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Tumor Treating Fields therapy in platinum-resistant ovarian cancer: Results of the ENGOT-ov50/GOG-3029/INNOVATE-3 pivotal phase 3 randomized study

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ABSTRACT

Purpose: Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical for cancer cell viability and tumor progression. The pivotal, phase 3 ENGOT-ov50/GOG-3029/INNOVATE-3 study evaluated efficacy and safety of TTFields therapy with paclitaxel (PTX) vs PTX in patients with platinum-resistant ovarian cancer (PROC).

Patients and methods: Adult patients with PROC with ≤ 5 total prior lines of therapy (LOT), including ≤ 2 prior LOT for platinum-resistant disease, and ECOG PS of 0–1 were randomized 1:1 to receive TTFields (200 kHz; ≥ 18 h/day) + PTX (80 mg/m^2 weekly) or PTX. Primary endpoint was overall survival (OS). Exploratory post-hoc analyses assessed OS in pegylated liposomal doxorubicin (PLD)-naive patients.

Results: Between March 2019 and November 2021, 558 patients (ECOG PS 0, 60.2 %; median [range] age, 62 [22–91] years) were assigned TTFields+PTX (n = 280) or PTX (n = 278). 24.4 % had 4 + prior LOT. Median OS was 12.2 months with TTFields+PTX vs 11.9 months with PTX (HR, 1.01; 95 % CI, 0.83–1.24; p = 0.89). Grade ≥ 3 adverse events (AEs) were similar between treatment groups. Grade 1/2 device-related skin AEs occurred in 83.6 % of patients receiving TTFields therapy. In exploratory post-hoc analysis in PLD-naive patients, median OS was 16 months with TTFields+PTX (n = 113) vs 11.7 months with PTX (n = 88; nominal HR, 0.67; 95 % CI, 0.49–0.94; p = 0.03).

Conclusions: No new safety signals were identified. TTFields+PTX did not significantly improve OS compared with PTX in the intent-to-treat population. An exploratory post-hoc analysis suggests a potentially favorable benefit-risk profile for TTFields therapy in PLD-naive patients.

1. Introduction

Among patients with advanced ovarian cancer, approximately 80 % experience recurrent disease after first-line therapy [1]. For platinum-resistant ovarian cancer (PROC; progression within 6 months of last platinum treatment), guidelines from the European Society for Medical Oncology, National Comprehensive Cancer Network®, and American Society of Clinical Oncology recommend non-platinum chemotherapy (eg, paclitaxel [PTX] and pegylated liposomal doxorubicin [PLD] ± bevacizumab) [2–4]. However, even with the 2024 addition of the antibody-drug conjugate mirvetuximab soravtansine to the armamentarium, treatment outcomes remain poor with non-platinum regimes [5]. Median progression-free survival (PFS) with PROC is typically 3–4 months, while median overall survival (OS) is ≤ 1 year [6]. Additionally, treatment options for later lines of therapy (LOT) are limited by toxicity [1,6]. There remains a significant unmet need for effective and tolerable treatment options.

Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical for cancer cell viability and tumor progression, including mitosis via microtubule destabilization, and autophagy upregulation, leading to a downstream anti-tumor immune response [7–14]. TTFields therapy has demonstrated intensity-dependent effects and, thus, may be impacted by tumor tissue alterations and local conductivity differences [15,16]. TTFields therapy is currently approved for glioblastoma, pleural mesothelioma, and metastatic non-small cell lung cancer following platinum-based therapy [17,18]. In an ovarian cancer mouse model, TTFields (200 kHz) with PTX significantly reduced tumor volume relative to either treatment alone [16]. In the pilot INNOVATE study (NCT02244502), TTFields therapy with paclitaxel (TTFields+PTX) demonstrated safety and feasibility in patients with PROC [19]. The pivotal ENGOT-ov50/GOG-3029/INNOVATE-3 study evaluated efficacy and safety of TTFields+PTX vs PTX in patients with PROC.

2. Materials and methods

2.1. Study design and oversight

ENGOT-ov50/GOG-3029/INNOVATE-3 (ClinicalTrials.gov; NCT03940196) was a randomized, pivotal (phase 3), open-label, multicenter study across 111 sites in 13 countries, conducted in collaboration with the European Network of Gynaecological Oncological Trial groups (ENGOT), GOG Foundation (GOG-F), and sponsor Novocure GmbH according to guidelines developed by ENGOT and GOG-F for studies with industry partners (model C) [20]. Written informed consent was obtained before enrollment, and the study adhered to the 1975 Declaration of Helsinki, Good Clinical Practice guidelines, and relevant national and regional regulations.

2.2. Patient population

Eligible female patients were ≥ 18 years old with a confirmed diagnosis of epithelial ovarian cancer of serous, endometrioid, mucinous, clear cell, mixed, undifferentiated, and other histologies with platinum-resistant disease (progression within 6 months of platinum-based treatment). Patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1, evaluable disease per RECIST v1.1 criteria, and life expectancy of ≥ 12 weeks. Included patients received ≤ 5 prior LOT, and ≤ 2 prior LOT following platinum resistance. Patients were excluded if they had primary platinum-refractory disease, prior progression on PTX for recurrent disease, brain metastases, or implantable electrical medical devices.

