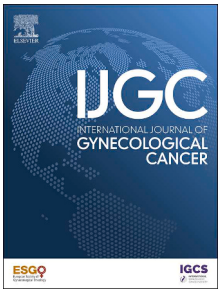
ORIGINAL RESEARCH

Patient-reported outcomes with tisotumab vedotin versus chemotherapy in patients with recurrent or metastatic cervical cancer: post hoc analyses from the open-label, randomized, phase 3 ENGOT-cx12/GOG-3057/innovaTV 301 trial



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ABSTRACT

Objective: In the phase 3, multi-national, open-label, randomized innovaTV 301/ENGOT-cx12/GOG-3057 trial (NCT04697628), tisotumab vedotin as second- or third-line therapy significantly improved survival versus chemotherapy in patients with recurrent or metastatic cervical cancer. We report a post hoc analysis of patient-reported outcomes on health-related quality of life from innovaTV 301.

Methods: Patients were randomized 1:1 to tisotumab vedotin or investigator's choice of chemotherapy. Pre-specified secondary end points included assessment of health-related quality of life using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module, and EuroQol 5-Dimension 5-Level. This post hoc analysis assessed change from baseline to cycle 13 using a mixed model for repeated measures and time to clinically meaningful deterioration ($\geq$10-point change) or disease progression/death using a Cox proportional hazards model in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module subscales, both adjusted for baseline factors. Proportion of patients with $\geq$10-point change from baseline in subscales were compared between arms.

Results: Mean compliance rates across patient-reported outcome instruments were high (>82%) from baseline to cycle 13. Mixed model for repeated measures analyses showed that patient-reported health-related quality of life, functioning, and symptoms were maintained with tisotumab vedotin therapy over the course of treatment, with no differences by arm. The proportion of patients reporting clinically meaningful ($\geq$10-point) improvement was greater with tisotumab vedotin versus chemotherapy for most

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tisotumab vedotin, a tissue factor–directed antibody–drug conjugate, is approved in multiple regions for the second- or third-line treatment of recurrent or metastatic cervical cancer based on significant improvement in overall survival over chemotherapy seen in the global, randomized, phase 3 innovaTV 301 study.

WHAT THIS STUDY ADDS

The results of this post hoc analysis of patient-reported outcomes from innovaTV 301 show that the use of tisotumab vedotin maintained health-related quality of life in patients with recurrent or metastatic cervical cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

These results reinforce the use of tisotumab vedotin as an appropriate therapeutic option for the second- or third-line treatment of recurrent or metastatic cervical cancer.

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European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module subscales. In patients who showed deterioration, time to clinically meaningful deterioration was slower with tisotumab vedotin versus chemotherapy for most European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module subscales, most notably nausea/vomiting, pain, dyspnea, insomnia, symptom experience, and lymphedema.

Conclusions: Results suggest tisotumab vedotin maintained health-related quality of life in patients with previously treated recurrent or metastatic cervical cancer and, together with clinical outcomes with innovaTV 301, support tisotumab vedotin as a treatment option in this setting.

Trial registration number: NCT04697628

Keywords:
Cervical Cancer; Tisotumab Vedotin; Patient-Reported Outcomes; Health-Related Quality of Life; Antibody—Drug Conjugate; Phase 3

ORIGINAL RESEARCH

INTRODUCTION

Patients with recurrent or metastatic cervical cancer have historically had a poor prognosis.[1,2] As recurrent or metastatic cervical cancer can be highly symptomatic, it is imperative that novel treatments not only improve survival but also do not pose an undue toxicity burden, so treatment will maintain or reduce symptom burden and, thus, the health-related quality of life (QoL) of patients with recurrent or metastatic cervical cancer.[3,4] Recent therapeutic advancements, including first-line treatment options (immunotherapy in combination with platinum-based chemotherapy with or without bevacizumab[5-8] and bevacizumab with chemotherapy[9]), have extended the overall survival of patients with recurrent or metastatic cervical cancer, with no negative effects on health-related QoL.[10,11]

Tisotumab vedotin, an antibody—drug conjugate consisting of a tissue factor—directed human monoclonal antibody with a monomethyl auristatin E payload,[12,13] is approved in multiple regions, including the USA, Japan, UK, and the European Union, for the second- or third-line treatment of recurrent or metastatic cervical cancer. These approvals were based on the significantly prolonged overall survival, with a hazard ratio (HR) of 0.70 (95% confidence interval [CI] 0.54 to 0.89; $p = .004$), reported in the open-label, randomized phase 3 innovaTV 301/ENGOT-cx12/GOG-3057 trial (NCT04697628) in patients with previously treated recurrent or metastatic cervical cancer randomized to either tisotumab vedotin or chemotherapy.[14,15] Based on these results, tisotumab vedotin was also recommended by the National Comprehensive Cancer Network as the preferred treatment for recurrent or metastatic cervical cancer in second and later lines of therapy.[16] Here, we report a post hoc analysis of patient-reported outcomes in the innovaTV 301 study to assess health-related QoL in the trial population.

METHODS

Study Design

The multi-national, open-label, randomized, phase 3 innovaTV 301 trial enrolled previously treated patients with recurrent or metastatic cervical cancer from February 2021 to May 2023. The study protocol was reviewed and approved by the WIRB-Copernicus Group, Inc. (WCG) Institutional Review Board (IRB; IRB tracking number 20203211; board action date December 17, 2020). Additional approval was obtained from institutional review boards or independent ethics committees at each participating site, as required. All patients provided written informed consent before entry into the trial.

