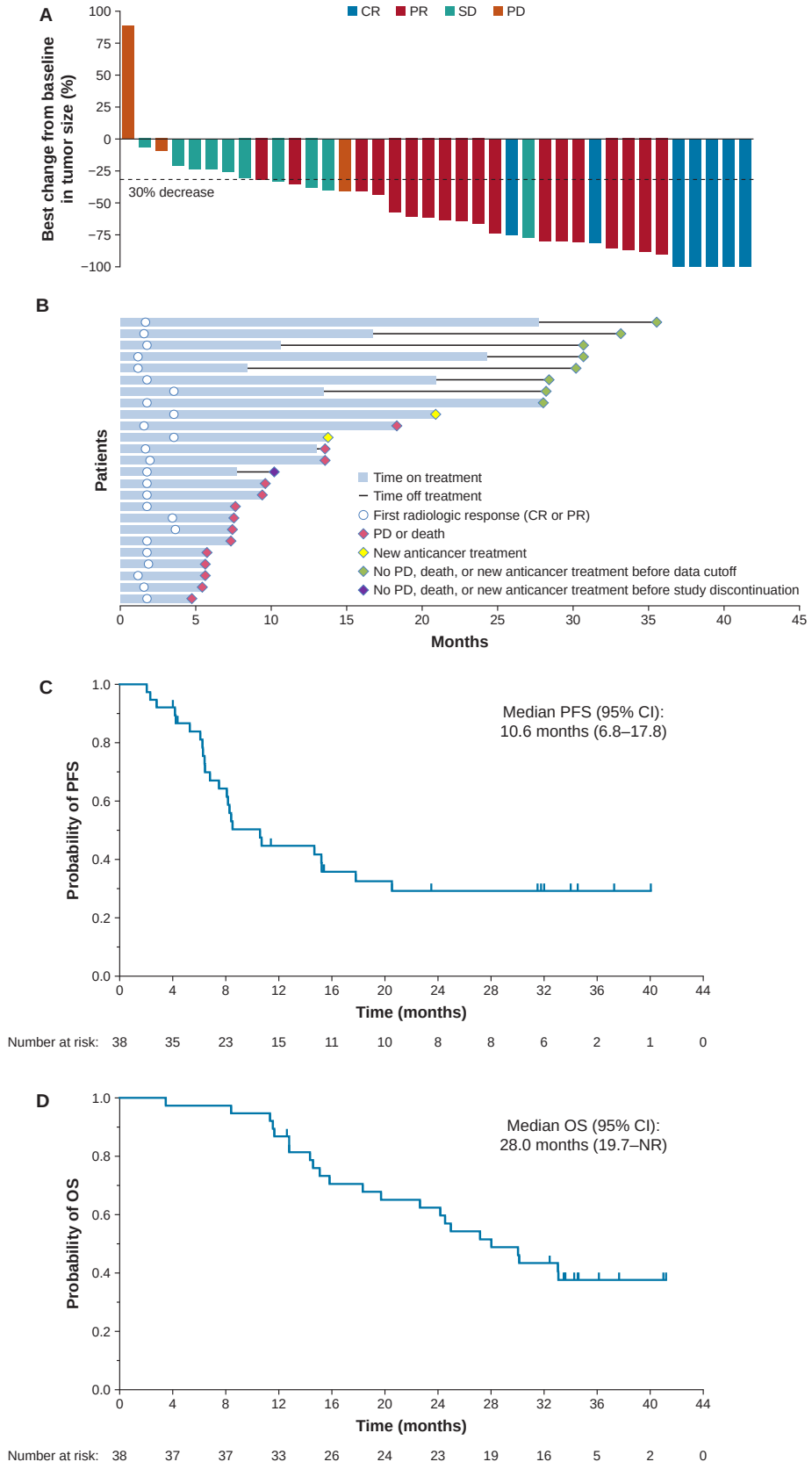

Fig. 2. Efficacy outcomes for patients with r/mCC treated with 1L TV + carboplatin + pembrolizumab ± bevacizumab (arm H). (**A**) Waterfall plot of best overall response (based on RECIST v1.1 and reduction in target lesion size). (**B**) Swimlane plot of TTR and DOR among confirmed responders per RECIST v1.1. Kaplan-Meier–estimated (**C**) PFS and (**D**) OS. 1L, first-line; CI, confidence interval; CR, complete response; DOR, duration of response; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; r/mCC, recurrent or metastatic cervical cancer; SD, stable disease; TTR, time to response; TV, tisotumab vedotin.

Table 3
Summary of TEAEs in TV dose expansion arms D–F and H of innovaTV 205/ENGOT-cx8/GOG-3024.