2.3. Procedures

Patients were randomized 1:1 to receive TTFields+PTX or PTX. TTFields therapy (200 kHz) was delivered continuously using the NovoTTF-200(O) System (an electric field generator and 2 pairs of arrays placed on the abdomen and pelvis [19]) with a recommendation to wear the device for ≥ 18 h/day on a monthly average (Supplementary Figure S1; device manufactured by Novocure, Root, Switzerland). Array layouts were investigator-determined based on disease location. Patients were trained to use the NovoTTF-200(O) system by an investigator, designated health care provider, and/or device support specialist

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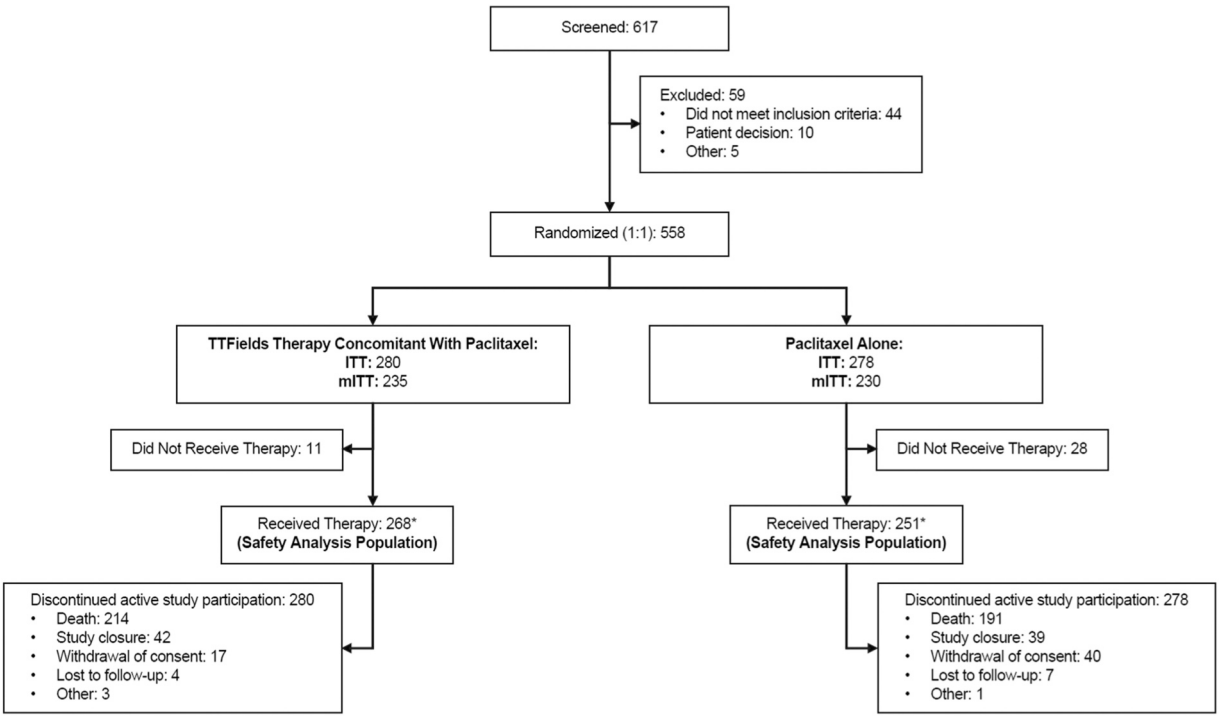

Fig. 1. Consort diagram. *One patient was allocated to TTFields therapy concomitant with paclitaxel but received paclitaxel. TTFields, Tumor Treating Fields.

(DSS; sponsor-provided). Intravenous PTX at 80 mg/m^2 was administered over 1 h, weekly for 8 weeks, and then on days 1, 8, and 15 of a subsequent 28-day cycle. To prevent potential dermatitis, skin care guidelines were followed, including instructions to alternate between different array locations 2 cm apart. A topical steroid was prescribed upon initial skin inflammation. Study therapy was administered until radiological progression per RECIST v1.1, clinical disease progression per investigator, or unacceptable toxicity. CT or MRI scans of the chest and abdomen were performed every 8 weeks until local disease progression. Safety was assessed by the investigator at each follow-up visit per the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. A modified grading system was used to characterize device–related skin adverse events (AEs; Supplementary Table S1).

2.4. Study endpoints and assessments

The primary endpoint was OS. Secondary endpoints included PFS, objective response rate (ORR), and safety. Patients were stratified by prior LOT following platinum resistance, prior bevacizumab use, and *BRCA* mutation status. OS was measured from randomization to death, PFS from randomization to disease progression, and ORR as the proportion of patients achieving partial response (PR) or complete response (CR) per RECIST v1.1 criteria. TTFields therapy usage time was calculated by dividing the device-captured treatment time by the prescribed number of 1-month treatment courses.

