Final survival analysis of topotecan and paclitaxel for first-line treatment of advanced cervical cancer: An NRG oncology randomized study☆

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HIGHLIGHTS

• Topotecan plus paclitaxel is not superior to cisplatin plus paclitaxel for recurrent/metastatic cervical cancer.
• Topotecan-paclitaxel plus bevacizumab is not superior to cisplatin-paclitaxel plus bevacizumab for cervical cancer.
• The non-platinum doublet, topotecan-paclitaxel, should not be routinely used for recurrent/metastatic cervical cancer.

ARTICLE INFO

ABSTRACT

Objective. To determine whether a non-platinum chemotherapy doublet improves overall survival (OS) among patients with recurrent/metastatic cervical carcinoma.

Methods. Gynecologic Oncology Group protocol 240 is a phase 3, randomized, open-label, clinical trial that studied the efficacy of paclitaxel 175 mg/m^2 plus topotecan 0.75 mg/m^2 days 1–3 ($n = 223$) vs cisplatin 50 mg/m^2 plus paclitaxel 135 or 175 mg/m^2 ($n = 229$), in 452 patients with recurrent/metastatic cervical cancer. Each chemotherapy doublet was also studied with and without bevacizumab (15 mg/kg). Cycles were repeated every 21 days until progression, unacceptable toxicity, or complete response. The primary endpoints were OS and the frequency and severity of adverse effects. We report the final analysis of OS.

Results. At the protocol-specified final analysis, median OS was 16.3 (cisplatin-paclitaxel backbone) and 13.8 months (topotecan-paclitaxel backbone) (HR 1.12; 95% CI, 0.91–1.38; $p = 0.28$). Median OS for cisplatin-paclitaxel and topotecan-paclitaxel was 15 vs 12 months, respectively (HR 1.10; 95% CI, 0.82–1.48; $p = 0.52$), and for cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-bevacizumab was 17.5 vs 16.2 months, respectively (HR 1.16; 95% CI, 0.86–1.56; $p = 0.34$). Among the 75% of patients in the study population previously exposed to platinum, median OS was 14.6 (cisplatin-paclitaxel backbone) vs 12.9 months (topotecan-paclitaxel backbone), respectively (HR 1.09; 95% CI, 0.86–1.38; $p = 0.48$). Post-progression survival was 7.9 (cisplatin-

paclitaxel backbone) vs 8.1 months (topotecan-paclitaxel backbone) (HR 0.95; 95% CI, 0.75–1.19). Grade 4 hematologic toxicity was similar between chemotherapy backbones.

Conclusions. Topotecan plus paclitaxel does not confer a survival benefit to women with recurrent/metastatic cervical cancer, even among platinum-exposed patients. Topotecan-paclitaxel should not be routinely recommended in this population. NCT00803062.

1. Introduction

Invasive cervical cancer continues to represent a major health problem among women in the United States and throughout the world. For 2023, the American Cancer Society estimates there will be 13,960 new cases and 4310 deaths [1] due to a disease that is preventable through screening via cervical cytology and/or high-risk human papillomavirus (HPV) DNA testing and vaccination using one of three available HPV vaccines developed using virus-like particle technology [2–4]. Globally, there are nearly 600,000 new cases annually, with over half of these patients dying each year [5]. With a median age of 54 years, many deaths occur among young women with small children at home and/or in the midst of professional careers [6].

While clinically early stage disease (i.e., FIGO stages IA_2-IB_2) can be treated by radical hysterectomy and bilateral pelvic lymphadenectomy followed by adjuvant chemoradiation if high-risk surgico-pathologic factors are identified, patients with locally advanced disease (FIGO stages IB_3-IVA) require cisplatin-based radiosensitizing fractionated chemoradiation and high-dose-rate intracavitary brachytherapy to bring the total dose to point A (i.e., the parametria) to approximately 85 Gy [7]. Select women with very early stage cancers may be candidates for fertility-preserving radical trachelectomy with lymphadenectomy, and some with locally advanced tumors may opt for lateral ovarian transposition and/or oocyte harvesting prior to commencing radiotherapy. Patients with isolated, centrally-located recurrent disease following pelvic irradiation may be salvaged through total pelvic exenteration with urinary diversion [7].

In 2007, the phase 3, randomized clinical trial, Gynecologic Oncology Group (GOG) protocol 204, was closed for futility at interim analysis as none of the three investigational platinum-based chemotherapy doublets (cisplatin-topotecan, cisplatin-vinorelbine, cisplatin-gemcitabine) were expected to out-perform the control, cisplatin-paclitaxel [8]. Additionally, with widespread adoption of cisplatin-based chemoradiation protocols for locally advanced disease, acquired resistance to platinum at relapse became a concern. Accordingly, the GOG was tasked by the National Cancer Institute to identify a non-platinum chemotherapy doublet and/or novel targeted agents to study in women with recurrent, persistent, and metastatic cervical carcinoma. Although the SCOTCERV trial using gemcitabine-docetaxel had not matured [9], laboratory data by Bahadori, et al. suggested synergy between topotecan and microtubule-inhibiting agents [10] and a phase II trial of topotecan-paclitaxel by Tiersten, et al. had demonstrated activity in a preirradiated population of women with recurrent cervical cancer [11]. Vascular endothelial growth factor had also recently emerged as a viable target for anti-angiogenesis platforms, and based on clinical, pathologic, therapeutic, and molecular rationale, the fully, humanized, monoclonal antibody, bevacizumab, was vetted for what would be the GOG's ninth phase 3 randomized trial in this patient population [12–17].

GOG-0240 activated in April 2009 and at the first interim analysis, topotecan-paclitaxel (with or without bevacizumab) did not significantly affect overall survival (OS) when compared with cisplatin-paclitaxel (with or without bevacizumab) (HR 1.20; 99% CI, 0.82–1.76) [12]. At the second interim analysis, the incorporation of bevacizumab was found to confer a survival advantage (17.0 vs 13.2 months; HR for death, 0.71; 98% CI, 0.54–0.95; $p = 0.004$) [12] and would directly lead to an approved indication in first-line treatment of recurrent/metastatic cervical cancer in over 60 countries on six continents. Here we present the protocol-specified analysis of OS using topotecan-paclitaxel.

2. Methods

2.1. Study design and participants

GOG-0240 is a phase III, open-label, randomized trial performed in the United States, Canada and in Spain through the GOG and Spanish Ovarian Cancer Group (GEICO). The study is listed at www.clinicaltrials.gov (NCI identifier #NCT00803062) and the master protocol is available at www.nrgoncology.org. Eligibility criteria included patients with metastatic, persistent, and recurrent cervical carcinoma. Patients with recurrent disease must not have been candidates for potentially curative pelvic exenteration. All cancers had central pathology review. GOG performance status scores of 0 or 1 (on a scale of 0 to 4 with 0 indicating that the patient is fully active and 1 indicating that the person is restricted in physically strenuous activities but ambulatory) were required, and patients had to have adequate renal, hepatic, and bone marrow function. All patients must have had measurable disease. Patients treated with chemotherapy for recurrence, and those with non-healing wounds, active bleeding conditions, and inadequately anticoagulated thromboembolism, were ineligible.