Parameters, n (%)	1L TV + carboplatin (arm D; $n = 33$)	1L TV + pembrolizumab (arm E; n = 33)	2L/3L TV + pembrolizumab (arm F; $n = 35$)	1L TV + carboplatin + pembrolizumab ± bevacizumab (arm H; $n = 38$)
Any TEAEs	33 (100)	33 (100)	35 (100)	38 (100)
Grade ≥ 3 TEAEs	26 (78.8)	22 (66.7)	26 (74.3)	35 (92.1)
Serious TEAEs	14 (42.4)	13 (39.4)	20 (57.1)	25 (65.8)
AESIs for TV				
Ocular AEs	22 (66.7)	23 (69.7)	19 (54.3)	30 (78.9)
Peripheral neuropathy	20 (60.6)	18 (54.5)	14 (40.0)	25 (65.8)
Bleeding AEs	19 (57.6)	22 (66.7)	24 (68.6)	23 (60.5)
TEAEs leading to discontinuation of any treatment	14 (42.4)	10 (30.3)	13 (37.1)	27 (71.1)
TEAEs leading to TV discontinuation	8 (24.2)	8 (24.2)	12 (34.3)	21 (55.3)
TEAEs leading to TV interruption	27 (81.8)	15 (45.5)	21 (60.0)	34 (89.5)
TEAEs leading to TV dose reduction	14 (42.4)	11 (33.3)	9 (25.7)	20 (52.6)
Fatal TEAEs	0	3 (9.1)	1 (2.9)	1 (2.6)
Fatal TEAEs related to any treatment	0	1 (3.0)	0	1 (2.6)
Any-grade AEs observed in ≥ 20% of patients in any arm				
Nausea	26 (78.8)	15 (45.5)	16 (45.7)	24 (63.2)
Diarrhea	15 (45.5)	18 (54.5)	19 (54.3)	24 (63.2)
Anemia	19 (57.6)	11 (33.3)	19 (54.3)	22 (57.9)
Alopecia	18 (54.5)	20 (60.6)	11 (31.4)	20 (52.6)
Fatigue	19 (57.6)	11 (33.3)	15 (42.9)	23 (60.5)
Epistaxis	15 (45.5)	16 (48.5)	13 (37.1)	18 (47.4)
Dry eye	15 (45.5)	14 (42.4)	9 (25.7)	21 (55.3)
Peripheral sensory neuropathy	14 (42.4)	13 (39.4)	9 (25.7)	21 (55.3)
Constipation	13 (39.4)	13 (39.4)	12 (34.3)	17 (44.7)
Decreased appetite	12 (36.4)	12 (36.4)	11 (31.4)	15 (39.5)
Conjunctivitis	11 (33.3)	16 (48.5)	9 (25.7)	12 (31.6)
Vomiting	10 (30.3)	7 (21.2)	11 (31.4)	13 (34.2)
Arthralgia	7 (21.2)	10 (30.3)	9 (25.7)	11 (28.9)
Pyrexia	5 (15.2)	11 (33.3)	7 (20.0)	10 (26.3)
Urinary tract infection	6 (18.2)	6 (18.2)	9 (25.7)	12 (31.6)
Weight decreased	6 (18.2)	7 (21.2)	6 (17.1)	13 (34.2)
Neutropenia	15 (45.5)	4 (12.1)	3 (8.6)	9 (23.7)
Hypokalemia	6 (18.2)	3 (9.1)	9 (25.7)	12 (31.6)
Abdominal pain	7 (21.2)	9 (27.3)	6 (17.1)	7 (18.4)
Myalgia	6 (18.2)	7 (21.2)	7 (20.0)	7 (18.4)
Asthenia	3 (9.1)	8 (24.2)	9 (25.7)	6 (15.8)
Hypomagnesemia	8 (24.2)	2 (6.1)	10 (28.6)	9 (23.7)
Dyspnea	8 (24.2)	4 (12.1)	7 (20.0)	6 (15.8)
Headache	3 (9.1)	6 (18.2)	5 (14.3)	10 (26.3)
White blood cell count decreased	7 (21.2)	4 (12.1)	5 (14.3)	1 (2.6)
Pruritus	2 (6.1)	11 (33.3)	4 (11.4)	4 (10.5)
ALT increased	4 (12.1)	7 (21.2)	6 (17.1)	5 (13.2)
Dysgeusia	8 (24.2)	2 (6.1)	4 (11.4)	6 (15.8)
AST increased	2 (6.1)	5 (15.2)	8 (22.9)	4 (10.5)
Cough	1 (3.0)	6 (18.2)	5 (14.3)	8 (21.1)
Thrombocytopenia	7 (21.2)	0	0	12 (31.6)
Platelet count decreased	8 (24.2)	2 (6.1)	2 (5.7)	7 (18.4)
Hot flush	5 (15.2)	7 (21.2)	3 (8.6)	2 (5.3)
Hypothyroidism	0	4 (12.1)	4 (11.4)	10 (26.3)
Dry mouth	2 (6.1)	7 (21.2)	2 (5.7)	3 (7.9)
Blood alkaline phosphatase increased	1 (3.0)	4 (12.1)	7 (20.0)	1 (2.6)
Nasal congestion	2 (6.1)	7 (21.2)	1 (2.9)	2 (5.3)
GGT increased	1 (3.0)	3 (9.1)	7 (20.0)	0