2.5. Statistical analysis

Efficacy analyses were conducted in the intent-to-treat population (ITT; all randomized patients regardless of treatment received) and the modified intent-to-treat population (mITT; all patients who received ≥ 1 complete 28-day cycle of study treatments). OS and PFS were assessed using the Kaplan–Meier method with a 2-stratified log-rank test at an overall alpha of 0.05 (0.00704 at interim analysis and 0.04776 at final analysis; calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function). OS analyses censored patients lost to follow-up or in follow-up at the last known alive date. A hierarchical testing approach addressed multiplicity: OS significance initiated PFS testing at an alpha of 0.05. ORR was not included in hierarchical testing and was analyzed using a chi-squared test with evaluable responses; unevaluable responses, defined as those with insufficient data, and missing data were removed. The safety analysis population included all patients who received any TTFields therapy or PTX. To detect a hazard ratio (HR) of < 0.75 for TTFields+PTX (corresponding to an increase in median OS from 12 to 16 months), a sample size of 270 patients per group (540 total) was required to achieve 80 % power, assuming 10 % loss to follow-up.

Exploratory subgroup analyses were conducted based on the following stratification factors: prior bevacizumab use, prior therapy following platinum resistance, and *BRCA* status. Post-hoc multivariable Cox regression analyses with stepwise narrowing tested the effect of prior PLD use, prior bevacizumab use, number of LOT following PROC treatment, total prior LOT, prior poly adenosine diphosphate-ribose polymerase inhibitor (PARPi) use, International Federation of Gynecology and Obstetrics (FIGO) stage, grade, ascites, platinum-free interval, age group, and ECOG PS on OS (threshold p-value ≤ 0.15). The final Cox model included prior PLD use, total number of prior LOT, ascites, and ECOG PS. Exploratory post-hoc analyses included OS and PFS in subgroups according to prior PLD use (PLD-naive and patients with prior PLD use).

3. Results

3.1. Patients

From March 4, 2019, to November 18, 2021, 617 patients were screened, and 558 patients were enrolled and randomized to receive TTFields+PTX (n = 280) or PTX (n = 278; Fig. 1). The data cutoff was July 27, 2023. Baseline characteristics were well balanced (Table 1). The median (range) age was 62 (22–91) years, and most patients had serous histology (88.7 %) and an ECOG PS of 0 (60.2 %). 24.4 % of patients had ≥ 4 prior total LOT and 40.7 % had ≥ 1 LOT following platinum-resistance. Prior therapies included taxanes (99.5 %), bevacizumab (65.9 %), and anthracyclines (64.0 %). PLD represented 93 %

Table 1
Baseline Patient and Disease Characteristics.

	TTFields+PTX (n = 280)	PTX (n = 278)
Age, y, median (range)	61 (22–85)	63 (25–91)
Region, n (%)		
North America	91 (32.5)	88 (31.7)
Eastern Europe	37 (13.2)	34 (12.2)
Western Europe and Israel	152 (54.3)	156 (56.1)
Race, n (%)		
White	268 (95.7)	263 (94.6)
Black or African American	6 (2.1)	8 (2.9)
Asian	2 (0.7)	1 (0.4)
Native Hawaiian or Pacific Islander	0	1 (0.4)
American Indian or Alaska Native	1 (0.4)	0
Other	3 (1.1)	5 (1.8)
ECOG PS, n (%)		
0	168 (60.0)	168 (60.4)
1	112 (40.0)	109 (39.2)
Missing	0	1 (0.4)
Primary tumor type, n (%)		
Ovarian cancer	252 (90.0)	231 (83.1)
Peritoneal cancer	13 (4.6)	14 (5.0)
Fallopian tube cancer	15 (5.4)	33 (11.9)
Histology at diagnosis, n (%)		
Serous	243 (86.8)	252 (90.6)
Endometrioid	11 (3.9)	10 (3.6)
Mucinous	1 (0.4)	0
Clear cell	12 (4.3)	4 (1.4)
Mixed	3 (1.1)	5 (1.8)
Undifferentiated	1 (0.4)	0
Other	9 (3.2)	7 (2.5)
Total number of prior lines of systemic therapy, n (%)		
1	30 (10.7)	24 (8.6)
2	98 (35.0)	83 (29.9)
3	92 (32.9)	94 (33.8)
4	46 (16.4)	55 (19.8)
5	14 (5.0)	21 (7.6)
Number of prior lines of systemic therapy for PROC, n (%)		
0	170 (60.7)	161 (57.9)
1	77 (27.5)	87 (31.3)
2	33 (11.8)	30 (10.8)
BRCA mutations, n (%)		
Yes	44 (15.7)	43 (15.5)
No/unknown*	236 (84.3)	235 (84.5)
Prior systemic agents, n (%)		
Platinum-based	280 (100)	278 (100)
PARP inhibitors	123 (43.9)	120 (43.2)
Taxanes	279 (99.6)	276 (99.3)
Pyrimidine analogues	113 (40.4)	131 (47.1)
Anthracyclines†	167 (59.6)	190 (68.3)
Bevacizumab	181 (64.6)	187 (67.3)

BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group Performance Status score; PARP, poly adenosine diphosphate-ribose polymerase; PROC, platinum-resistant ovarian cancer; PTX, paclitaxel; TTFields, tumor-treating fields.
*Captured data do not differentiate between BRCA wild type or unknown.
† Pegylated liposomal doxorubicin represented 93 % of anthracycline use, and the remaining 7 % represented a non-specified doxorubicin formulation.

of anthracycline use, and the remaining 7 % represented a non-specified doxorubicin formulation.