2.2. Procedures

Patients were randomly assigned to one of four treatment regimens which were repeated at 21-day intervals. Control treatment consisted of cisplatin (50 mg/m²) plus paclitaxel (135 or 175 mg/m²). The non-platinum doublet topotecan (0.75 mg/m² days 1–3) plus paclitaxel (175 mg/m²) was included in two of the experimental arms. Each chemotherapy backbone was studied with and without bevacizumab (15 mg/kg day 1). Treatment was discontinued at the onset of disease progression, unacceptable adverse events (AEs), voluntary withdrawal by the patient, or upon complete response (CR).

Details related to disease assessment and tumor measurements using Response Evaluation Criteria in Solid Tumors (RECIST v.1) appear in the master protocol. Safety, as assessed by the National Cancer Institute's Common Terminology Criteria for Adverse Events, was monitored during each cycle. Following treatment discontinuation, disease was assessed every three months for two years, followed by every six months for three years until progression. Three validated and sensitive instruments were used to measure health-related quality of life (HRQoL) and patient reported outcomes (PROs).

2.3. Statistical analysis

Assuming absence of interaction between experimental agents, the study utilized a 2 × 2 factorial design to investigate the ability of either regimen containing the non-platinum chemotherapy doublet (topotecan-paclitaxel) or anti-angiogenesis therapy (bevacizumab) to significantly impact patient outcomes. The study employed the intent-to-treat principle. Patients were prospectively stratified by GOG performance

status (0 vs 1), prior radiosensitizing platinum, and disease status (recurrence/persistence versus stage IVB primary).

OS (based on a pooled analysis for each of the treatment factors under investigation) and the frequency and severity of AEs with each regimen were the primary endpoints. Secondary endpoints were to compare progression-free survival (PFS) and objective tumor responses among the different treatment arms. Differences in OS and PFS by factor level were assessed primarily by the log-rank test, stratified by clinical prognostic markers and the level of the other treatment factor [18]. Hazard ratios (HR) were estimated with a Cox proportional hazards model [19].

Exploratory analyses included a prospective validation of poor prognostic markers [15] identified in pooled analyses from prior studies, the impact of tumor histology, and several novel translational endpoints involving circulating tumor cells (CTC). For the Moore prognostic scoring system, patients were considered high risk if they had 4 or 5 equally weighted clinical factors (i.e., performance status >0, disease-free interval < 12 months, African American ethnicity, pelvic disease, and prior platinum exposure) [15]. Mid-risk patients had 2 or 3 factors, and low-risk patients had 0 or 1 factor [15]. CTC analyses were performed pre-cycle 1 and 36 days post-cycle 1. The median cut-off observed value of 7 CTCs/sample was used to separate those with high levels of CTCs from those with low levels of CTCs.

A sample size of approximately 450 was accrued to potentially observe 346 deaths in the final analysis to provide a study with 90% power when either factor was capable of reducing the hazard of death by at least 30%, while limiting the one-sided type I error for each to 2.5% (experiment-wise error rate >5% for the treatment regimens; none of the other exploratory analyses controlled for the experiment-wise error). An interim analysis was scheduled near 173 deaths to drop a factor or to stop the study for futility or to report regimen activity early according to the spending function in the event of dramatic improvement in survival [20,21]. A final analysis for survival required 346 deaths to have occurred. Since the study was designed with futility rules, the alternative hypotheses, critical regions, and p-values for the primary analyses of efficacy were listed as one-sided.

To monitor for unacceptable toxicity in the experimental arms, two 2-stage sequential toxicity analyses were embedded early in the conduct of the study (i.e., first 50 patients assigned to investigational treatment), with specific guidelines dictating when a meeting of the Data Safety Monitoring Board (DSMB) would need to be convened. AEs were reported until 30 days after the last study treatment and summarized for patients who received any therapy and submitted AE information. Changes in HRQoL and PROs were evaluated using a mixed model for analysis of repeated measures [22].

2.3.1. Reiteration of the interim analysis report

With the occurrence of 174 events, the pre-planned interim analysis was triggered and the DSMB concluded that topotecan was not a superior substitute for cisplatin when combined with paclitaxel by OS (HR 1.20; 99% CI, 0.82–1.76; $p = 0.88$). This information was communicated to physicians and patients participating in the study via 'Dear Investigator' and 'Dear Patient' letters prepared by the Study Chair. The analysis did not indicate that the topotecan regimens (with and without bevacizumab) performed worse than the cisplatin regimens by OS. Patients receiving therapy with any of the four arms of GOG 240 could remain on their current treatment assignment unless progression, unacceptable
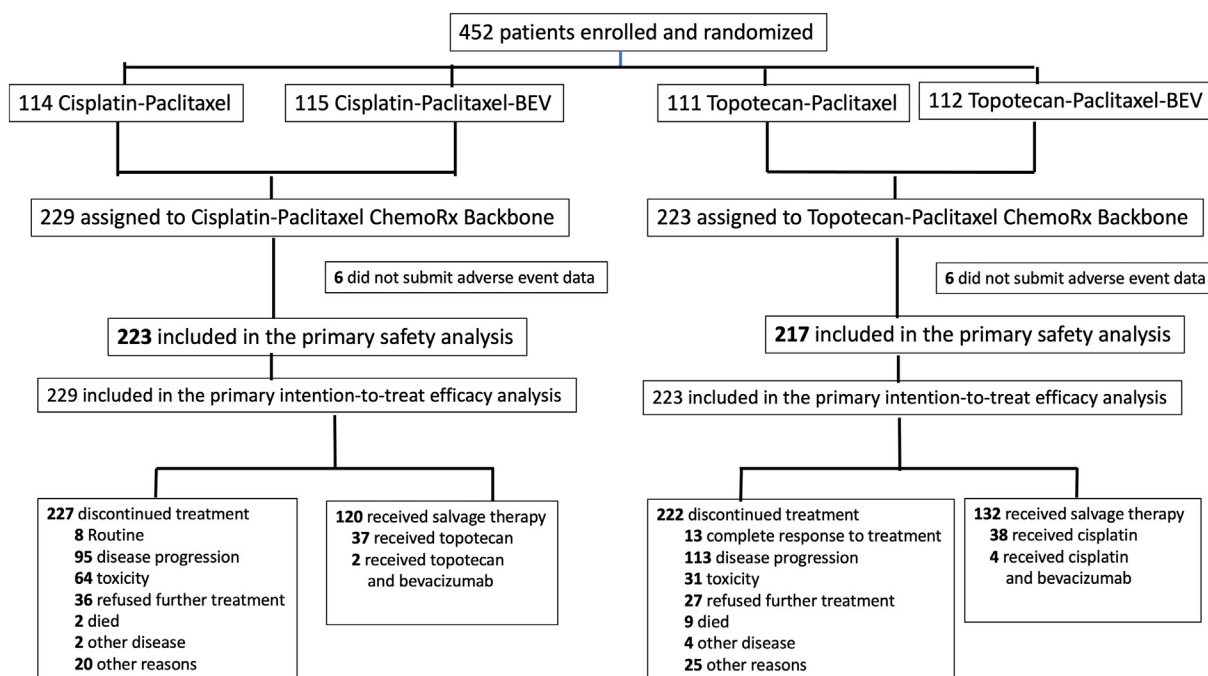
Table 1
Baseline characteristics.

