

ORIGINAL ARTICLE

Tisotumab Vedotin as Second- or Third-Line Therapy for Recurrent Cervical Cancer

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ABSTRACT

BACKGROUND

Recurrent cervical cancer is a life-threatening disease, with limited treatment options available when disease progression occurs after first-line combination therapy.

METHODS

We conducted a phase 3, multinational, open-label trial of tisotumab vedotin as second- or third-line therapy in patients with recurrent or metastatic cervical cancer. Patients were randomly assigned, in a 1:1 ratio, to receive tisotumab vedotin monotherapy (2.0 mg per kilogram of body weight every 3 weeks) or the investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed). The primary end point was overall survival.

RESULTS

A total of 502 patients underwent randomization (253 were assigned to the tisotumab vedotin group and 249 to the chemotherapy group); the groups were similar with respect to demographic and disease characteristics. The median overall survival was significantly longer in the tisotumab vedotin group than in the chemotherapy group (11.5 months [95% confidence interval {CI}, 9.8 to 14.9] vs. 9.5 months [95% CI, 7.9 to 10.7]), results that represented a 30% lower risk of death with tisotumab vedotin than with chemotherapy (hazard ratio, 0.70; 95% CI, 0.54 to 0.89; two-sided $P=0.004$). The median progression-free survival was 4.2 months (95% CI, 4.0 to 4.4) with tisotumab vedotin and 2.9 months (95% CI, 2.6 to 3.1) with chemotherapy (hazard ratio, 0.67; 95% CI, 0.54 to 0.82; two-sided $P<0.001$). The confirmed objective response rate was 17.8% in the tisotumab vedotin group and 5.2% in the chemotherapy group (odds ratio, 4.0; 95% CI, 2.1 to 7.6; two-sided $P<0.001$). A total of 98.4% of patients in the tisotumab vedotin group and 99.2% in the chemotherapy group had at least one adverse event that occurred during the treatment period (defined as the period from day 1 of dose 1 until 30 days after the last dose); grade 3 or greater events occurred in 52.0% and 62.3%, respectively. A total of 14.8% of patients stopped tisotumab vedotin treatment because of toxic effects.

CONCLUSIONS

In patients with recurrent cervical cancer, second- or third-line treatment with tisotumab vedotin resulted in significantly greater efficacy than chemotherapy. (Funded by Genmab and Seagen [acquired by Pfizer]; innovaTV 301 ClinicalTrials.gov number, NCT04697628.)

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*A list of all innovaTV 301/ENGOT-cx12/GOG-3057 collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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THE PROGNOSIS FOR PATIENTS WITH cervical cancer is poor, with 5-year overall survival less than 19% among patients with distant disease.^{1,2} Recurrent cervical cancer remains a deadly disease despite positive results of recent clinical trials that incorporated immunotherapy into treatment algorithms.^{3,5} Anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) therapy (pembrolizumab or atezolizumab) in combination with the previous standard of care — a doublet of platinum and paclitaxel with or without bevacizumab — has shown an overall survival benefit in two phase 3 studies.^{3,5} Cemiplimab monotherapy has also shown an overall survival benefit superior to that with chemotherapy for second-line or later treatment of recurrent cervical cancer, although patients who had previously received PD-1 or PD-L1 therapy were excluded.⁴ Despite these advances, patient outcomes remain poor and additional treatment options are needed.

Tisotumab vedotin is an investigational antibody–drug conjugate composed of a tissue factor–directed human monoclonal antibody covalently linked to the microtubule-disrupting agent monomethyl auristatin E. Tissue factor is elevated in several solid tumors, including recurrent cervical cancer.^{6–9} Tisotumab vedotin showed encouraging and durable responses as a second-line and third-line treatment in patients with recurrent cervical cancer in a phase 2 trial (innovaTV 204/ENGOT-cx6/GOG-3023),⁸ which led to its accelerated approval in the United States. In addition, tisotumab vedotin in combination with the checkpoint inhibitor pembrolizumab has shown encouraging antitumor activity in patients with recurrent cervical cancer who have not previously received treatment and in patients with previously treated recurrent cervical cancer who have not previously received immunotherapy.¹⁰ Here we present the results of a prespecified interim analysis of the phase 3 innovaTV 301/ENGOT-cx12/GOG-3057 trial of tisotumab vedotin as compared with the investigator’s choice of chemotherapy in patients with recurrent cervical cancer after first-line systemic therapy.

METHODS

TRIAL OVERSIGHT

The trial received approval from the independent institutional review board or ethics committee at

each site and was conducted in accordance with the ethics principles of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Council for Harmonisation), applicable regulatory requirements, and the policy of the trial sponsors regarding bioethics and human biologic samples, according to the European Network of Gynaecological Oncological Trial groups–Gynecologic Oncology Group Model C.¹¹ All patients provided written informed consent before entry into the trial. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The first author wrote the first draft of the manuscript, which was critically reviewed and revised by all the authors. An employee of Pfizer provided medical writing and editorial support with an earlier version of the manuscript, in accordance with Good Publication Practices guidelines.