In the safety population (n = 268), median (range) TTFields therapy duration was 15.9 (0.1–159.7) weeks. Median (range) TTFields device usage was 67.7 % (0 %–96.5 %) of each day. A monthly average device usage of ≥ 18 h/day (75 % of each day) was achieved by 33.6 % of patients. The most common reason for TTFields device discontinuation was local disease progression (63.1 %; Supplementary Table S2). Median duration of PTX exposure was 14.7 weeks (4 cycles) with TTFields+PTX and 15.3 weeks (5 cycles) with PTX. Most commonly, patients discontinued PTX due to local disease progression (TTFields+PTX, 65.4 %; PTX, 59.7 %).

3.2. Efficacy

After a median follow-up of 10.7 months for patients receiving TTFields+PTX and 9.9 months for PTX, median OS (95 % CI) with TTFields+PTX was 12.2 (10.3–13.8) months vs 11.9 (10.8–13.6) months with PTX (HR [95 % CI], 1.01 [0.83–1.24]; p = 0.89; Fig. 2**A**) in the ITT population. In the mITT population, median OS (95 % CI) with TTFields+PTX was 13.6 (11.4–15.2) months vs 12.4 (11.0–14.4) months with PTX (HR [95 % CI], 0.95 [0.77–1.17]; p = 0.61; Fig. 2**B**). Median PFS (95 % CI) in the ITT population was 4.1 (3.8–4.9) months with TTFields+PTX vs 4.7 (3.9–5.3) months with PTX (HR [95 % CI], 1.06 [0.88–1.29]; p = 0.53; Fig. 2**C**). Median PFS (95 % CI) in the mITT population was 4.8 (3.9–5.5) months with TTFields+PTX vs 4.9 (3.9–5.4) months with PTX (HR [95 % CI], 1.0 [0.82–1.23]; p = 0.97; Fig. 2**D**). ORR was 30.3 % and 31.6 % in patients who received TTFields+PTX and PTX, respectively (Table 2). Among patients who received TTFields+PTX compared with PTX, CR was observed in 8 vs 6 patients, respectively.

3.3. Safety

AEs were reported in 99.3 % (266/268) of patients treated with TTFields+PTX and 97.2 % (244/251) of patients treated with PTX (Table 3). AEs were similar between treatment groups. Leukopenia, anemia, and fatigue were the most common overall AEs, occurring in 44.0 %, 47.8 %, and 47.0 % of the TTFields+PTX cohort and in 42.6 %, 51.8 %, and 51.0 % of the PTX cohort, respectively. Grades 3–5 AEs were reported in 60.1 % (312/519) of patients. The most frequent grades 3–5 AEs observed were blood and lymphatic system disorders with TTFields+PTX (29.5 %) and PTX (31.1 %; Supplementary Table S3). The percentage of patients experiencing ≥ 1 serious AE (SAE) was similar across the TTFields+PTX (90/268, 33.6 %) and PTX treatment arms (94/251, 37.5 %; Supplementary Table S4). AEs leading to treatment discontinuation occurred in 25.7 % of patients receiving TTFields+PTX and 18.7 % of patients receiving PTX. AEs leading to death occurred in 12 and 13 patients who received TTFields+PTX and PTX, respectively.

TTFields device–related skin AEs, all of which were grade 1–2 (modified grading; Supplementary Table S1), occurred in 224 patients (83.6 %). Three SAEs were considered related to TTFields therapy (Supplementary Table S5). There were no grade 4 toxicities or deaths attributable to TTFields therapy. No increase in severe systemic toxicities and no new safety signals related to TTFields therapy were reported.

3.4. Exploratory post-hoc analyses

OS according to baseline characteristics is shown in Supplementary Figure S2. The only 2 subgroups with survival benefit from the addition of TTFields were patients with only 1 prior treatment line and patients that were PLD naive. In the final Cox model, prior PLD use was the only independent predictor that affected model outcomes aside from ECOG PS and ascites (Supplementary Figure S3). PLD-naive patients had, in an exploratory post-hoc analysis, a 35 % risk reduction for death with TTFields+PTX vs PTX.

The overall PLD-naive subgroup consisted of 201 patients (36 % of the ITT population; TTFields+PTX, n = 113; PTX, n = 88). Baseline characteristics in the PLD-naive subgroup were balanced and consistent with the prior PLD use subgroup and overall ITT population (Table 4). As expected, the PLD-naive patients were less heavily pretreated than patients with prior PLD use.