Detailed eligibility criteria for innovaTV 301 were reported previously.[14] Patients were randomized 1:1 to tisotumab vedotin monotherapy (2.0 mg/kg every 3 weeks intravenously) or investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) intravenously. The primary end point was overall survival, and key secondary end points were investigator-assessed progression-free survival and objective response rate.[14] Other secondary end points included time to response, duration of response, safety, and patient-reported health-related QoL. The results of the pre-specified secondary end point of the assessment of health-related QoL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) were previously reported and evaluated patients from baseline to cycle 5.[14] This report includes additional patient-reported outcomes data and post hoc analyses.

Patient-Reported Outcome Assessments

Patients completed the EORTC QLQ-C30 (a cancer—specific health-related QoL questionnaire)[17] and EORTC QLQ-Cervical Cancer Module (CX24, a cervical cancer—specific health-related QoL questionnaire)[18] at baseline (within $\leq$7 days of cycle 1 day 1) and on day 1 of each subsequent cycle for $\leq$20 cycles.

The EORTC QLQ-C30 measures health-related QoL, function impairment, and symptom burden in patients with cancer generally.[17] It is a 30-item instrument evaluating 15 domains: global health status (GHS)/QoL, 5 functional scales (physical, role, emotional, cognitive, and social functioning), and 9 symptom scales or single items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).[17]

The EORTC QLQ-CX24 measures symptom burden and functioning in patients with cervical cancer.[18] It is a 24-item instrument incorporating 3 multi-item scales (symptom experience, body image, and sexual/vaginal function) and 6 single items (lymphoedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity, and sexual enjoyment).[18] All the EORTC QLQ-C30 and EORTC QLQ-CX24 scales and single-item measures range in score from 0 to 100, and a $\geq$10-point change from baseline in the respective score was considered clinically meaningful.[19]

The EuroQol 5-Dimension 5-Level (EQ-5D-5L) health questionnaire was also administered as a measure of health utility for cost-effectiveness analysis.[20] EQ-5D-5L questionnaires were administered at baseline (within $\leq$7 days of cycle 1 day 1) and on day 1 of each subsequent cycle for $\leq$20 cycles, as well as during

survival follow-up. EQ-5D-5L index scores range from −0.59 to 1, where 1 is the best possible health state. A ≥0.03-point change from baseline was considered clinically meaningful.[21]

Compliance and completion rates for each patient-reported outcome questionnaire were recorded at baseline and at every cycle. Compliance rate was defined as the number of completed questionnaires divided by the number of patients at each visit. Completion rate was defined as the number of completed questionnaires divided by the number of patients in the intention-to-treat population. The sexual enjoyment and sexual/vaginal functioning subscales of the EORTC QLQ-CX24 questionnaire were optional and were completed only by patients who reported sexual activity.

Statistical Analysis

Patient-reported outcomes were assessed in the patient-reported outcome full analysis set, which included all randomized patients who received any amount of study treatment and completed a patient-reported outcome assessment at baseline and ≥1 post-baseline assessment. Descriptive un-adjusted analyses of the EORTC QLQ-C30, EORTC QLQ-CX24, and EQ-5D-5L scales from start of treatment until end of follow-up were pre-specified in the statistical analysis plan. All other analyses reported here are post hoc analyses. Analyses were conducted using R version 4.4.1 software (R Foundation, Vienna, Austria).[22]

Patient-reported outcomes were assessed in the overall population and in a subset of patients who received only 1 prior systemic treatment (second-line treatment). This second-line treatment subgroup was analyzed for hypothesis generation to investigate whether patients were able to maintain QoL for potential subsequent lines of treatment.

Average health-related QoL at each cycle and change from baseline were assessed using a mixed model for repeated measures.[23] Time was included in the model as a categorical variable, and an un-structured variance—covariance matrix was used to model the covariance structure among each patient's repeated measures. Analyses were adjusted based on baseline Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), prior bevacizumab administration (yes vs no), and prior anti—programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) therapy (yes vs no), which were also used as stratification factors for the analyses of overall survival and progression-free survival.[14]

The proportion of patients with clinically meaningful (≥10-point) improvement from baseline in EORTC QLQ-C30 and EORTC QLQ-CX24 subscales was assessed at cycle 5, which was the median number of cycles received per patient in the tisotumab vedotin arm.[14]

A Cox proportional hazards model was used to analyze time to deterioration or disease progression/death in the EORTC subscales and to estimate HRs with corresponding 95% CIs, also adjusted for the above baseline characteristics. The proportion of patients whose symptoms or function improved versus remained stable or worsened (defined as a ≥10-point change from baseline in the respective health-related QoL score) was evaluated; analyses were descriptive and un-adjusted.

Data Availability Statement

Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data.

See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

RESULTS

At the data cut-off date (July 24, 2023), 502 patients were randomized and comprised the intention-to-treat population (as reported previously in the primary analysis).[14] Of these, 434 patients (231 in the tisotumab vedotin arm and 203 in the chemotherapy arm) received ≥1 dose of study treatment, completed the baseline patient-reported outcome assessment, and were included in the patient-reported outcome full analysis set (Fig. S1). The second-line treatment subgroup consisted of 65 patients who received tisotumab vedotin and 52 who received chemotherapy. Overall, median follow-up for patients in the patient-reported outcome full analysis set was 250 days; median time of instrument completion for patients who completed the EORTC QLQ-C30, EORTC QLQ-CX24, and EQ-5D-5L patient-reported outcome instruments was 146, 141, and 226 days, respectively.