PATIENTS

Patients were eligible if they had recurrent or metastatic cervical cancer with squamous-cell, adenocarcinoma, or adenosquamous histologic features; an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (assessed on a 5-point scale, with higher scores indicating greater disability); measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,¹² as assessed by the investigator; and a life expectancy of 3 months or more. Patients were also required to have had disease progression during or after previous treatment with the standard-of-care systemic chemotherapy doublet — defined as paclitaxel plus cisplatin, carboplatin, or topotecan (also known as nogitecan hydrochloride) — along with bevacizumab and an anti-PD-1 or anti-PD-L1 agent, if both biologic agents were available and if patients were eligible to receive them. Amendment 3 of the protocol was implemented on April 6, 2022, to reflect the contemporary treatment landscape. (This amendment mandated previous treatment with an anti-PD-1 or anti-PD-L1 agent in patients who were eligible for and had access to these treatments after the approval of pembrolizumab in combination with chemotherapy for first-line treatment of recurrent cervical cancer; see the protocol for additional details.) Patients should have received one or two previous systemic therapies for recurrent or metastatic cervical can-



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cer, not including chemotherapy in an adjuvant, maintenance, or neoadjuvant context or in combination with radiation therapy.

Patients were excluded if the cancer had primary neuroendocrine, lymphoid, sarcomatoid, or other histologic features or if the patients had clinically significant bleeding or cardiovascular issues or risks (such as diffuse alveolar hemorrhage from vasculitis or ongoing major bleeding). The full patient eligibility criteria are provided in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org.

STUDY DESIGN

In this phase 3, multinational, open-label, randomized trial, patients were assigned, in a 1:1 ratio, to receive either tisotumab vedotin intravenously at a dose of 2.0 mg per kilogram of body weight every 3 weeks or the investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) intravenously (Fig. S1 in the Supplementary Appendix). Cross-over between treatment groups was not allowed. Randomization was stratified according to ECOG performance-status score (0 vs. 1), previous receipt of bevacizumab (yes vs. no), geographic region (United States, Europe, Asia, or other), and previous receipt of an anti-PD-1 or anti-PD-L1 agent (yes vs. no).

END POINTS AND ASSESSMENTS

The primary end point of this trial was overall survival. Key secondary end points were progression-free survival as assessed by the investigator (defined as the time from randomization to the first documentation by the investigator of disease progression according to RECIST, version 1.1, or to the date of death from any cause, whichever occurred first) and confirmed objective response rate as assessed by the investigator (defined as the percentage of patients with an investigator-confirmed complete response or partial response according to RECIST, version 1.1). Other secondary end points were the time to response, duration of response, safety, side-effect profile, and patient-reported outcomes. The percentage of patients with a complete response, partial response, or stable disease was also assessed; confirmation was required for complete and partial responses, and the minimum criterion for duration of stable disease was at least 5 weeks after randomization. Adverse events were graded ac-

ording to the Common Terminology Criteria for Adverse Events, version 5.0. All patients underwent a baseline ophthalmic examination, and patients who received tisotumab vedotin were referred to an eye specialist if new or worsening ocular symptoms developed (see the Supplementary Methods). Patient-reported outcomes were assessed with the use of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), the EORTC cervical cancer module, and the EuroQoL 5-Dimension 5-Level questionnaire. The mean change in the global health status–quality-of-life scores, assessed on the EORTC QLQ-C30, from baseline to cycle 5 (the median number of cycles of treatment received in the tisotumab vedotin group) is reported for both groups.

Imaging was performed every 6 weeks for the first 30 weeks and then every 12 weeks until the occurrence of radiographic evidence of disease progression according to RECIST, version 1.1, as documented by the investigator, or until the start of new anticancer treatment, withdrawal of consent, death, or the end of the trial, whichever occurred first. An independent data monitoring committee was formed to assess the safety of patients in the trial and to monitor the overall conduct of the clinical trial. The independent data monitoring committee also provided feedback with respect to efficacy at the planned interim efficacy analysis.

STATISTICAL ANALYSIS

We planned to enroll approximately 482 patients, and we calculated that occurrence of 336 total deaths would provide the trial with an overall power of 90%. A prespecified interim efficacy analysis was performed when approximately 75% of the total number of events (252 of 336 events) had occurred. A hierarchical sequential procedure was used to control the overall two-sided type I error at 5% for the statistical hypothesis regarding overall survival, progression-free survival, and confirmed objective response rate.¹³ The actual P value boundaries were calculated on the basis of the observed number of events with the use of the Lan–deMets spending function with an O'Brien–Fleming boundary for overall survival and the Lan–deMets spending function with a Pocock boundary for progression-free survival.¹⁴ P values reported for overall survival, pro-

gression-free survival, and objective response rate are two-sided. Stratified analyses of efficacy end points included adjustment for the prespecified stratification factors as recorded at randomization, with the exception of geographic region, in accordance with the statistical analysis plan.