	Platinum-Based Chemotherapy Backbone N = 229	Non-Platinum Chemotherapy Doublet Backbone N = 223
Age (years)	Median 46 (range, 20–85)	median 48 (range, 22–82)
Histology		
Squamous	71%	65%
Adenocarcinoma	19%	19%
Adenosquamous	9%	10%
Other	0%	5%
Race		
White	78%	77%
Black	13%	13%
Asian	5%	4%
Pacific Islander	0.4%	0.0%
Other	3%	6%
Disease status		
Recurrent	75%	69%
Persistent	9%	14%
Metastatic	16%	17%
GOG performance status		
0	57%	59%
1	43%	41%
Previous platinum-based radiosensitizing chemotherapy	76%	74%
Pelvic disease	50%	57%
Prior radiation therapy	80%	79%
Target lesion in radiation field		
Yes	39%	40%
No	60%	59%
Unknown	1%	0%

toxicity, or CR manifested. It was noted that the results concerning the topotecan regimens in GOG 240 were independent of bevacizumab in this study population. At the time of dissemination of the interim analysis results, GOG 240 had closed to accrual.

3. Results

Between April 6, 2009, and January 3, 2012, a total of 452 eligible patients from 164 institutions in the United States and Spain were enrolled and randomized to one of two regimens containing the cisplatin-paclitaxel chemotherapy backbone ($n = 229$, 50.7%) and to one of two regimens containing the non-platinum chemotherapy doublet backbone of topotecan-paclitaxel ($n = 223$, 49.3%) (see CONSORT Diagram). On March 7, 2014, with 348 deaths, the protocol-specified 346 deaths had been exceeded to trigger the final analysis of OS. Patients were well-matched for GOG performance status, ethnicity, histology, disease status, and in-field pelvic recurrences (Table 1). Importantly, 337 (75%) of 452 patients had previously received platinum-based radiosensitizing chemotherapy, and this proportion was also evenly distributed between those receiving the two chemotherapy regimens.CONSORT Diagramdepicting the random allocation of patients to four treatment arms and subsequent attrition due to progression, toxicity, and complete response.

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                        ┌─────────────────────────────────┐
                        │  452 patients enrolled and       │
                        │  randomized                      │
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| 114 Cisplatin-Paclitaxel | 115 Cisplatin-Paclitaxel-BEV | 111 Topotecan-Paclitaxel | 112 Topotecan-Paclitaxel-BEV |

| 229 assigned to Cisplatin-Paclitaxel ChemoRx Backbone | 223 assigned to Topotecan-Paclitaxel ChemoRx Backbone |

6 did not submit adverse event data

223 included in the primary safety analysis

229 included in the primary intention-to-treat efficacy analysis

6 did not submit adverse event data

217 included in the primary safety analysis

223 included in the primary intention-to-treat efficacy analysis

227 discontinued treatment
8 Routine
95 disease progression
64 toxicity
36 refused further treatment
2 died
2 other disease
20 other reasons

120 received salvage therapy
37 received topotecan
2 received topotecan and bevacizumab

222 discontinued treatment
13 complete response to treatment
113 disease progression
31 toxicity
27 refused further treatment
9 died
4 other disease
25 other reasons

132 received salvage therapy
38 received cisplatin
4 received cisplatin and bevacizumab

In the final analysis of OS, there was no significant survival benefit conferred by the non-platinum chemotherapy doublet backbone with median OS of 16.3 months (cisplatin-paclitaxel backbone with and without bevacizumab) and 13.8 months (topotecan-paclitaxel backbone with and without bevacizumab) (HR 1.12; 95% CI, 0.91–1.38; $p = 0.28$) (Fig. 1A). Updated PFS indicated a higher risk in the topotecan regimen (7.8 vs 6.0 months, respectively) (HR 1.24; 95% CI 1.02–1.50; $p = 0.03$) (Fig. 1B). The final OS of cisplatin-paclitaxel vs topotecan-paclitaxel was 15 vs 12 months, respectively (HR 1.10; 95% CI, 0.82–1.48;; $p = 0.52$) and the final OS of cisplatin-paclitaxel-bevacizumab vs topotecan-paclitaxel-bevacizumab was 17.5 vs 16.2 months, respectively (HR 1.16; 95% CI, 0.86–1.56; $p = 0.34$) (Figs. 1C-D).

The final median OS for patients with prior platinum exposure treated with the cisplatin-paclitaxel backbone was 14.6 months and 12.9 months for the topotecan-paclitaxel backbone (HR 1.09; 95% CI, 0.86–1.38; $p = 0.48$) (Fig. 1E). Among those patients who had not received prior radiotherapy, the final OS was 20.2 vs 17.1 months for cisplatin-paclitaxel with and without bevacizumab vs topotecan-paclitaxel with and without bevacizumab, respectively (HR 1.25; 95% CI, 0.74–2.09; $p = 0.40$) (Fig. 1F). Post-progression survival was 7.9 vs 8.1 months, respectively (HR 0.95; 95% CI, 0.75–1.19; $p = 0.63$) (Fig. 1G).

A forest plot of prognostic factors appears in Fig. 2A. When analyzing the patient-reported outcomes using the Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index (FACT-Cx TOI), there was no significant difference in HRQoL between treatment with either chemotherapy backbone (Fig. 2B, difference 0.5; $p = 0.66$). Compared with the cisplatin-paclitaxel backbone, the topotecan-paclitaxel backbone was associated with less grade 3 or worse neurosensory toxicity (OR 0.25; 95% CI, 0.09–0.69; $p = 0.004$) but there were no differences in grade 3 or worse other neurotoxicity (OR 0.76; 95% CI, 0.26–2.24; $p = 0.78$) as measured with the FACT/GOG-Ntx subscale short form (difference, 0.43; $p = 0.45$). Similarly, no significant differences were observed complaining of grade 3 or worse pain in either backbone (OR 0.90; 95% CI, 0.5–1.63; $p = 76?$). Exploratory analyses of the Moore clinical scoring system were not informative when comparing the platinum-based and non-platinum chemotherapy backbones for high risk patients (median OS 8.0 vs 8.2 months, respectively; HR 0.81; 95% CI, 0.48–1.39), mid risk patients (16.5 vs 13.8 months; HR 1.16; 95% CI, 0.89–1.52), and low