Patient baseline and demographic characteristics were generally balanced across the treatment groups (Table S1). At baseline, participants in the tisotumab vedotin and chemotherapy arms had similar scores for EORTC QLQ-C30 mean GHS/QoL, function or symptom burden, most EORTC QLQ-CX24 symptom subscales, and EQ-5D-5L index scores (Table S2). The number of patients in the patient-reported outcome full analysis set who were alive and receiving study treatment decreased with each cycle, from 231 in the tisotumab vedotin arm and 203 in the chemotherapy arm at baseline to 15 and 12 patients, respectively, at cycle 13.

The mean compliance rate from baseline to cycle 13 was 87.9% (range 81.3-93.9) for the tisotumab vedotin arm and 83.9% (75.2-94.1) for the chemotherapy arm for EORTC QLQ-C30; 87.1% (75.0-92.0) and 82.4% (75.7-94.1), respectively, for the EORTC QLQ-CX24 main scales; and 87.9% (81.3-93.9) and 85.7% (75.7-94.1), respectively, for EQ-5D-5L (Table S3). For the optional EORTC QLQ-CX24 subscales (sexual enjoyment and sexual/vaginal functioning), compliance rates were low from baseline to cycle 13, with mean compliance rates of 9.8% (range 6.1-20.0) and 8.0% (0.0-14.3) and completion rates of 4.5% (0.4-20.0) and 3.1% (0.0-14.2) from baseline to cycle 13 in the tisotumab vedotin and chemotherapy arms, respectively. Compliance and completion rates in the second-line treatment subgroup are shown in Table S4.

Adjusted changes from baseline to cycle 13 in EORTC QLQ-C30 and EORTC QLQ-CX24 subscale scores assessed by a mixed model for repeated measures in the overall population are shown in Figures 1 and 2 and Figures S2 and S3. Across subscales, scores were generally maintained from baseline for both treatment arms.

In accordance with results in the overall population, EORTC QLQ-C30 and EORTC QLQ-CX24 subscale scores also generally remained stable (with <10-point change from baseline) in the second-line treatment subgroup (Figs. S4 and S5). Mixed model