The analysis of efficacy end points was performed in the intention-to-treat population. Overall survival and progression-free survival end points were estimated with the use of the Kaplan–Meier method, with 95% confidence intervals presented with the medians and hazard ratios, according to treatment group. A stratified Cox model was used to estimate hazard ratios and 95% confidence intervals. We examined the

proportional-hazards assumption for treatment groups using a plot of the log of the negative log of the Kaplan–Meier estimation of the survival function against the log of time according to treatment group and with the use of a plot of the Schoenfeld residuals over time. The 95% confidence intervals reported with the hazard ratios have not been adjusted for multiplicity and may not be used in place of hypothesis testing. We calculated overall survival by censoring survival time at the last date patients were known to be alive among patients who had not died at the time of the analysis. The safety analysis population included all patients who underwent randomization and received any amount of study

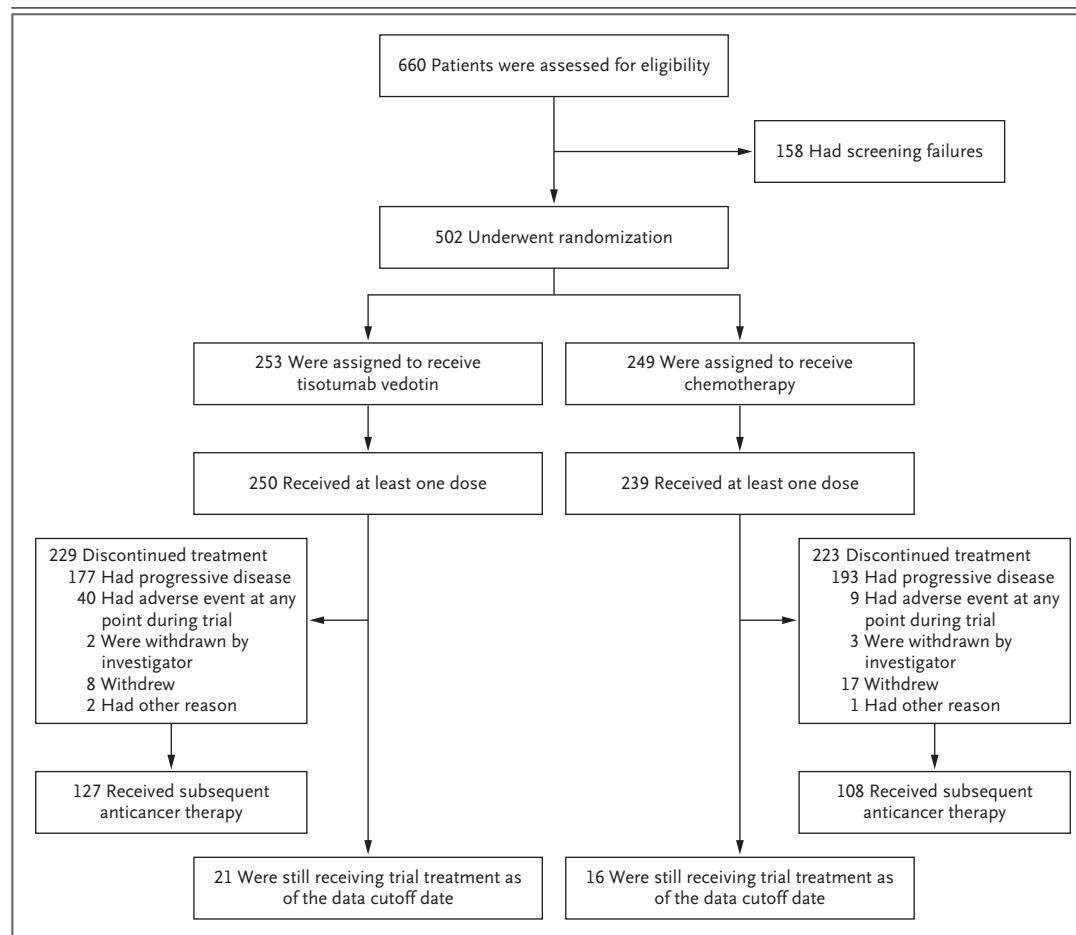


Figure 1. Screening, Randomization, and Treatment.

Patients were randomly assigned to receive either tisotumab vedotin or the investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed). The reasons for screening failures were eligibility criteria not met (135 patients), withdrawal of consent (14 patients), death (5 patients), investigator decision (2 patients), or other (2 patients). The 127 patients in the tisotumab vedotin group and the 108 patients in the chemotherapy group who received subsequent anticancer therapy were among the patients who discontinued treatment.