risk (26.0 vs 20.5 months; HR 1.10; 95% CI, 0.62–1.95) (Figs. 3A-C). There were also no significant differences in OS observed by histologic type and treatment assignation. The median OS among patients with adenocarcinoma alone was 23.2 (platinum-based backbone) vs 13.7 months (non-platinum backbone) (HR 1.58; 95% CI, 0.97–2.57) and the median OS for all adenocarcinoma (i.e., including adenosquamous histology) was 16.7 (platinum-based backbone) vs 14.7 months (non-platinum backbone) (HR 1.29; 95% CI, 0.88–1.90). The median OS among patients with squamous cell carcinoma alone was 16.1 (platinum-based backbone) vs 12.9 months (non-platinum backbone) (HR 1.12; 95% CI, 0.87–1.44), and the median OS for all squamous cell carcinomas (i.e., including adenosquamous histology) was 15.3 (platinum-based backbone) vs 13.8 months (non-platinum backbone) (HR 1.09; 95% CI, 0.85–1.38) (Figs. 3D-G).

For the evaluation of pre-cycle 1 CTC counts, the chemotherapy backbone used was not associated with a survival benefit when studying patients with low (17.2 vs 17.1 months) (HR 0.964; 95% CI, 0.57–1.63) or high CTC counts (20.5 vs 17.1 months) (HR 1.32; 95% CI, 0.81–2.16). There was also no discernible impact on PFS based on pre-cycle 1 CTC counts: low CTCs median PFS 6.0 vs 6.4 months (HR 0.82; 95% CI, 0.51–1.33); high CTCs median PFS 9.2 vs 7.3 months (HR 1.20; 95% CI, 0.76–1.88). For the CTC analyses 36 days post-cycle 1, the topotecan-containing chemotherapy backbone had a non-significant trend for worse survival in the cohort with low CTCs: median OS 27.9 vs 14.3 months (HR 1.98; 95% CI, 1.14–3.42). For high CTCs, the median OS was 17.2 vs 18.4 months (HR 0.89; 95% CI, 0.55–1.43). PFS also appeared worse in the topotecan-containing regimens in the low CTC post-therapy group: median PFS 10.5 vs 4.9 months (HR 1.88; 95% CI, 1.14–3.08). For high CTCs, the median PFS was 8.1 vs 8.2 months (HR 0.93; 95% CI, 0.60–1.44). These data appear in Figs. 3H-O.

3.1. Toxicology

The adverse events assigned to each of the chemotherapy backbones appear in Table 2. As stipulated in the protocol, there were no safety signals identified with dosing of the first 50 patients on the topotecan-paclitaxel backbone that required the DSMB to be convened. In the entire study population, there were no toxic deaths attributed to either chemotherapy backbone.

A: Final OS Platinum vs Non-Platinum

B: Updated PFS Platinum vs Non-Platinum

C: Final OS CDDP-Paclitaxel vs Topotecan-Paclitaxel

D: Final OS CDDP-Paclitaxel-Bevacizumab vs Topotecan-Paclitaxel-Bevacizumab
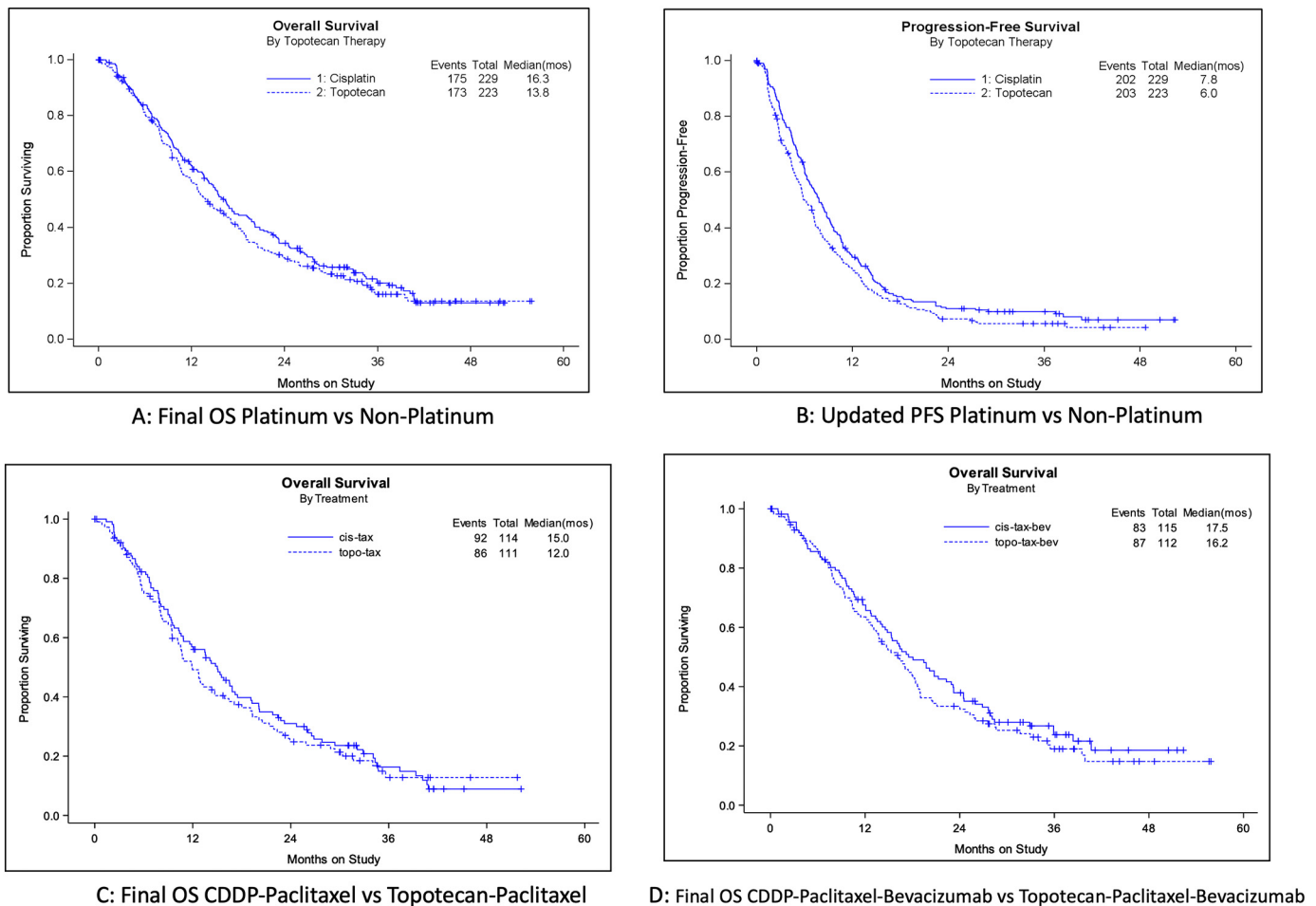
Fig. 1. Kaplan-Meier curves comparing protocol-specified Final Overall Survival, updated Progression-Free Survival, and Post-Progression Survival between the cisplatin-containing chemotherapy backbone and the topotecan-containing chemotherapy backbone. Panel A: Final OS for the overall population comparing cisplatin-paclitaxel with and without bevaciaumab vs topotecan-paclitaxel with and without bevacizumab. Panel B: Updated PFS for the overall population comparing cisplatin-paclitaxel with and without bevaciaumab vs topotecan-paclitaxel with and without bevacizumab. Panel C: Final OS comparing cisplatin-paclitaxel without bevacizumab to topotecan-paclitaxel without bevacizumab. Panel D: Final OS comparing the cisplatin-paclitaxel-bevacizumab triplet to the topotecan-paclitaxel-bevacizumab triplet. Panel E: Final OS among the cohort of patients who previously were exposed to cisplatin for treatment of locally advanced disease using chemoradiation: cisplatin-paclitaxel with and without bevacizumab vs topotecan-paclitaxel with and without bevacizumab. Panel F: Final OS among the cohort of patients who were radiation naïve (i.e., presented with FIGO stage IVB disease): cisplatin-paclitaxel with and without bevacizumab vs topotecan-paclitaxel with and without bevacizumab. Panel G: Post-Progression Survival for the overall population comparing cisplatin-paclitaxel with and without bevaciaumab vs topotecan-paclitaxel with and without bevacizumab.