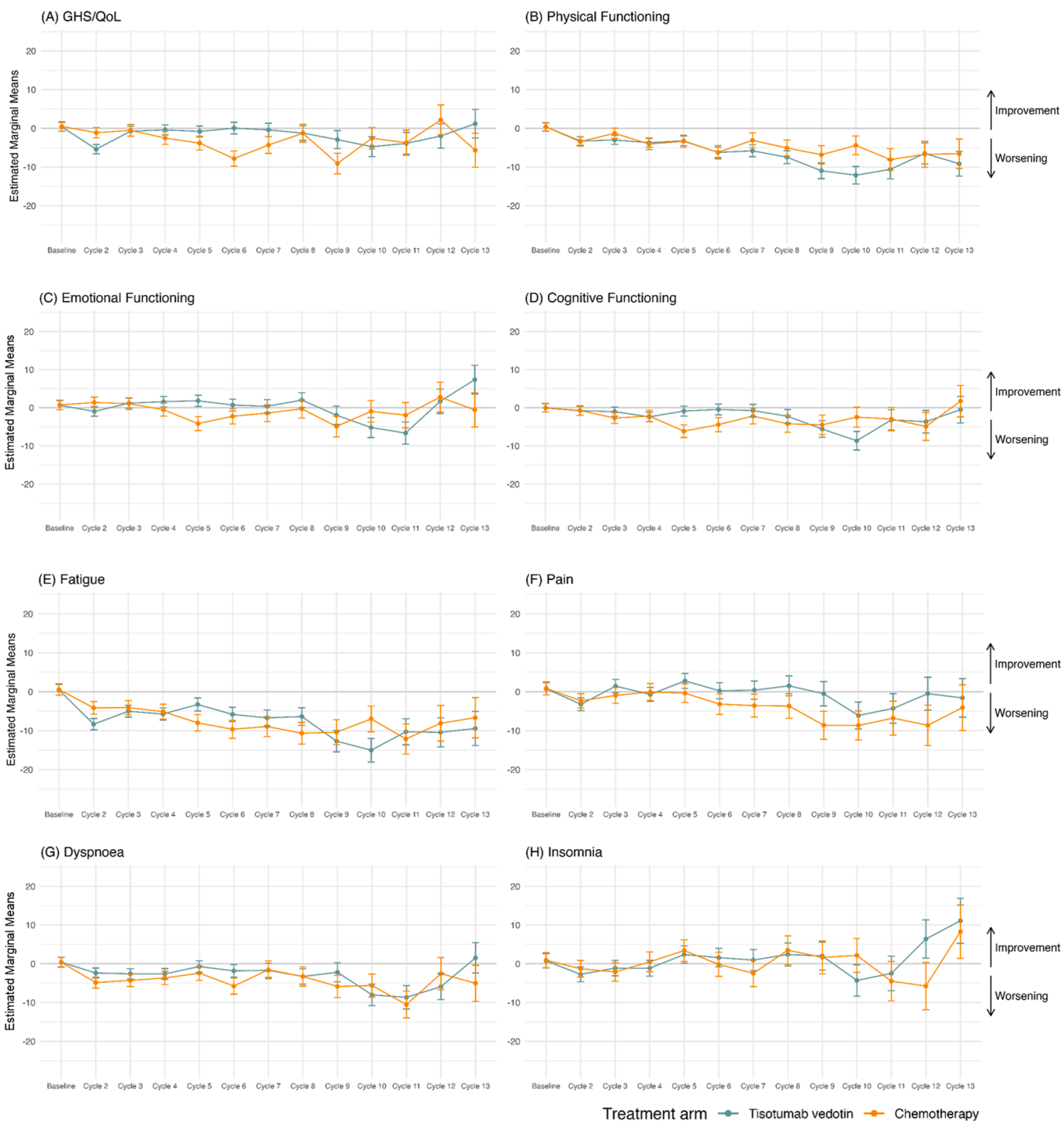

Figure 1 Estimated marginal means for change from baseline to cycle 13 by treatment arm in EORTC QLQ-C30 (**A**) GHS/QoL, (**B**) physical functioning, (**C**) emotional functioning, (**D**) cognitive functioning, (**E**) fatigue, (**F**) pain, (**G**) dyspnea, and (**H**) insomnia scores in the overall population. Estimated marginal means for change from baseline were assessed using a mixed model for repeated measures. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GHS/QoL, global health status/quality of life.

for repeated measures estimates of the adjusted change from baseline in EQ-5D-5L index scores by treatment arm in the overall population showed a slight deterioration (−0.10 for the tisotumab vedotin arm) from baseline to cycle 13 (Fig. S6A). EQ-5D-5L scores in the second-line treatment subgroup are shown in Figure S6B.

A slower time to clinically meaningful deterioration (≥10-point change) or disease progression/death was observed with tisotumab vedotin for all EORTC QLQ-C30 subscales across all cycles compared with chemotherapy, most notably nausea and vomiting (HR 1.43, 95% CI 1.16 to 1.76), pain (HR 1.25, 95% CI 1.02 to 1.55), dyspnea (HR 1.28, 95% CI 1.04 to 1.59) and insomnia (HR 1.29, 95% CI 1.04 to 1.60) (Fig. 3A). Trends in the second-line treatment subgroup were consistent with those seen in the overall population (Fig. S7A). For EORTC QLQ-CX24, a slower

Figure 2 Estimated marginal means for change from baseline to cycle 13 by treatment arm in EORTC QLQ-CX24 (**A**) symptom experience, (**B**) body image, (**C**) sexual/vaginal functioning, (**D**) lymphoedema, (**E**) menopausal symptoms and (**F**) sexual worry scores in the overall population. Estimated marginal means for change from baseline were assessed using a mixed model for repeated measures. EORTC QLQ-CX24, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module.

rate of clinically meaningful deterioration (≥10-point change) for symptom experience (HR 1.28, 95% CI 1.04 to 1.58), lymphoedema (HR 1.32, 95% CI 1.07 to 1.63), and menopausal symptoms (HR 1.23, 95% CI 1.00 to 1.52) was seen with tisotumab vedotin compared with chemotherapy (Fig. 3B). Trends in the second-line treatment subgroup were consistent with those seen in the overall population (Fig. S7B).

For most EORTC QLQ-C30 and EORTC QLQ-CX24 subscales, the proportion of patients with clinically meaningful (≥10-point) improvement was higher in the tisotumab vedotin versus the chemotherapy arm in the overall population at cycle 5 (Figs. 4 and 5). Subscales with a >5% difference in the proportion of patients with clinically meaningful (≥10-point) improvement between the tisotumab vedotin and chemotherapy arms were physical functioning (15.8% vs 10.3%), role functioning (24.8% vs 19.2%), emotional functioning (25.6% vs 12.8%), cognitive functioning (22.6% vs 9.0%), social functioning (24.8% vs 17.9%), fatigue (30.8% vs 24.4%), pain (33.8% vs 21.8%), insomnia (26.3% vs 15.4%), financial difficulties (21.1% vs 9.0%), symptom experience (12.3% vs 3.9%), lymphedema (12.3% vs 5.2%), peripheral neuropathy (13.1% vs 18.2%), menopausal symptoms (17.7% vs 23.4%), sexual activity (3.8% vs 9.1%), and sexual enjoyment (10.0% vs 25.0%). Proportions of patients with clinically meaningful improvements in the EORTC QLQ-C30 and EORTC QLQ-CX24 subscales in the second-line treatment subgroup are shown in Table S5.

DISCUSSION

Summary of Main Results

This post hoc analysis of patient-reported outcomes from innovaTV 301 showed that patient-reported health-related QoL was generally maintained in patients with recurrent or metastatic cervical cancer over the course of treatment for both treatment arms. Importantly, in the tisotumab vedotin arm, delayed time to