1L, first-line; 2L, second-line; 3L, third-line; AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TEAE, treatment-emergent adverse event; TV, tisotumab vedotin.

respectively), regardless of PD-L1 status (combined positive score ≥ 1% in 84.2% vs 88.6% in arm H and KEYNOTE-826, respectively) [13]. The TV-pembrolizumab combination is now a recommended 2L+ therapy in the United States for patients with PD-L1–positive r/mCC [3].

Patients were eligible to participate in the innovaTV 205/ENGOT-cx8/GOG-3024 study regardless of PD-L1 status or TF expression, and an analysis of the effectiveness of TV combination therapy by PD-L1 expression status may be of clinical interest. However, most patients enrolled in arms D, E, F, and H had PD-L1–positive disease at screening (combined positive score > 1%: 78.8% [26/33], 90.9% [30/33], 65.7% [23/35], and 84.2% [32/38], respectively) (Table 1), which limits interpretation of efficacy in PD-L1–negative disease.

This extended follow-up of ≥ 5.5 years confirmed the previously reported safety profile of TV-based doublets, [11] with nonoverlapping toxicity of the individual agents inclusive of AESIs (ocular AEs, peripheral neuropathy, and bleeding). The AEs observed with TV triplet/quadruplet therapy (arm H) were generally consistent with those seen with the TV doublets, although there were higher rates of grade ≥ 3 treatment-emergent adverse events (TEAEs) and TEAEs leading to TV discontinuation, which may be expected given the more intensive triplet/quadruplet regimen and longer treatment exposure (median number of treatment cycles in arm H: 12.5 cycles vs 6.0, 7.0, and 6.0 cycles in arms D–F, respectively). The eye care mitigation plan was implemented across all arms. Ocular AEs resolved or improved in 86%, 96%, 100%, and 87% of patients in arms D, E, F, and

Table 4
Subsequent systemic anticancer therapy for patients in TV dose expansion arms D–F and H of innovaTV 205/ENGOT-cx8/GOG-3024.

Patients, n (%)	1L TV + carboplatin (arm D; n = 33)	1L TV + pembrolizumab (arm E; n = 33)	2L/3L TV + pembrolizumab (arm F; n = 35)	1L TV + carboplatin + pembrolizumab ± bevacizumab (arm H; n = 38)
Patients receiving ≥ 1 subsequent line of systemic treatment*	22 (66.7)	17 (51.5)	18 (51.4)	20 (52.6)
1 line	13 (39.4)	11 (33.3)	8 (22.9)	9 (23.7)
2 lines	4 (12.1)	1 (3.0)	8 (22.9)	11 (28.9)
3 lines	5 (15.2)	2 (6.1)	0	0
>3 lines	0	3 (9.1)	2 (5.7)	0
Subsequent systemic treatment				
Chemotherapy	14 (42.4)	17 (51.5)	17 (48.6)	13 (34.2)
Immunotherapy	14 (42.4)	1 (3.0)	3 (8.6)	5 (13.2)
Bevacizumab	7 (21.2)	6 (18.2)	1 (2.9)	3 (7.9)
Investigational agent	3 (9.1)	2 (6.1)	0	0
Small molecule/TKI	2 (6.1)	0	1 (2.9)	2 (5.3)
Antibody–drug conjugate	0	1 (3.0)	0	3 (7.9)

1L, first-line; 2L, second-line; 3L, third-line; TKI, tyrosine kinase inhibitor; TV, tisotumab vedotin.
* Median follow-up (range) was 58.0 months (0.8–65.5 months) in arm D, 66.4 months (0.5+ to 68.7 months) in arm E, 66.5 months (1.3+ to 68.3 months) in arm F, and 34.5 months (3.5+ to 41.2 months) in arm H.