Characteristic	Tisotumab Vedotin (N=253)	Chemotherapy† (N=249)	All Patients (N=502)
Median age (range) — yr	51 (26–80)	50 (27–78)	50 (26–80)
Baseline ECOG performance-status score — no. (%)‡			
0	137 (54.2)	136 (54.6)	273 (54.4)
1	116 (45.8)	113 (45.4)	229 (45.6)
Geographic region — no. (%)			
United States	16 (6.3)	14 (5.6)	30 (6.0)
Europe	106 (41.9)	104 (41.8)	210 (41.8)
Asia	85 (33.6)	88 (35.3)	173 (34.5)
Other	46 (18.2)	43 (17.3)	89 (17.7)
No. of previous lines of systemic therapy for recurrent or metastatic disease — no. of patients (%)			
1	159 (62.8)	149 (59.8)	308 (61.4)
2	93 (36.8)	100 (40.2)	193 (38.4)
Unknown	1 (0.4)	0	1 (0.2)
Previous systemic therapy or radiation for cervical cancer — no. (%)	253 (100)	249 (100)	502 (100)
Previous receipt of bevacizumab — no. (%)	164 (64.8)	157 (63.1)	321 (63.9)
Previous receipt of anti-PD-1 or anti-PD-L1 agent — no. (%)	71 (28.1)	67 (26.9)	138 (27.5)
Race or ethnic group — no. (%)§			
White	122 (48.2)	122 (49.0)	244 (48.6)
Asian	90 (35.6)	90 (36.1)	180 (35.9)
American Indian or Alaska Native	7 (2.8)	7 (2.8)	14 (2.8)
Black	4 (1.6)	6 (2.4)	10 (2.0)
Other	2 (0.8)	1 (0.4)	3 (0.6)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)
Not reported	19 (7.5)	17 (6.8)	36 (7.2)
Unknown	8 (3.2)	6 (2.4)	14 (2.8)
Disease status at trial entry — no. (%)			
Pelvic recurrent only	27 (10.7)	24 (9.6)	51 (10.2)
Extrapelvic metastatic	226 (89.3)	225 (90.4)	451 (89.8)
Histologic feature — no. (%)			
Squamous-cell carcinoma	160 (63.2)	157 (63.1)	317 (63.1)
Adenocarcinoma	85 (33.6)	75 (30.1)	160 (31.9)
Adenosquamous carcinoma	8 (3.2)	17 (6.8)	25 (5.0)
Evaluable biopsy sample — no. (%)¶	210 (83.0)	194 (77.9)	404 (80.5)
Positive membrane tissue factor expression — no./total no. (%)	194/210 (92.4)	183/194 (94.3)	377/404 (93.3)

* PD-1 denotes programmed cell death protein 1, and PD-L1 programmed cell death ligand 1.

† Patients in this group received the investigator's choice of chemotherapy: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.

§ Race or ethnic group was reported by the patients. The race and ethnic categories presented are those that are included in the U.S. Census Bureau categories, along with an additional "Other" category.

¶ Data were not available for some patients owing to inadequate tissue quality or quantity.

|| Tissue factor expression is defined as a membrane tissue factor expression of 1% or more.

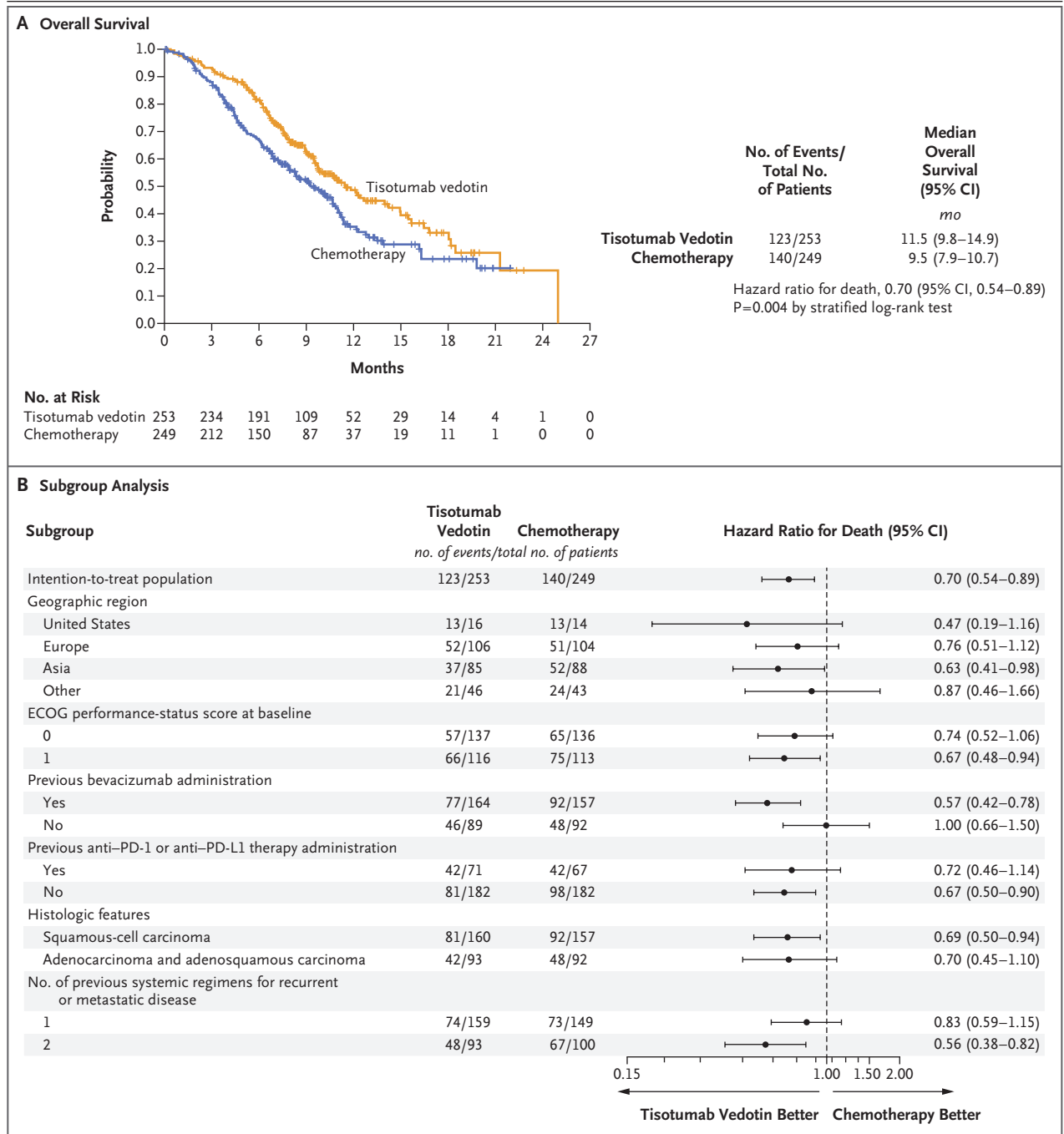
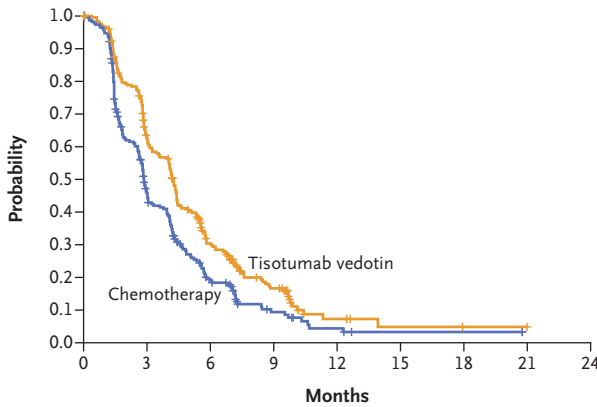