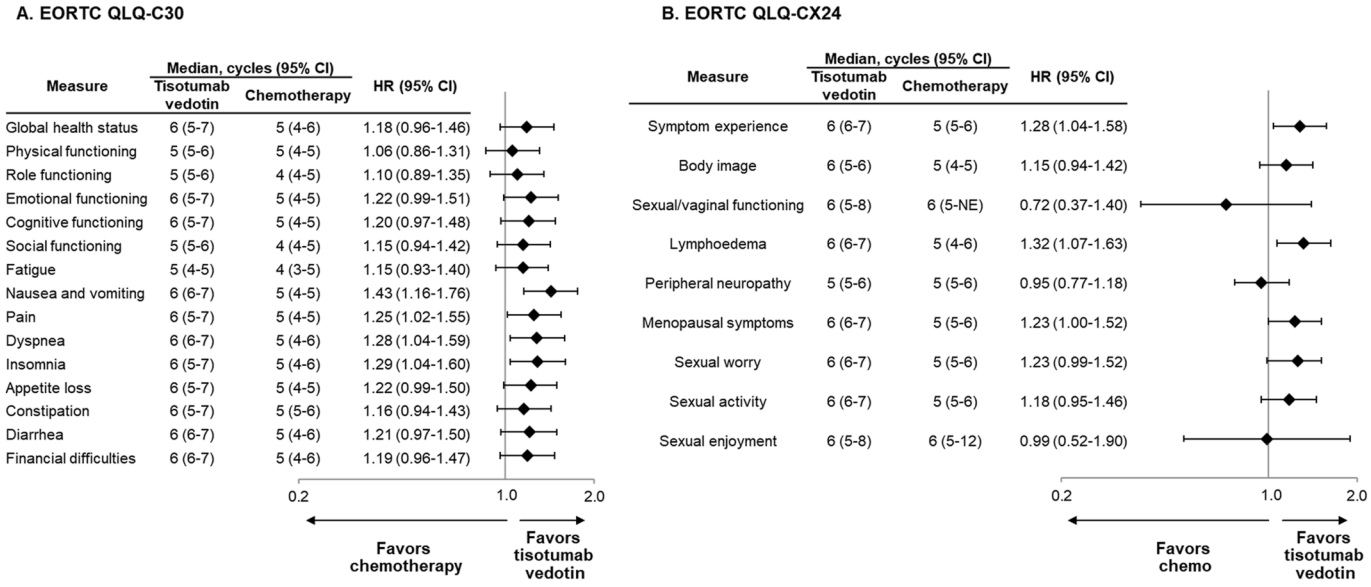

Figure 3 Time to clinically meaningful deterioration of (**A**) EORTC QLQ-C30 and (**B**) EORTC QLQ-CX24 subscales by treatment arm in the overall population. Clinically meaningful deterioration was defined as a ≥10-point change from baseline, progression or death. Chemo, chemotherapy; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EORTC QLQ-CX24, EORTC QLQ-Cervical Cancer Module; HR, hazard ratio; NE, not estimable.

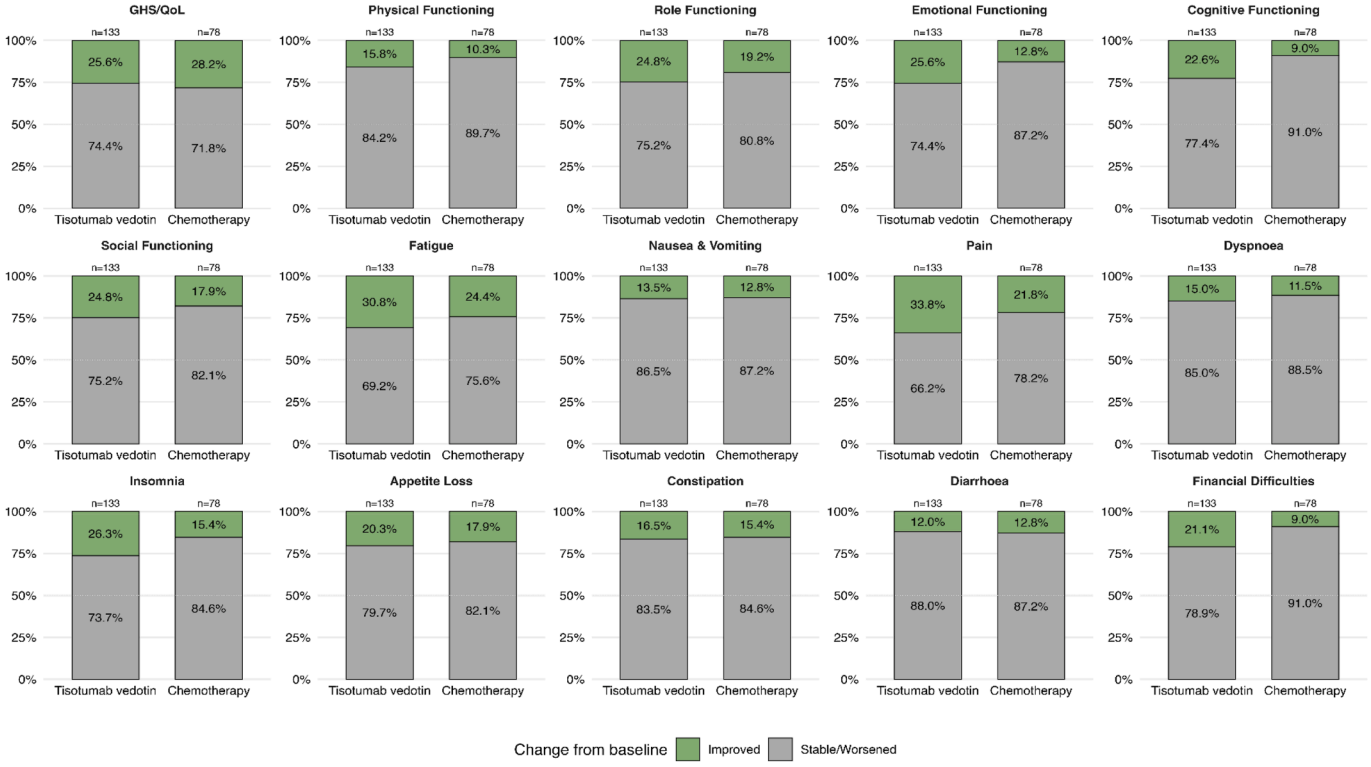

Figure 4 Proportion of patients with clinically meaningful improvement (≥10-point change) from baseline to cycle 5 in EORTC QLQ-C30 scores in the overall population. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GHS/QoL, global health status/quality of life.

clinically meaningful deterioration was seen for most EORTC QLQ-C30 and QLQ-CX24 subscales or disease progression/death versus chemotherapy, and a greater proportion of patients in the tisotumab vedotin arm showed clinically meaningful improvement in most subscale scores from baseline to cycle 13.