Hematologic toxicity was similar between each chemotherapy backbone, with a trend for increased grade 3 and grade 4 leukopenia and neutropenia observed among patients treated with the topotecan-paclitaxel backbone. Although not statistically significant, there were more grade 3 nausea, vomiting, gastrointestinal, metabolic, neurosensory, and allergic events reported among patients treated with the cisplatin-paclitaxel chemotherapy backbone.

4. Discussion

The non-platinum chemotherapy doublet, topotecan-paclitaxel, did not improve survival over platinum among patients treated with first-line systemic therapy for recurrent and/or metastatic disease. As previously reported, the interaction term was not significant, indicating that there was no interaction between the two treatment regimens (non-platinum doublet and bevacizumab) under investigation. Interestingly, whereas high-risk Moore score patients treated with chemotherapy plus bevacizumab (using either chemotherapy backbones) derived the greatest survival benefit compared to those with mid-risk and low-risk scores, similar observations were not found when these exploratory analyses isolated the contribution of topotecan-paclitaxel. In addition,

the contribution of topotecan-paclitaxel was not impacted by the presence (or absence) of circulating tumor cells.

Although QoL was not significantly impacted by topotecan-paclitaxel, there are notable differences in the adverse effect profiles attributed to each of the chemotherapy backbones. Incorporation of topotecan-paclitaxel with bevacizumab may represent a reasonable option for patients who wish to avoid the emetogenic, gastrointestinal, neurosensory, and metabolic toxicity which occur more frequently when cisplatin-paclitaxel is used. However, we should note that one year following the interim analysis report from GOG-0240, the Japanese Clinical Oncology Group reported on the non-inferiority of carboplatin when substituted for cisplatin as first line treatment of recurrent disease, particularly among patients who were platinum-naïve (JCOG 0505; NCT00295789) [23]. Carboplatin is relatively more tolerable than cisplatin, and the carboplatin-paclitaxel-bevacizumab triplet was found to have encouraging activity (61% ORR, median OS 25.0 months) and a fistula rate similar to GOG-0240 in the phase 2 CELICIA study (NCT024679070) [24]. The topotecan-paclitaxel-bevacizumab triplet may best be reserved for patients who manifest significant delayed hypersensitivity to the platinum drugs.
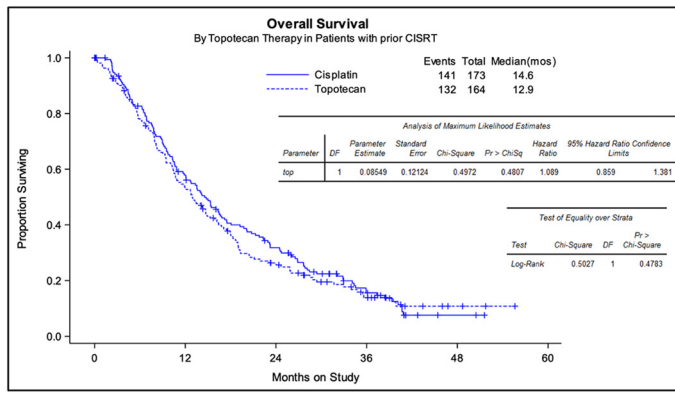
E: Final OS Prior CDDP
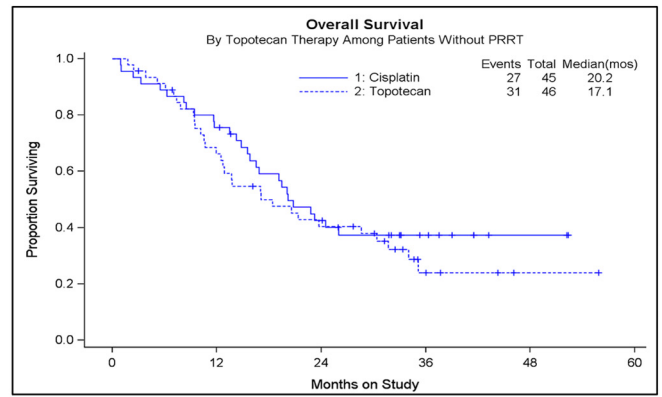

F: Final OS Radiation-Naive
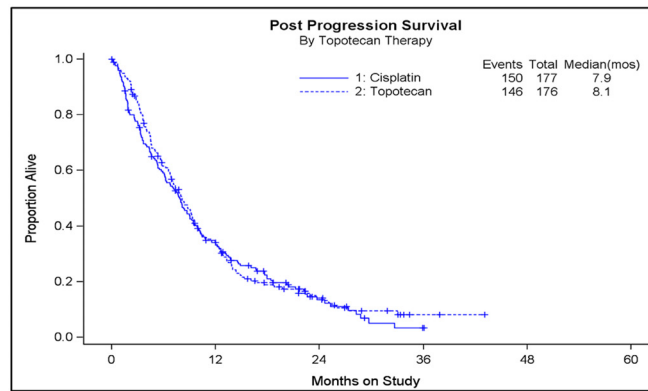
G: Post-Progression Survival

Fig. 1 (*continued*).