Figure 2. Overall Survival in the Total Population and in Key Subgroups.

The primary end point was overall survival, defined as the time from randomization to the date of death from any cause. The hazard ratio was computed from the stratified Cox proportional-hazards model with the use of stratification factors as recorded at randomization, excluding geographic region. Panel A shows the Kaplan–Meier estimates of overall survival according to treatment group. Tick marks indicate censored data. Panel B shows a forest plot of overall survival in prespecified subgroups. The hazard ratio of 1.0 is denoted by the dotted line. The threshold for statistical significance was 0.0226 (two-sided) on the basis of the actual number of deaths at the interim analysis according to the Lan–DeMets spending function with an O’Brien–Fleming boundary.¹⁴ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability. PD-1 denotes programmed cell death protein 1, and PD-L1, programmed cell death ligand 1.

A Progression-free Survival



	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI) <i>mo</i>
Tisotumab Vedotin	198/253	4.2 (4.0–4.4)
Chemotherapy	194/249	2.9 (2.6–3.1)

Hazard ratio for disease progression or death, 0.67 (95% CI, 0.54–0.82)
P<0.001 by stratified log-rank test

No. at Risk

	0	3	6	9	12	15	18	21	24
Tisotumab vedotin	253	148	62	25	5	2	1	0	0
Chemotherapy	249	96	34	11	4	1	1	0	0

B Subgroup Analysis

Subgroup	Tisotumab Vedotin <i>no. of events/total no. of patients</i>	Chemotherapy	Hazard Ratio for Disease Progression or Death (95% CI)
Intention-to-treat population	198/253	194/249	0.67 (0.54–0.82)
Geographic region			
United States	13/16	8/14	0.37 (0.12–1.10)
Europe	86/106	81/104	0.71 (0.51–0.97)
Asia	69/85	73/88	0.60 (0.43–0.85)
Other	30/46	32/43	0.76 (0.44–1.30)
ECOG performance-status score at baseline			
0	104/137	106/136	0.70 (0.53–0.92)
1	94/116	88/113	0.62 (0.46–0.84)
Previous bevacizumab administration			
Yes	130/164	122/157	0.59 (0.46–0.76)
No	68/89	72/92	0.83 (0.59–1.16)
Previous anti-PD-1 or anti-PD-L1 therapy administration			
Yes	53/71	50/67	0.66 (0.44–0.99)
No	145/182	144/182	0.67 (0.53–0.85)
Histologic features			
Squamous-cell carcinoma	124/160	122/157	0.71 (0.55–0.93)
Adenocarcinoma and adenosquamous carcinoma	74/93	72/92	0.63 (0.44–0.89)
No. of previous systemic regimens for recurrent or metastatic disease			
1	123/159	119/149	0.68 (0.52–0.88)
2	74/93	75/100	0.66 (0.47–0.92)

treatment. All adverse events were reported from trial day 1 of dose 1 (before the first dose of treatment) through the last treatment visit or until 30 days after the last treatment administration, whichever was later. The treatment period is defined as the period from day 1 of dose 1 until 30 days after the last dose.

RESULTS

PATIENTS

As of the data-cutoff date (July 24, 2023), a total of 502 patients were enrolled at 168 sites multi-nationally (in 27 countries across Europe, North America, Latin America, and Asia Pacific) and were

Figure 3 (facing page). Progression-free Survival in the Total Population and in Key Subgroups.