The exploratory second-line treatment subgroup showed a consistent trend with the full analysis set and a generally slower time to clinically meaningful deterioration with tisotumab vedotin versus chemotherapy across most EORTC QLQ-C30 and EORTC QLQ-CX24 subscales. These results suggest that health-related

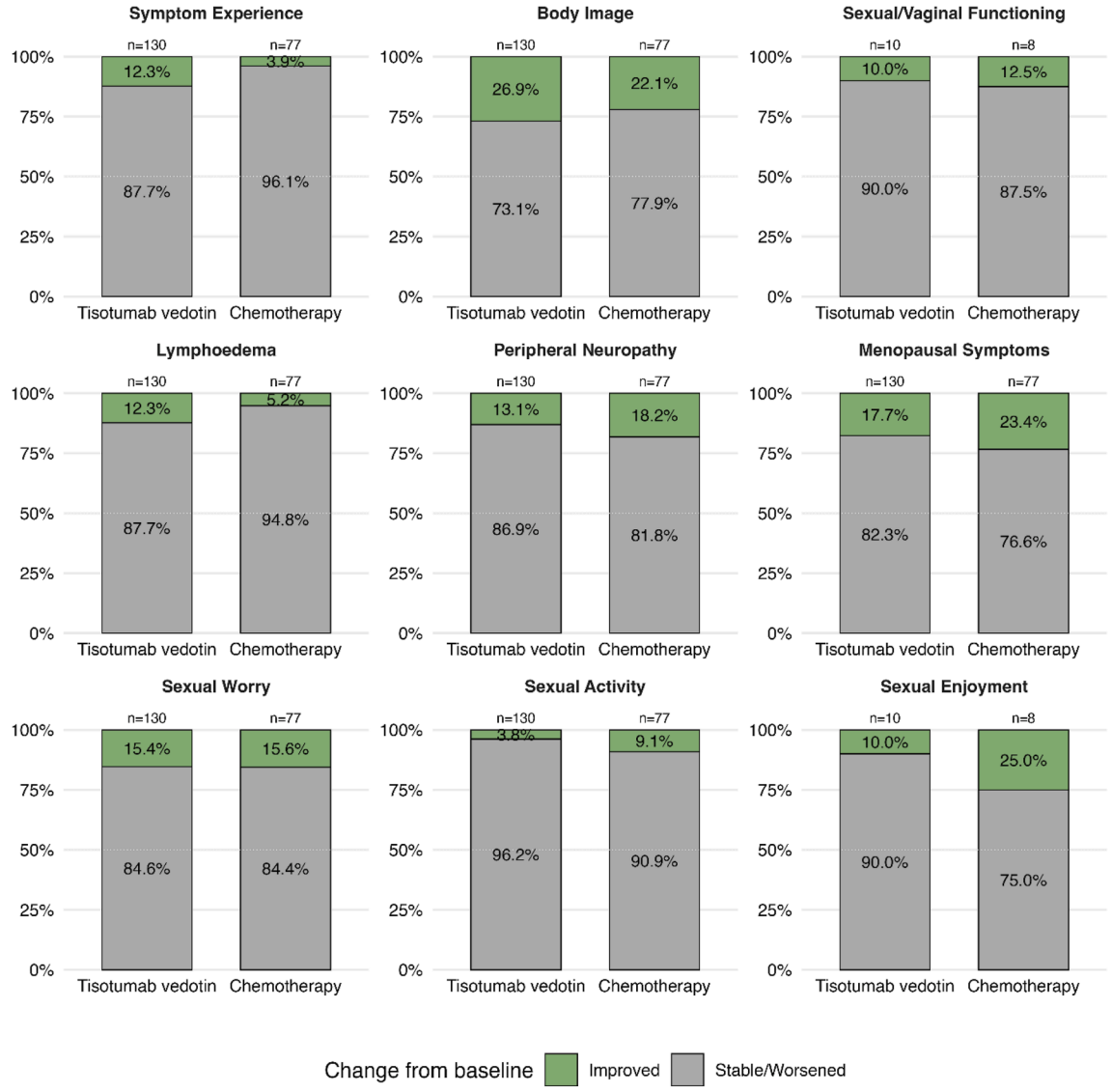

Figure 5 Proportion of patients with clinically meaningful improvement (≥10-point change) from baseline to cycle 5 in EORTC QLQ-CX24 scores in the overall population. EORTC QLQ-CX24, European Organisation for Research and Treatment of Cancer—Cervical Cancer Module.

QoL was maintained for these patients who may require and are eligible for additional treatment after second-line tisotumab vedotin.

Mixed model for repeated measures analyses of the changes from baseline to cycle 13 in EORTC QLQ-C30 and QLQ-CX24 subscales as well as the EQ-5D-5L index score were performed because they allow for reliable estimates of longitudinal data without requiring imputation and enable assessment across the course of treatment.[23] Analyses of time to clinically meaningful deterioration and mixed model for repeated measures analyses of changes from baseline in the EORTC QLQ-C30 and EORTC QLQ-CX24 subscales were adjusted for potential confounders, including ECOG performance status, prior bevacizumab administration, and prior anti—PD-1/PD-L1 therapy, which were also used as randomization stratification factors for the analyses of overall survival and progression-free survival.[14] These confounders were included as co-variates in the model, allowing evaluation of the impact of treatment adjusted for these characteristics.