In PLD-naive patients in the overall population, OS was significantly longer among patients treated with TTFields+PTX vs PTX (16.0 vs 11.7

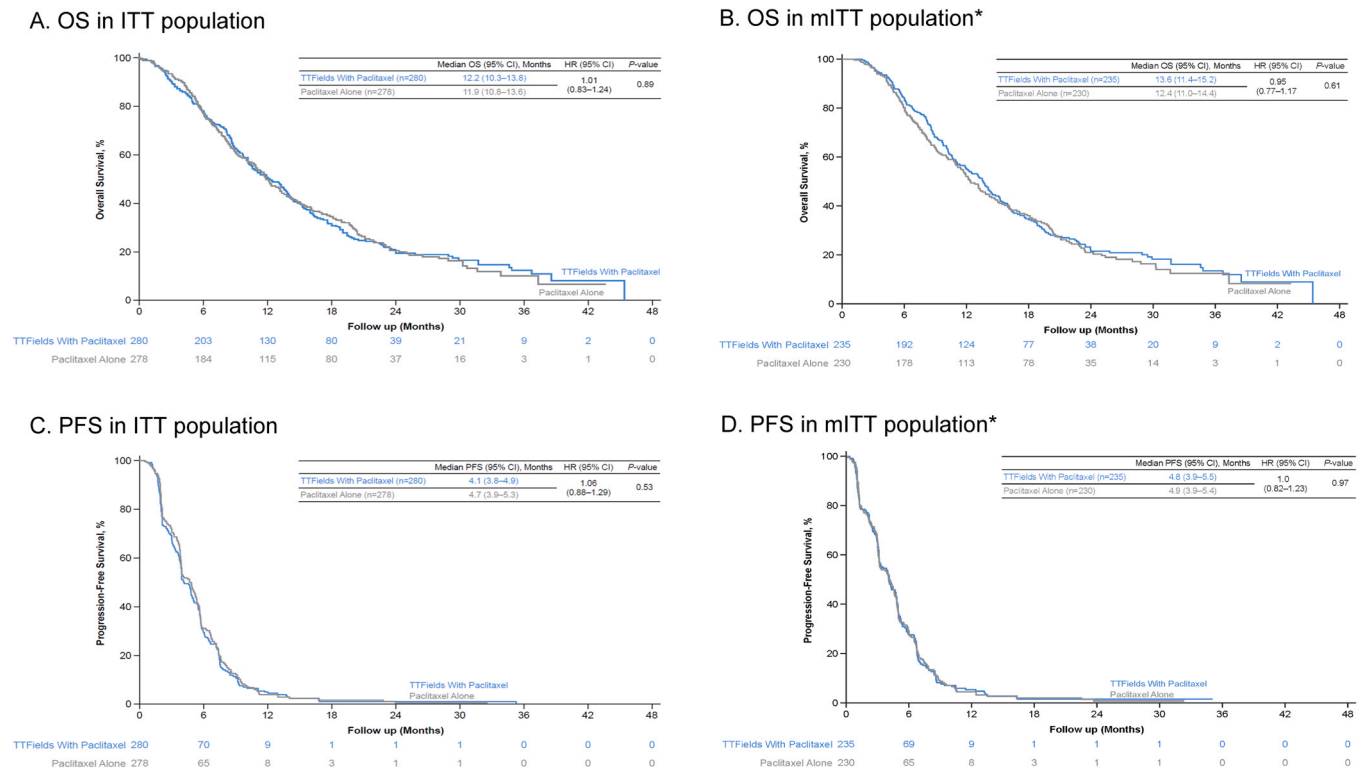

Fig. 2. Kaplan–Meier curve of OS in ITT population (A), OS in mITT population (B), PFS in ITT population (C), and PFS in mITT population (D). *The mITT population includes all patients who received ≥ 1 complete 28-day cycle of study treatments. HR, hazard ratio; ITT, intent-to-treat; mITT modified intent-to-treat; PFS, progression-free survival; OS, overall survival; TTFields, Tumor Treating Fields.

Table 2
Summary of ORR (RECIST).

	TTFields+PTX (n = 280)	PTX (n = 278)
Patients with ≥ 1 post-baseline scan, n (%)	231 (82.5)	215 (77.3)
Best overall response, n (%)		
Complete response	8 (3.5)	6 (2.8)
Partial response	62 (26.8)	62 (28.8)
Stable disease	110 (47.6)	107 (49.8)
Progressive disease	49 (21.2)	39 (18.1)
Not evaluable	2 (0.9)	1 (0.5)
ORR*, % (95 % CI)	30.3 (24.5–36.7)	31.6 (25.5–38.3)
ORR difference, % (95 % CI)	–1.3 (–10.1–7.4)	
P-value	0.76	

ORR, objective response rate; PTX, paclitaxel; TTFields, Tumor Treating Fields. *Patients with not evaluable response were counted as nonresponders in the denominator.

months; HR [95 % CI], 0.67 [0.49–0.94]; p = 0.03; Fig. 3A). OS was also significantly longer among PLD-naive patients in the modified population receiving TTFields+PTX vs PTX (18.0 vs 11.9 months; HR [95 % CI], 0.59 [0.42–0.85]; p = 0.005; Fig. 3B). PFS was not significantly different between groups (Fig. 3C and 3D). Among PLD-naive patients, ORR was 43.6 % vs 41.7 % in patients who received TTFields+PTX compared with PTX, respectively. Among patients with prior PLD use, there was no difference in ORR between treatment groups (data not shown). No new safety signals were identified in the subgroups according to prior PLD use (Supplementary Table S6).