GOG-0240 represents a proof of concept of anti-angiogenesis therapy for cervical cancer and a proof of principle of supportive care. With the exhaustion of chemotherapy options studied in 9 phase 3 randomized trials of the GOG, these data may also be viewed as the capstone on systemic chemotherapy in this disease. When the trial launched in 2009, it was the only study evaluating a novel therapeutic agent in this disease. During the interim period, the Cervical Cancer Genome Atlas was published and novel amplifications were identified in the immune targets PD-L1 and PD-L2 [25]. Importantly, it was recognized that amplification of these immunologic sequences were triggered by viral integration of the human papillomavirus [26].

A: Forest Plot of Prognostic Factors
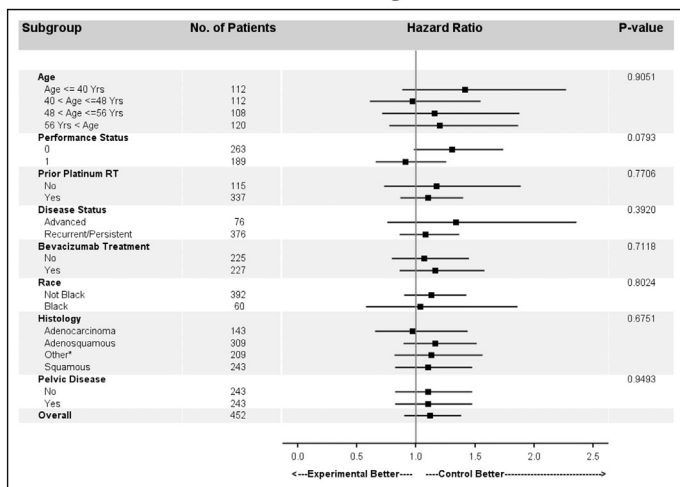
B: FACT Cx TOI Platinum vs Non-Platinum
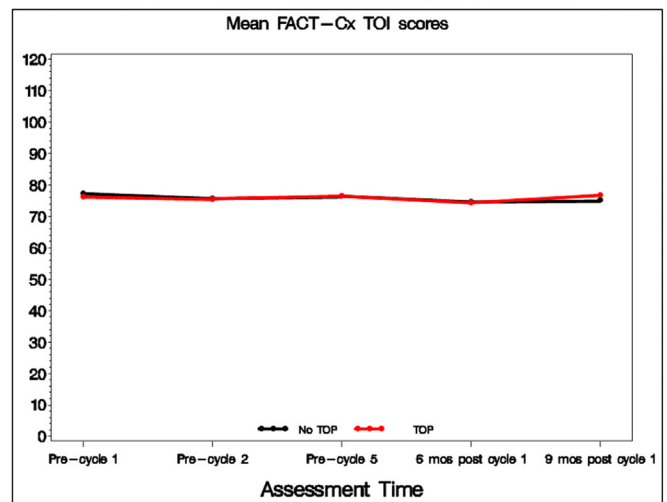
Fig. 2. Prognostic factors and Health-Related Quality of Life. Panel A: Forest plot of prognostic factors depicting distribution of the hazard of death for the experimental regimen (i.e., topotecan-paclitaxel chemotherapy backbone) and the control regimen (i.e., cisplatin-paclitaxel chemotherapy backbone).

A-C: Moore Prognostic Scoring System

A: Moore High Risk
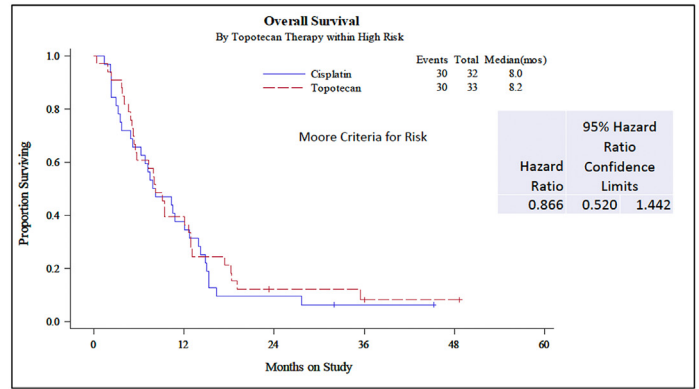
B: Moore Mid-Risk
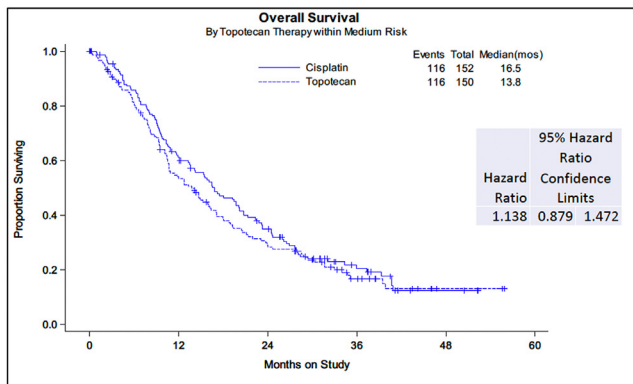
C: Moore Low Risk
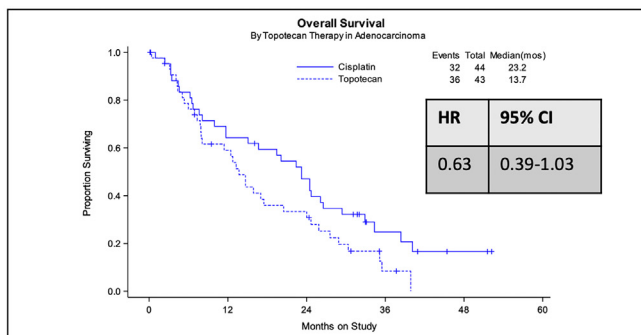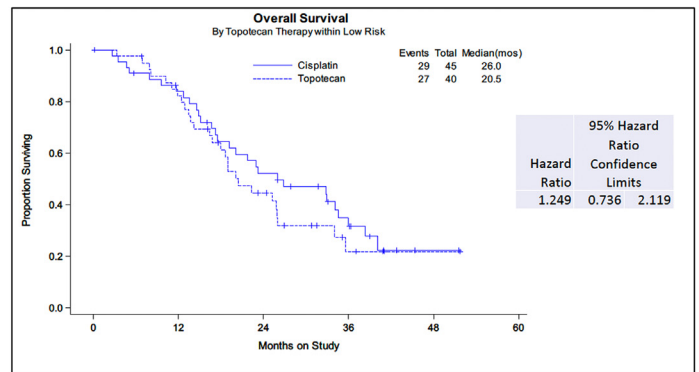
D: Adenocarcinoma alone by CDDP vs Topotecan
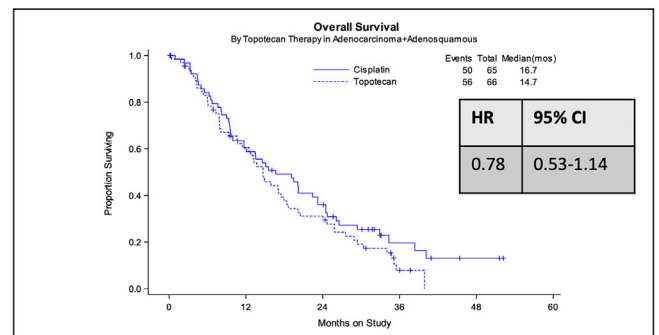
E: Adenocarcinoma + Adenosquamous by CDDP vs Topotecan
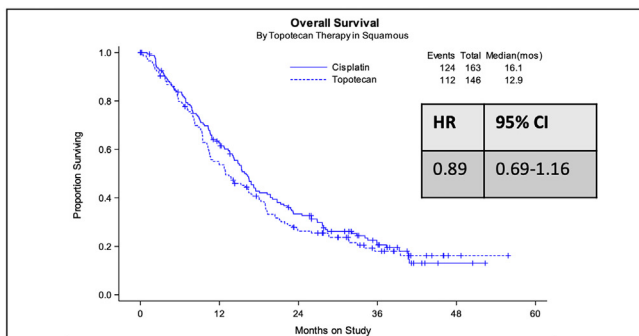
F: Squamous cell carcinoma alone by CDDP vs Topotecan
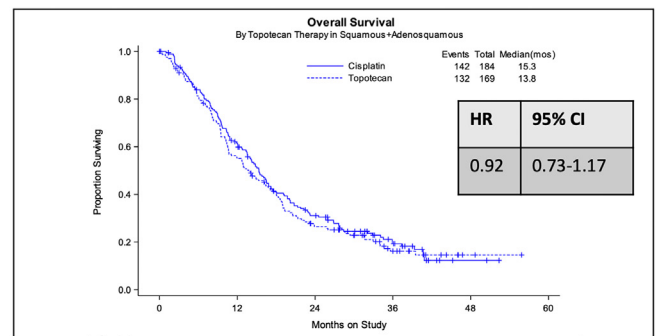
G: Squamous cell plus Adenosquamous by CDDP vs Topotecan