The HR point estimate of <1 for time to clinically meaningful deterioration of peripheral neuropathy favored the chemotherapy arm over the tisotumab vedotin arm; however, this observation should be interpreted in the context of the favorable global QoL score observed with tisotumab vedotin. This finding reflects the well-documented adverse event of interest, peripheral neuropathy, associated with monomethyl auristatin—based antibody—drug conjugates.[24] Furthermore, the results for sexual/vaginal functioning and sexual enjoyment need to be interpreted with caution due to small sample sizes. To answer these questions in the EORTC QLQ-CX24, patients needed to have had sexual activity during the period being assessed. In this group of patients with cervical cancer, the numbers of patients who responded to these questions were low in both arms, with mean completion and compliance rates of <10%.

Results in the Context of Published Literature

Results from this analysis showed that the significant improvements seen in overall survival and progression-free survival with

tisotumab vedotin in innovaTV 301[14] were accompanied by maintenance of health-related QoL and cervical cancer symptom burden compared with chemotherapy. The patient population in this study included a substantial proportion of patients who received prior bevacizumab (65%) or prior immunotherapy (29%), reflecting the current treatment landscape in recurrent or metastatic cervical cancer and the evolving role of immunotherapy in earlier lines of treatment.

The patient-reported outcome tools used in this analysis, including the EORTC QLQ-C30 and QLQ-CX24 questionnaires and the EQ-5D-5L index score, align with those used in other phase 3 studies of biologic agents to assess health-related QoL in patients with recurrent or metastatic cervical cancer.[10,25] Although these instruments are not designed to assess ocular symptoms, it should be noted that ocular events, which are known to be associated with tisotumab vedotin treatment,[15] and associated monitoring, do not appear to have impacted overall patient-reported outcome scores with tisotumab vedotin versus chemotherapy in this analysis. This may be due to effective management of ocular symptoms and patient adaptation to potential side effects and warrants future study.

Strengths and Weaknesses

A major strength of this study is its design, with prospectively planned collection of patient-reported outcome data as prespecified secondary end points in the global, randomized, phase 3 innovaTV 301 study that were then further analyzed post hoc in this report. These analyses provide valuable insights into the health-related QoL and symptom burden of recurrent or metastatic cervical cancer in patients treated with tisotumab vedotin, with the use of both generic (EORTC QLQ-C30 and EQ-5D-5L) and cervical cancer–specific (EORTC QLQ-CX24) questionnaires. Additionally, the patient population in this trial reflects the modern treatment landscape, including a substantial proportion of patients who received prior bevacizumab and prior immunotherapy treatment.

Limitations of this analysis include its post hoc nature and the open-label design of the trial. The trial was statistically powered for its primary clinical end point and, therefore, the patient-reported outcome analyses reported here are not statistically powered. Additionally, the 10-point threshold used to represent clinically meaningful change from baseline in EORTC QLQ-C30 and QLQ-CX24 scores is based upon general guidance[19,26] and may not be appropriate for every subscale.[27] In the future, further analyses to identify potential correlation between clinical response and patient-reported outcomes could enhance understanding of tisotumab vedotin treatment benefit in recurrent or metastatic cervical cancer.

Implications for Practice and Future Research

With a rapidly evolving treatment landscape in recurrent or metastatic cervical cancer, multiple treatments have been approved recently and provide improved survival for patients, including tisotumab vedotin. In addition to prolonged survival and improved clinical outcomes, it is important to understand how these novel treatments affect patients' health-related QoL.

Results shown here suggest that health-related QoL was maintained throughout the treatment course with tisotumab vedotin and that QoL did not deteriorate with tisotumab vedotin versus chemotherapy, thus reinforcing the use of tisotumab vedotin as an appropriate therapeutic option for the second- or third-line treatment of recurrent or metastatic cervical cancer. Although results of the subgroup analyses suggest consistency between the second-line treatment subgroup and the overall patient-reported outcome-evaluable population, the results should be interpreted with caution and considered hypothesis-generating.

Importantly, these results are of relevance to gynecologic and medical oncologists as well as community practitioners as they bolster available data on the benefit-risk profile of tisotumab vedotin versus chemotherapy and can potentially aid in clinical decision-making.

CONCLUSIONS

Results from this analysis of patient-reported outcomes in the innovaTV 301 study suggest that the use of tisotumab vedotin maintained health-related QoL in patients with recurrent or metastatic cervical cancer. Together with the clinical outcomes from the innovaTV 301 study,[14] these results reinforced the use of tisotumab vedotin as an appropriate therapeutic option for the second- or third-line treatment of recurrent or metastatic cervical cancer.