4. Discussion

In the overall ITT population of ENGOT-ov50/GOG-3029/INNOVATE-3 study, the addition of TTFields therapy did not improve OS vs PTX. While unexpected, this is not uncommon in the PROC patient population. Patients with PROC have limited available therapies and are often heavily pretreated. Recent phase 3 studies in patients with PROC, such as UPLIFT, EPIK-O, NRG-GY005, and AXLerate, have also not met their primary endpoints [21–24], even in populations with ≤ 3 prior LOT. Trials, including those investigating alpelisib with olaparib vs investigators' choice of PTX or PLD, and batiraxcept with PTX vs PTX, did not improve PFS [25–27]. Notably, the ENGOT-ov50/GOG-3029/INNOVATE-3 study enrolled a heavily pretreated and heterogeneous population that included patients with ≤ 5 prior total LOT, ≤ 2 prior LOT following platinum resistance, and multiple histology types. Prior therapies can impact treatment outcomes in patients with ovarian cancer [28]. Data from a retrospective analysis in > 3300 patients with PROC demonstrated that survival was progressively reduced with each relapse after treatment, regardless of therapy choice [29].

Surprisingly, prior PLD use was the only independent factor identified via multivariable analyses to predict outcomes in this study, apart from the well-established prognostic factors ECOG PS and ascites [28]. In PLD-naive patients, representing 36 % (201/558) of the overall study population, exploratory post-hoc analyses demonstrated significantly longer OS with TTFields+PTX vs PTX (16.0 vs 11.7 months; p = 0.03). These findings are supported by new analyses from the INNOVATE pilot study, suggesting favorable survival in the PLD-naive (n = 13) vs prior PLD (n = 18) subgroups (HR [95 % CI], 0.222 [0.046–1.059], p = 0.04) [19,30]. Results from these exploratory post-hoc analyses may be explained by the known tumor microenvironment alteration, such as increases in regulatory T-cells and macrophage-inflammatory-protein-1-beta following PLD administration [31,32]. Additionally, in a preclinical ovarian cancer model, collagen IV staining was increased 3-fold and tissue conductivity was decreased 50 % after doxorubicin administration [31]; however, additional research is needed to further characterize this and explore the effects with other chemotherapies.

Exploratory post-hoc findings from this study suggest that PLD-naive patients represent a PROC subpopulation who may benefit from this

Table 3
Summary of Adverse Events Reported in ≥ 10 % of Patients.

	TTFields+PTX (n = 268)		PTX (n = 251)		
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**p-values (all grades)**
Any AE, n (%)	266 (99.3)	174 (64.9)	244 (97.2)	163 (64.9)	0.097
Most frequent AEs (reported in ≥10 % of patients), n (%)					
Anemia	128 (47.8)	21 (7.8)	130 (51.8)	35 (13.9)	0.38
Fatigue	126 (47.0)	12 (4.5)	128 (51.0)	17 (6.8)	0.381
Dermatitis	120 (44.8)	7 (2.6)	12 (4.8)	0	< 0.001
Leukopenia	118 (44.0)	64 (23.9)	107 (42.6)	51 (20.3)	0.79
Peripheral neuropathy	108 (40.3)	5 (1.9)	88 (35.1)	6 (2.4)	0.239
Nausea	85 (31.7)	4 (1.5)	72 (28.7)	4 (1.6)	0.503
Abdominal pain	78 (29.1)	14 (5.2)	81 (32.3)	8 (3.2)	0.447
Musculoskeletal pain	74 (27.6)	0	76 (30.3)	5 (2.0)	0.561
Diarrhea	66 (24.6)	5 (1.9)	72 (28.7)	4 (1.6)	0.321
Erythema	64 (23.9)	1 (0.4)	8 (3.2)	0	< 0.001
Pruritus	62 (23.1)	2 (0.7)	12 (4.8)	0	< 0.001
Alopecia	55 (20.5)	2 (0.7)	73 (29.1)	0	0.025
Skin ulcer	58 (21.6)	6 (2.2)	17 (6.8)	1 (0.4)	< 0.001
Constipation	54 (20.1)	3 (1.1)	67 (26.7)	2 (0.8)	0.096
Localized edema	54 (20.1)	0	61 (24.3)	2 (0.8)	0.29
Vomiting	48 (17.9)	5 (1.9)	53 (21.1)	4 (1.6)	0.376
Dyspnea	43 (16.0)	1 (0.4)	51 (20.3)	3 (1.2)	0.212
Nail disorder	46 (17.2)	2 (0.7)	46 (18.3)	4 (1.6)	0.732
Pain	43 (16.0)	1 (0.4)	23 (9.2)	0	0.024
Intestinal obstruction	27 (10.1)	24 (9.0)	27 (10.8)	24 (9.6)	0.886
Anorexia	39 (14.6)	1 (0.4)	37 (14.7)	4 (1.6)	1
Hypokalemia	35 (13.1)	3 (1.1)	32 (12.7)	7 (2.8)	1
Maculopapular rash	33 (12.3)	3 (1.1)	13 (5.2)	1 (0.4)	0.005
Paresthesia	33 (12.3)	1 (0.4)	30 (12.0)	2 (0.8)	1
Elevated hepatic enzyme	29 (10.8)	8 (3.0)	33 (13.1)	5 (2.0)	0.421
Urinary tract infection	28 (10.4)	2 (0.7)	29 (11.6)	6 (2.4)	0.779
Ascites	24 (9.0)	7 (2.6)	27 (10.8)	12 (4.8)	0.556
Hypomagnesemia	28 (10.4)	1 (0.4)	35 (13.9)	4 (1.6)	0.23
Abdominal distension	12 (4.5)	1 (0.4)	31 (12.4)	1 (0.4)	0.001
Pyrexia	21 (7.8)	0	26 (10.4)	2 (0.8)	0.36
Micturition disorder	23 (8.6)	0	34 (13.5)	0	0.091
Cough	21 (7.8)	0	27 (10.8)	1 (0.4)	0.289
SAEs	90 (33.6)		94 (37.5)		0.36
AEs leading to discontinuation	69 (25.7)		47 (18.7)		0.058
AEs leading to death	12 (4.5)		13 (5.2)		0.838