Progression-free survival as assessed by the investigator, a key secondary end point, was defined as the time from randomization to the first documentation by the investigator of disease progression according to Response Evaluation Criteria in Solid Tumors, version 1.1, or to the date of death from any cause, whichever occurred first. The hazard ratio was computed from the stratified Cox proportional-hazards model with the use of stratification factors as recorded at randomization, excluding geographic region. Differences in restricted mean survival time between the tisotumab vedotin group and the chemotherapy group were provided as an additional metric for subgroups that may show a plausible deviation in the proportional-hazards assumption (adenocarcinoma and adenosquamous carcinoma histologic features, ECOG score of 1, and one previous recurrent or metastatic systemic regimen, with the differences in restricted mean survival time being 1.2 months, 1.5 months, and 1.0 month, respectively). The restricted mean survival time was computed up to the minimum of the largest observed event time for the tisotumab vedotin group and for the chemotherapy group. Panel A shows the Kaplan–Meier estimates of progression-free survival as assessed by the investigator according to treatment group. Tick marks indicate censored data. Panel B shows a forest plot of progression-free survival as assessed by the investigator in prespecified subgroups. The hazard ratio of 1.0 is denoted by the dotted line. The threshold for statistical significance was 0.0453 (two-sided) on the basis of the actual number of progression-free survival events at the interim analysis according to Lan–DeMets spending function with a Pocock boundary.¹⁴

randomly assigned, in a 1:1 ratio, to the tisotumab vedotin group (253 patients) or the chemotherapy group (249 patients) (Fig. 1 and Fig. S1). A total of 250 patients in the tisotumab vedotin group and 239 patients in the chemotherapy group received at least one dose of trial treatment; 177 patients (70.0%) and 193 patients (77.5%), respectively, discontinued treatment owing to progressive disease. A total of 101 patients (39.9%) in the tisotumab vedotin group and 75 patients (30.1%) in the chemotherapy group remained in long-term follow-up at the time of data cutoff.

Baseline demographic and disease characteristics were generally similar in the two groups (Table 1 and Table S1). Enrolled patients were generally reflective of the population of patients with recurrent cervical cancer in regions around the world represented by the trial sites (Table S2). Black patients were underrepresented in the trial population. The median age was 50 years.

Overall, 63.9% of patients had previously received bevacizumab and 27.5% had previously received an anti-PD-1 or anti-PD-L1 agent. With respect to geographic region, 6.0% of patients lived in the United States, 41.8% lived in Europe, 34.5% lived in Asia, and 17.7% lived in other regions.

EFFICACY

At the planned interim analysis, overall survival was significantly longer in the tisotumab vedotin group than in the chemotherapy group. With a median follow-up time of 10.8 months (95% confidence interval [CI], 10.3 to 11.6) and with 263 deaths having occurred, the median overall survival was 11.5 months (95% CI, 9.8 to 14.9) in the tisotumab vedotin group and 9.5 months (95% CI, 7.9 to 10.7) in the chemotherapy group (Fig. 2A). This 2-month difference in median survival represents a 30% lower risk of death with tisotumab vedotin than with chemotherapy (hazard ratio, 0.70; 95% CI, 0.54 to 0.89; $P=0.004$ against a two-sided significance level of 0.0226). Overall survival at 12 months was 48.7% (95% CI, 41.0 to 55.8) and 35.3% (95% CI, 28.0 to 42.7) in the tisotumab vedotin group and the chemotherapy group, respectively. Overall survival in the prespecified subgroups is shown in Figure 2B.

The median progression-free survival as assessed by the investigator was longer in the tisotumab vedotin group than in the chemotherapy group — 4.2 months (95% CI, 4.0 to 4.4) and 2.9 months (95% CI, 2.6 to 3.1), respectively (Fig. 3A) — with a 33% lower risk of disease progression or death in the tisotumab vedotin group than in the chemotherapy group (hazard ratio, 0.67; 95% CI, 0.54 to 0.82; $P<0.001$ against a two-sided significance level of 0.0453). At 6 months, the progression-free survival was 30.4% (95% CI, 24.5 to 36.5) and 18.9% (95% CI, 13.8 to 24.7), respectively. Progression-free survival in the prespecified subgroups is shown in Figure 3B.

The confirmed objective response rate was significantly higher with tisotumab vedotin than with chemotherapy (17.8% [95% CI, 13.3 to 23.1] vs. 5.2% [95% CI, 2.8 to 8.8]; odds ratio, 4.0 [95% CI, 2.1 to 7.6]; $P<0.001$ against a two-sided significance level of 0.05) (Table S3 and Fig. S2). The percentage of patients with a confirmed complete or partial response or with stable disease lasting at least 5 weeks after randomization was 75.9% (95% CI, 70.1 to 81.0) in the tisotu-

mab vedotin group and 58.2% (95% CI, 51.8 to 64.4) in the chemotherapy group (Table S3). The median duration of response as assessed by the investigator was 5.3 months (95% CI, 4.2 to 8.3) among patients treated with tisotumab vedotin and 5.7 months (95% CI, 2.8 to not reached) among patients treated with chemotherapy; the median time to response was 1.6 months and 1.7 months, respectively.