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REFERENCES

1. Gennigens C, Jerusalem G, Lapaille L, et al. Recurrent or primary metastatic cervical cancer: current and future treatments. *ESMO Open*. 2022;7(5):100579. https://doi.org/10.1016/j.esmoop.2022.100579.
2. National Cancer Institute, Cancer Stat Facts. SEER. Accessed December 2025. https://seer.cancer.gov/statfacts/html/cervix.html.
3. Osann K, Hsieh S, Nelson EL, et al. Factors associated with poor quality of life among cervical cancer survivors: implications for clinical care and clinical trials. *Gynecol Oncol*. 2014;135(2):266–272. https://doi.org/10.1016/j.ygyno.2014.08.036.
4. Thapa N, Maharjan M, Xiong Y, et al. Impact of cervical cancer on quality of life of women in Hubei, China. *Sci Rep*. 2018;8(1):11993. https://doi.org/10.1038/s41598-018-30506-6.
5. Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med*. 2021;385(20):1856–1867. https://doi.org/10.1056/NEJMoa2112435.
6. Oaknin A, Gladieff L, Martínez-García J, et al. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. *Lancet*. 2024;403(10421):31–43. https://doi.org/10.1016/S0140-6736(23)02405-4.
7. Chuang LT, Temin S, Berek JS. Management and Care of Patients with Invasive Cervical Cancer Resource-Stratified Guideline Expert Panel. Management and care of patients with invasive cervical cancer: ASCO resource-stratified guideline rapid recommendation update. *JCO Glob Oncol*. 2022;8:e2200027. https://doi.org/10.1200/GO.22.00027.
8. Cibula D, Raspollini MR, Planchamp F, et al. ESGO/ESTRO/ESP guidelines for the management of patients with cervical cancer - update 2023. *Int J Gynecol Cancer*. 2023;33(5):649–666. https://doi.org/10.1136/ijgc-2023-004429.
9. Tewari KS, Sill MW, Long HJ, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med*. 2014;370(8):734–743. https://doi.org/10.1056/NEJMoa1309748.
10. Monk BJ, Tewari KS, Dubot C, et al. Health-related quality of life with pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2023;24(4):392–402. https://doi.org/10.1016/S1470-2045(23)00052-9.
11. Gladieff L, Martinez-Garcia J, Takekuma M, et al. 722P Long-term patient-reported outcomes (PROs) with atezolizumab (atezo) + bevacizumab (bev) and chemotherapy (CT) for metastatic, persistent or recurrent cervical cancer (R/M CC): BEATcc (ENGOT-Cx10/GEICO 68-C/JGOG1084/GOG-3030) randomised phase III trial. *Ann Oncol*. 2024;35:S552. https://doi.org/10.1016/j.annonc.2024.08.784.
12. Hong DS, Concin N, Vergote I, et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer. *Clin Cancer Res*. 2020;26(6):1220–1228. https://doi.org/10.1158/1078-0432.CCR-19-2962.
13. Breij ECW, de Goeij BECG, Verploegen S, et al. An antibody-drug conjugate that targets tissue factor exhibits potent therapeutic activity against a broad range of solid tumors. *Cancer Res*. 2014;74(4):1214–1226. https://doi.org/10.1158/0008-5472.CAN-13-2440.
14. Vergote I, González-Martín A, Fujiwara K, et al. Tisotumab vedotin as second- or third-line therapy for recurrent cervical cancer. *N Engl J Med*. 2024;391(1):44–55. https://doi.org/10.1056/NEJMoa2313811.
15. Tivdak (tisotumab vedotin). Prescribing Information. Pfizer Inc; 2026. Accessed 2026 August. https://webfiles.pfizer.com/Tivdak_Large_Print_Tabbed_PI.pdf.
16. Abu-Rustum NR, Yashar CM, Arend R, et al. NCCN Guidelines® insights: cervical cancer, version 1.2024. *J Natl Compr Cancer Netw*. 2023;21(12):1224–1233. https://doi.org/10.6004/jnccn.2023.0062.
17. Kaasa S, Bjordal K, Aaronson N, et al. The EORTC core Quality of Life Questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. *Eur J Cancer*. 1995;31A(13-14):2260–2263. https://doi.org/10.1016/0959-8049(95)00296-0.
18. Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer*. 2006;107(8):1812–1822. https://doi.org/10.1002/cncr.22217.
19. King MT. The interpretation of scores from the EORTC Quality of Life Questionnaire QLQ-C30. *Qual Life Res*. 1996;5(6):555–567. https://doi.org/10.1007/BF00439229.
20. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727–1736. https://doi.org/10.1007/s11136-011-9903-x.
21. Bourke S, Bennett B, Oluboyede Y, et al. Estimating the minimally important difference for the EQ-5D-5L and EORTC QLQ-C30 in cancer. *Health Qual Life Outcomes*. 2024;22(1):81. https://doi.org/10.1186/s12955-024-02294-3.
22. *R: a Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2024. https://www.r-project.org/.
23. Mallinckrodt CH, Sanger TM, Dubé S, et al. Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. *Biol Psychiatry*. 2003;53(8):754–760. https://doi.org/10.1016/S0006-3223(02)01867-X.
24. Best RL, LaPointe NE, Azarenko O, et al. Microtubule and tubulin binding and regulation of microtubule dynamics by the antibody drug conjugate (ADC) payload, monomethyl auristatin E (MMAE): mechanistic insights into MMAE ADC peripheral neuropathy. *Toxicol Appl Pharmacol*. 2021;421:115534. https://doi.org/10.1016/j.taap.2021.115534.
25. Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. *N Engl J Med*. 2022;386(6):544–555. https://doi.org/10.1056/NEJMoa2112187.
26. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139–144. https://doi.org/10.1200/JCO.1998.16.1.139.
27. Musoro JZ, Coens C, Sprangers MAG, et al. Minimally important differences for interpreting EORTC QLQ-C30 change scores over time: a synthesis across 21 clinical trials involving nine different cancer types. *Eur J Cancer*. 2023;188:171–182. https://doi.org/10.1016/j.ejca.2023.04.027.