AE, adverse event; PTX, paclitaxel; SAE, serious adverse event; TTFields, Tumor Treating Fields.

Table 4
Baseline Patient and Disease Characteristics in Subgroups According to Prior PLD Use.

	PLD-naive		Prior PLD use	
	TTFields+PTX (n = 113)	PTX (n = 88)	TTFields+PTX (n = 167)	PTX (n = 190)
Age, y, median (range)	62 (26–78)	63 (25–80)	60 (22–85)	63 (32–91)
ECOG PS, n (%)				
0	66 (58.4)	58 (65.9)	102 (61.1)	110 (57.9)
1	47 (41.6)	30 (34.1)	65 (38.9)	79 (41.6)
Primary tumor type, n (%)				
Ovarian cancer	99 (87.6)	71 (80.7)	153 (91.6)	160 (84.2)
Peritoneal cancer	6 (5.3)	6 (6.8)	7 (4.2)	8 (4.2)
Fallopian tube cancer	8 (7.1)	11 (12.5)	7 (4.2)	22 (11.6)
Histology at diagnosis, n (%)				
Serous	96 (85.0)	83 (94.3)	147 (88.0)	169 (88.9)
Endometrioid	3 (2.7)	3 (3.4)	8 (4.8)	7 (3.7)
Clear cell	8 (7.1)	0	4 (2.4)	4 (2.1)
Mixed	0	1 (1.1)	3 (1.8)	4 (2.1)
Other	4 (3.5)	1 (1.1)	5 (3.0)	6 (3.2)
Total number of prior lines of systemic therapy, n (%)				
1	30 (26.5)	22 (25.0)	0	2 (1.1)
2	43 (38.1)	32 (36.4)	55 (32.9)	51 (26.8)
3	31 (27.4)	24 (27.3)	61 (36.5)	70 (36.8)
4	8 (7.1)	5 (5.7)	38 (22.8)	50 (26.3)
5	1 (0.9)	4 (4.5)	13 (7.8)	17 (8.9)
Number of prior lines of systemic therapy for PROC, n (%)				
0	89 (78.8)	67 (76.1)	81 (48.5)	94 (49.5)
1	19 (16.8)	17 (19.3)	58 (34.7)	70 (36.8)
2	5 (4.4)	4 (4.5)	28 (16.8)	26 (13.7)
BRCA mutation status, n (%)				
Mutated *BRCA*	15 (13.3)	13 (14.8)	29 (17.4)	30 (15.8)
Wild type *BRCA*/ unknown	98 (86.7)	75 (85.2)	138 (82.6)	160 (84.2)
Prior systemic agents, n (%)				
Bevacizumab	66 (58.4)	53 (60.2)	115 (68.9)	136 (71.6)
Region, n (%)				
North America	39 (34.5)	24 (27.3)	52 (31.1)	64 (33.7)
Eastern Europe	54 (47.8)	48 (54.5)	98 (58.7)	108 (56.8)
Western Europe and Israel	20 (17.7)	16 (18.2)	17 (10.2)	18 (9.5)

BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group Performance Status score; PLD, pegylated liposomal doxorubicin; PROC, platinum-resistant ovarian cancer; PTX, paclitaxel; TTFields, Tumor Treating Fields.