Fig. 3. Exploratory analyses comparing the Final Overall Survival and Progression-Free Survival of the cisplatin-containing chemotherapy backbone to the topotecan-containing chemotherapy backbone. Panel A: Moore High-Risk clinical prognostic scoring system. Panel B: Moore Mid-Risk clinical prognostic scoring system. Panel C: Moore Low-Risk clinical prognostic scoring system. Panel D: Adenocarcinoma histology. Panel E: Adenocarcinoma plus Adenosquamous histology. Panel F: Squamous cell carcinoma histology. Panel G: Squamous cell carcinoma plus Adenosquamous histology. Panel H: Pre-Cycle 1 Low Circulating Tumor Cells Final OS. Panel I: Pre-Cycle 1 High Circulating Tumor Cells Final OS. Panel J: Pre-Cycle 1 Low Circulating Tumor Cells PFS. Panel K: Pre-Cycle 1 High Circulating Tumor Cells PFS. Panel L: Post-Cycle 1 Low Circulating Tumor Cells Final OS. Panel M: Post-Cycle 1 High Circulating Tumor Cells Final OS. Panel N: Post-Cycle 1 Low Circulating Tumor Cells PFS. Panel O: Post-Cycle 1 High Circulating Tumor Cells PFS.
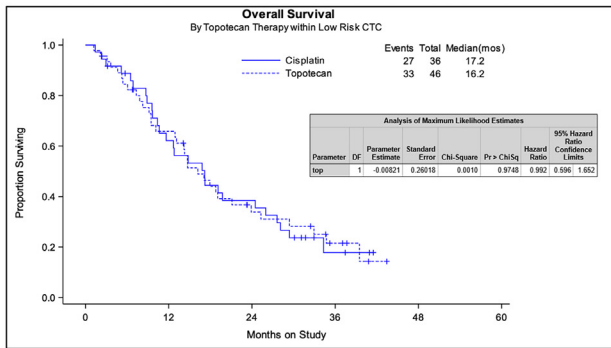
H: OS by Low CTC counts (Pre-Cycle 1)
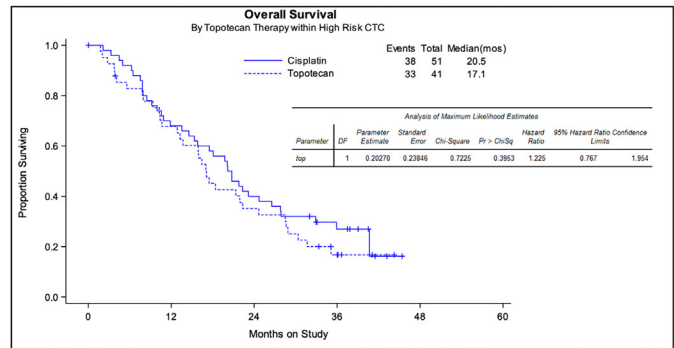
I: OS by High CTC counts (Pre-Cycle 1)
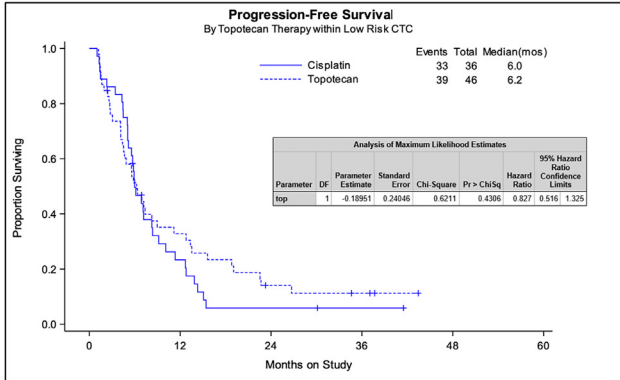
J: PFS by Low CTC counts (Pre-Cycle 1)
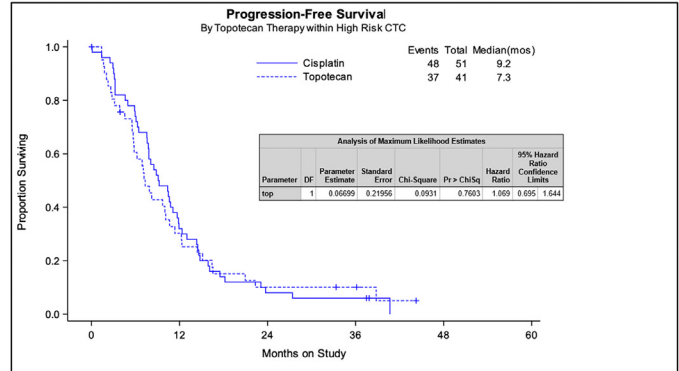
K: PFS by High CTC counts (Pre-Cycle 1)
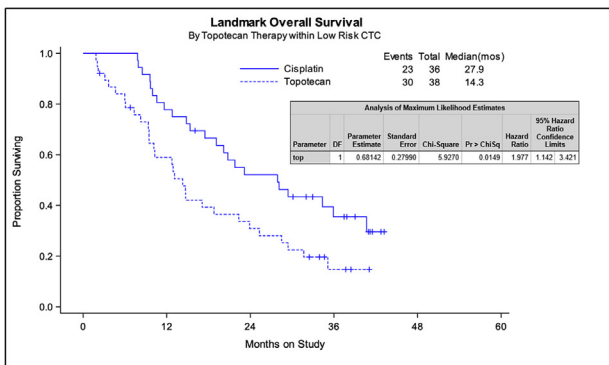
L: OS by Low CTC counts (36 days post-Cycle 1)
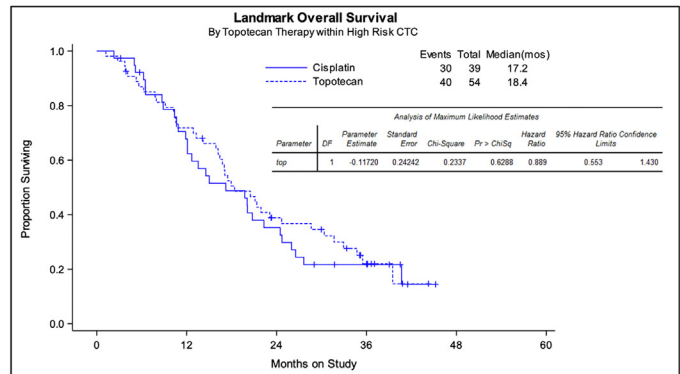
M: OS by High CTC counts (36 days post-Cycle 1)
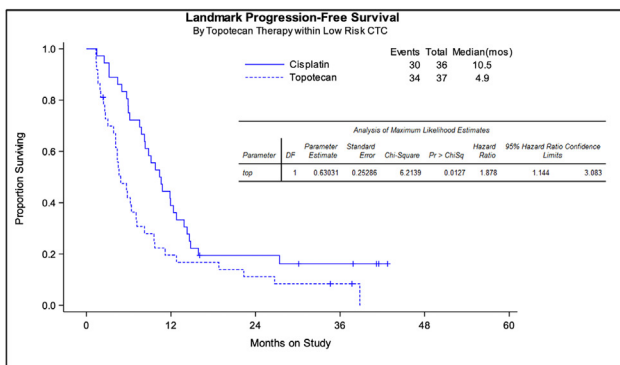
N: PFS by Low CTC counts (36 days post-Cycle 1)
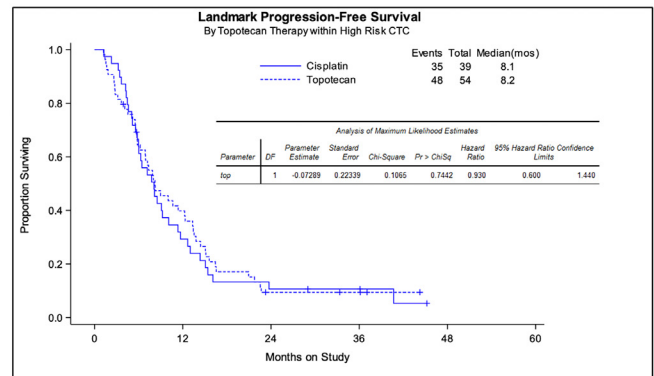
0: PFS by high CTC counts (36 days post-Cycle 1)