H, respectively, and most ongoing ocular events at last follow-up were grade 1/2. An ongoing study (NCT06952660) will further characterize the incidence, severity, and timing (including onset and follow-up after the end of the administration of TV) of ocular AEs associated with TV in r/mCC.

The treatment discontinuation rate due to AEs for TV triplet/quadruplet therapy was 55.3% and appeared to be driven primarily by peripheral neuropathy (**Fig. S5D**). The rate and severity of peripheral neuropathy observed with TV triplet/quadruplet therapy in arm H (65.8% any-grade; 5.3% grade 3; no grade ≥ 4) were in line with those observed with 1L TV + carboplatin in arm D (60.6% any-grade; 12.1% grade 3; no grade ≥ 4).

Historical safety data from the pembrolizumab plus chemotherapy (± bevacizumab) arm of KEYNOTE-826 in patients with r/mCC [4] may provide context for arm H of the innovaTV 205/ENGOT-cx8/GOG-3024 study, although cross-trial comparisons should be interpreted with caution. Grade ≥ 3 TEAEs occurred in 92.1% of patients in arm H of the current study and 81.8% of patients in the pembrolizumab plus chemotherapy (± bevacizumab) arm of KEYNOTE-826 ($n = 307$), respectively. The most common treatment-related grade ≥ 3 TEAEs (occurring in ≥ 10% of patients in either study) were largely hematologic (arm H/KEYNOTE-826: anemia [39.5%/24.8%], neutropenia [23.7%/25.1%], thrombocytopenia [15.8%/6.8%], and fatigue [13.2%/2.6%]).

The median number of treatment cycles with the TV combinations ranged from six to 12.5 cycles; however, some patients received prolonged treatment (up to 89 cycles of TV in the TV-pembrolizumab doublet arms and 33 cycles of TV in the triplet/quadruplet arm). In arm H, the median duration of TV exposure was 6.6 months (range: 1.0–27.0), and patients received a median of 12.5 cycles of any combination of the regimen components, which is in line with exposure data observed in the pembrolizumab plus chemotherapy (± bevacizumab) arm of KEYNOTE-826 (median duration of treatment 10.0 months [range: 0–26.9] and median of 14 administrations in all treated patients) [4]. Continuation of the remaining regimen components when one drug was discontinued in innovaTV 205/ENGOT-cx8/GOG-3024 suggests a potential role for maintenance therapy, particularly with pembrolizumab and bevacizumab, following more intensive therapy in patients with r/mCC. Furthermore, more than half of patients across treatment arms received subsequent systemic anticancer therapies.

5. Conclusion

In the innovaTV 205/ENGOT-cx8/GOG-3024 dose-expansion arms D–F, treatment with TV combined with carboplatin or pembrolizumab demonstrated meaningful long-term benefit in patients with r/mCC across 1L and 2L+. At 4 to 5 years of follow-up, ORR and PFS outcomes remained consistent with prior analysis, and OS results were encouraging, with a portion of patients remaining progression-free at the end of follow-up. For patients in dose-expansion arm H, TV in combination with carboplatin and pembrolizumab with or without bevacizumab was feasible as an intensive triplet/quadruplet regimen and showed robust antitumor activity in the 1L r/mCC setting. Overall, safety outcomes were consistent with the known profile of the individual agents and toxicities were as expected. Taken together, these data suggest that TV is a versatile combination partner with standard-of-care regimens in r/mCC.

Data sharing statement

De-identified 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 is provided via publicly accessible study registries/databases as required by law. For more information, please contact clinicaltrials@genmab.com.

CRediT authorship contribution statement

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Declaration of competing interest

E Van Nieuwenhuysen: Consulting or advisory role: AstraZeneca, Eisai, Oncoinvent, Merck Serono, MSD, Regeneron, and Verastem; travel, accommodations, or expenses: AstraZeneca, GlaxoSmithKline, and MSD.

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LM Randall: Honoraria: BluPrint Oncology, Curio Science, and PER; consulting or advisory role: AADi, AstraZeneca, Caris Life Sciences, Clovis Oncology, Eisai, Genentech/Roche, GOG Foundation, ImmunoGen, Merck, Mersana, Myriad Genetics, Novocure, On Target Laboratories, Rubius Therapeutics, and Seagen; speaker bureau: AstraZeneca and Genmab/Seagen; research funding (institution): Acrivon Therapeutics, Adaptimmune, Akeso Biopharma, GEICO, GOG Foundation, Karyopharm Therapeutics, Merck, Mersana, Regeneron, and Zentalis; travel, accommodations, or expenses: AstraZeneca, Genmab, GOG Foundation, and Seagen.

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Appendix A. Supplementary data

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