In an exploratory analysis, expression of tissue factor was assessed with the use of tumor biopsy samples from 404 of the 502 patients (80.5%) (see the Supplementary Appendix). Of these patients, 377 (93.3%) had tumors that were positive for membrane tissue factor expression (Table 1). Among the patients in whom tissue factor expression was assessed, 374 could be evaluated for response according to RECIST, version 1.1. The distribution of tissue factor expression was similar among groups stratified according to confirmed best overall response (Fig. S3).

SAFETY

Most patients received the planned course of therapy, with a median relative dose intensity of 96.1% in the tisotumab vedotin group and 90.0% in the chemotherapy group (Table S4). The median duration of exposure was 3.7 months in the tisotumab vedotin group and 2.8 months in the chemotherapy group. Among patients who received at least one dose of trial medication, adverse events that occurred during the treatment period and resulted in treatment discontinuation occurred in 37 of 250 patients (14.8%) in the tisotumab vedotin group and in 9 of 239 patients (3.8%) in the chemotherapy group (Table S5). Treatment discontinuations in the tisotumab vedotin group were driven primarily by protocol-mandated dose modifications in response to ocular and peripheral neuropathy adverse events.

A total of 246 patients (98.4%) in the tisotumab vedotin group and 237 patients (99.2%) in the chemotherapy group had at least one adverse event that occurred during the treatment period; grade 3 or higher events occurred in 130 patients (52.0%) and 149 patients (62.3%), respectively (Table 2). The most common adverse events of any grade that occurred in either group during the treatment period were nausea (in 33.2% of the patients in the tisotumab vedotin group vs. 40.2% of the patients in the chemotherapy

group), conjunctivitis (in 31.2% vs. 0.4%), and anemia (in 23.2% vs. 52.3%). The most common grade 3 or higher adverse events that occurred in either group during the treatment period were anemia (in 8.4% in the tisotumab vedotin group vs. 27.6% in the chemotherapy group), urinary tract infection (in 4.4% vs. 7.1%), and neutropenia (in 3.6% vs. 13.4%). Treatment-related adverse events are listed in Table S6. Serious adverse events occurred during the treatment period in 82 patients (32.8%) and 94 patients (39.3%) in the tisotumab vedotin group and the chemotherapy group, respectively (Table S7). Fatal adverse events occurred in 4 patients in the tisotumab vedotin group and 5 patients in the chemotherapy group; two fatal events were considered to be related to tisotumab vedotin, and one fatal event to chemotherapy (Table S8).

Adverse events of special interest were prespecified and included ocular, peripheral neuropathy, and bleeding events (Table S9). Ocular events occurred in 132 patients (52.8%) in the tisotumab vedotin group and 15 patients (6.3%) in the chemotherapy group (grade ≥ 3 events occurred in 10 patients [4.0%] vs. 0 patients); peripheral neuropathy events occurred in 96 patients (38.4%) and 10 patients (4.2%), respectively (grade ≥ 3 events occurred in 14 patients [5.6%] vs. 1 patient [0.4%]); and bleeding events occurred in 105 patients (42.0%) and 34 patients (14.2%) (grade ≥ 3 events occurred in 6 patients [2.4%] vs. 7 patients [2.9%]). No grade 5 adverse events of special interest and no grade 4 ocular or peripheral neuropathy events were observed.

PATIENT-REPORTED OUTCOMES

At baseline, all patients enrolled in the trial completed the EORTC QLQ-C30 questionnaire. At cycle 5, of the patients who were alive and receiving trial treatment, 93.0% in the tisotumab vedotin group and 88.6% in the chemotherapy group completed the questionnaire. Quality of life was maintained in both groups from baseline to cycle 5, as measured by a change of less than 10 points on the QLQ-C30 global health status–quality-of-life scales (estimated mean change, -1.1 [95% CI, -4.3 to 2.1] in the tisotumab vedotin group and -5.0 [95% CI, -8.1 to -1.9] in the chemotherapy group) (Table S10); however, the chemotherapy group showed a trend toward declining quality of life. The per-

Table 2. Adverse Events That Occurred during the Treatment Period.*

Event	Tisotumab Vedotin (N = 250)		Chemotherapy† (N = 239)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of patients (percent)</i>			
Any event	246 (98.4)	130 (52.0)	237 (99.2)	149 (62.3)
Nausea	83 (33.2)	1 (0.4)	96 (40.2)	5 (2.1)
Conjunctivitis	78 (31.2)	0	1 (0.4)	0
Peripheral sensory neuropathy	71 (28.4)	7 (2.8)	6 (2.5)	0
Epistaxis	65 (26.0)	0	6 (2.5)	0
Constipation	62 (24.8)	3 (1.2)	39 (16.3)	0
Alopecia	61 (24.4)	0	7 (2.9)	0
Decreased appetite	59 (23.6)	2 (0.8)	42 (17.6)	1 (0.4)
Anemia	58 (23.2)	21 (8.4)	125 (52.3)	66 (27.6)
Diarrhea	54 (21.6)	4 (1.6)	36 (15.1)	3 (1.3)
Vomiting	44 (17.6)	4 (1.6)	44 (18.4)	3 (1.3)
Pyrexia	42 (16.8)	1 (0.4)	50 (20.9)	2 (0.8)
Asthenia	40 (16.0)	5 (2.0)	38 (15.9)	5 (2.1)
Keratitis	39 (15.6)	5 (2.0)	0	0
Abdominal pain	34 (13.6)	10 (4.0)	23 (9.6)	4 (1.7)
Dry eye	33 (13.2)	0	1 (0.4)	0
Urinary tract infection	33 (13.2)	11 (4.4)	38 (15.9)	17 (7.1)
Fatigue	32 (12.8)	9 (3.6)	39 (16.3)	10 (4.2)
Pruritus	25 (10.0)	1 (0.4)	7 (2.9)	0
Vaginal hemorrhage	25 (10.0)	3 (1.2)	13 (5.4)	1 (0.4)
Increased alanine aminotransferase	18 (7.2)	4 (1.6)	26 (10.9)	5 (2.1)
Increased aspartate aminotransferase	17 (6.8)	1 (0.4)	27 (11.3)	3 (1.3)
Neutropenia	17 (6.8)	9 (3.6)	54 (22.6)	32 (13.4)
Peripheral edema	9 (3.6)	0	30 (12.6)	5 (2.1)