Fig. 3 (*continued*).

Table 2
Adverse Events.

Adverse event	Chemotherapy Backbone	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematologic							
Leukopenia	CDDP-Paclitaxel	42	24	76	71	10	0
	Topotecan-Paclitaxel	28	26	49	79	35	0
Neutropenia	CDDP-Paclitaxel	54	19	42	49	59	0
	Topotecan-Paclitaxel	47	6	24	61	79	0
Anemia	CDDP-Paclitaxel	17	47	103	50	6	0
	Topotecan-Paclitaxel	12	50	104	44	7	0
Thrombocytopenia	CDDP-Paclitaxel	130	65	18	8	2	0
	Topotecan-Paclitaxel	110	82	11	7	7	0
Non-hematologic							
Nausea	CDDP-Paclitaxel	76	85	44	18	0	0
	Topotecan-Paclitaxel	100	77	34	6	0	0
Vomiting	CDDP-Paclitaxel	142	37	32	11	1	0
	Topotecan-Paclitaxel	165	33	13	6	0	0
Gastrointestinal	CDDP-Paclitaxel	51	80	61	29	1	1
	Topotecan-Paclitaxel	70	63	63	19	1	1
Metabolic	CDDP-Paclitaxel	118	44	29	31	1	0
	Topotecan-Paclitaxel	141	38	25	12	1	0
Neurosensory	CDDP-Paclitaxel	84	75	44	20	0	0
	Topotecan-Paclitaxel	85	91	36	5	0	0
Allergy	CDDP-Paclitaxel	178	18	19	8	0	0
	Topotecan-Paclitaxel	203	9	2	3	0	0

In 2018, the phase 2 study, KeyNote-158 (NCT02628067), led to accelerated approval of pembrolizumab as a second-line treatment option for PD-L1+ cervical cancer based on an objective response rate of 14% [27]. In 2021, the EMPOWER-Cervix/GOG-3016/ENGOT-Cx9 phase III randomized trial, reported a survival benefit using the anti-PD-1, cemiplimab, over physician's choice chemotherapy in the second-line setting [28]. This was closely followed by the announcement that the phase 3 randomized study, KeyNote-826 (NCT03635567), met its dual primary endpoints of OS and PFS, demonstrating the clinical benefit conferred by the incorporation of pembrolizumab over chemotherapy alone in the first-line setting [29]. On October 13, 2021, the U.S. Food and Drug Administration approved pembrolizumab in combination with chemotherapy, with or without bevacizumab, for first-line treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 as determined by the Combined Positive Score ≥ 1.

In summary, the non-platinum doublet of topotecan-paclitaxel did not demonstrate increased activity in patients previously exposed to platinum. While not statistically significant, the platinum-containing doublet was numerically superior to topotecan-paclitaxel for efficacy. Although the NCCN lists both chemotherapy backbones combined with bevacizumab as Category 1 based on interim analysis data, the final analysis of OS reported in this paper indicates that the non-platinum doublet should not be routinely recommended in this patient population.

Author contributions

Study concept and design: Drs. Tewari, Sill, Birrer, Penson, Moore and Monk.

Provision of materials or patients: Drs. Tewari, Moore, Ramondetta, Landrum, Oaknin, Reid and Leitao.

Acquisition of Data: Drs Ramondetta, Landrum, Oaknin, Reid and Leitao.

Analysis and Interpretation of Data: Drs. Tewari, Sill, Birrer, Penson, Moore, Monk and Ms. Huang.

Manuscript Writing: Drs Tewari, Sill Birrer, Penson, Moore and Monk.

Critical Review of the Manuscript: All authors contributed.
Final Approval of Manuscript: All authors contributed.

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