* Included are adverse events that occurred in at least 10% of patients in either the tisotumab vedotin group or the chemotherapy group. Adverse events that led to death occurred in 4 patients (1.6%) in the tisotumab vedotin group and 5 patients (2.1%) in the chemotherapy group (Table S7).

† Patients in this group received the investigator's choice of chemotherapy: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.

centage of patients who reported an improvement in the QLQ-C30 global health status–quality-of-life scores of 10 points or more from baseline to cycle 5 was higher in the tisotumab vedotin group than in the chemotherapy group (13.9% vs. 3.4%).

DISCUSSION

In this phase 3, multinational trial involving patients with recurrent cervical cancer, tisotumab vedotin as second-line or third-line therapy resulted in significantly better overall survival outcomes

than the investigator's choice of chemotherapy, with a 30% lower risk of death and a median overall survival that was 2 months longer. The Kaplan–Meier plot in Figure 2A shows that the overall survival curves separated early and that the separation was maintained throughout the follow-up period. Progression-free survival and the objective response rate as assessed by the investigator, which were the key secondary efficacy end points, were also significantly better in patients treated with tisotumab vedotin than in patients treated with chemotherapy (hazard ratio, 0.67, and odds

ratio, 4.0, respectively). The demographic and disease characteristics of patients enrolled in the trial were similar in the two groups and representative of multiple geographic regions, with the majority of patients being from Europe (41.8%) and Asia (34.5%); Black patients were underrepresented according to epidemiologic data in the United States.² The median overall survival in the chemotherapy group (9.5 months) was higher than the historical values reported for second-line and later treatment of recurrent or metastatic cervical cancer.^{4,15,16}

Although the subgroup analyses were helpful for assessing consistency in the treatment effect in the intention-to-treat population, the results should be interpreted with caution and considered hypothesis-generating. Overall survival and progression-free survival trends in the prespecified subgroups resulted in confidence intervals that overlapped with those in the intention-to-treat population. To our knowledge, no biologic reason is known for the differing outcomes of subsequent therapy between patients who have received bevacizumab previously and those who have not.¹⁷ In a previous trial involving tisotumab vedotin (innovaTV 204), the subgroup of patients who had not received previous bevacizumab therapy had a higher objective response rate than patients who had received previous bevacizumab therapy.⁸ Given the evolving role of immunotherapy in earlier lines of treatment, our trial showed the benefit of tisotumab vedotin over chemotherapy in patients with recurrent cervical cancer regardless of previous receipt of an anti-PD-1 or anti-PD-L1 agent. Finally, tissue factor expression was similar in the two groups regardless of best overall response.

No new safety signals were reported for tisotumab vedotin in this trial. A total of 52.0% of patients in the tisotumab vedotin group and 62.3% in the chemotherapy group had grade 3 or higher adverse events that occurred during treatment. Moreover, 14.8% of patients in the tisotumab vedotin group discontinued therapy because of an adverse event. Ocular events reported in the study were mostly mild to moderate in sever-

ity, and most patients had achieved resolution or improvement at last follow-up (Table S11). Peripheral neuropathy is a known risk associated with monomethyl auristatin E–based antibody–drug conjugates,¹⁸ and protocol-specified dose modifications were used to manage these events. Most peripheral neuropathy events were low grade (grade 1 or 2) and sensory; nonetheless, patients should be monitored for these events. Bleeding was defined as an adverse event of special interest because tissue factor is involved in the blood coagulation cascade.¹⁹ The incidence of grade 3 or greater bleeding events was similar in the two treatment groups. Bleeding adverse events associated with tisotumab vedotin consisted mostly of grade 1 epistaxis; none of the patients discontinued treatment because of bleeding events. Adverse events of special interest were usually alleviated with dose modification and supportive care.

The innovaTV 301 trial showed that tisotumab vedotin resulted in significantly greater efficacy, including longer overall survival, than chemotherapy in patients with recurrent cervical cancer. Taken together, these data suggest that tisotumab vedotin may be a preferred second-line or third-line treatment option over chemotherapy for patients with recurrent cervical cancer.

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APPENDIX

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