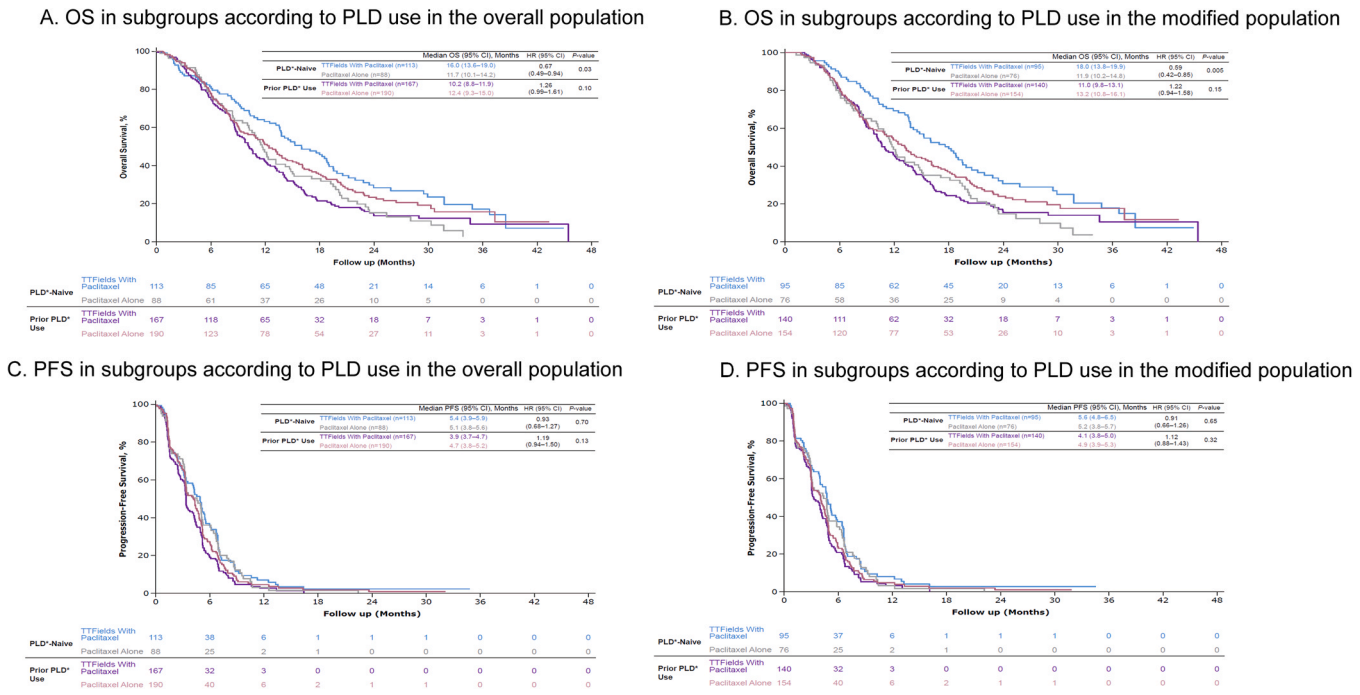

Fig. 3. Kaplan–Meier curve of OS in subgroups according to PLD* use in the overall population (A), OS in subgroups according to PLD* use in the modified population (patients receiving ≥ 1 complete 28-day cycle of study treatments) (B), PFS in subgroups according to PLD* use in the overall population (C), and PFS in subgroups according to PLD* use in the modified population (D). *PLD represented 93 % of the anthracyclines used, and the remaining 7 % was a non-specified doxorubicin formulation. HR, hazard ratio; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; OS, overall survival; TTFields, Tumor Treating Fields.

novel treatment approach. Other therapies, such as mirvetuximab soravtansine-gynx [33], were approved in a more restrictive patient population of high-grade serous ovarian cancer with high folate receptor *a* (FRα-high) tumor expression and ≤ 3 prior LOT. However, only approximately 40 % of patients with PROC are FRα-high [34].

TTFields therapy was well tolerated, with no TTFields-related increase in severe systemic toxicities or SAEs; overall AEs were consistent with PTX treatment in the second-line setting [35,36]. Grade ≥ 3 AEs were similar across treatment arms; TTFields therapy was associated with grades 1–2 skin AEs, which is expected owing to the skin-placed arrays. Skin AEs reflect irritating contact dermatitis, likely associated with exposure of the epidermis to adhesives or hydrogel on the arrays [37]. These safety data are consistent with the pilot INNOVATE study [19] and other clinical and real-world studies of TTFields therapy in additional tumor types [38–42], including post-marketing surveillance data on > 25,000 patients that demonstrated TTFields therapy was not associated with systemic toxicities [43]. Mild-to-moderate skin AEs occurring with TTFields therapy are generally manageable with recommended monitoring and prophylaxis (eg, shifting array locations 2 cm, topical steroid or cream calcineurin inhibitors for skin inflammation, topical antibiotic when the dermis is breached) [44]. Although not assessed in this study, patients needed to adapt to carrying the device even though the second-generation device is smaller and lighter. DSS assistance is available to support patients with TTFields therapy management, including skin care guidelines [37,44].

A significant unmet need remains for safe and effective therapies for PROC. Exploratory post-hoc analysis suggested a potentially favorable benefit-risk profile for TTFields therapy in PLD-naive patients. These findings warrant confirmation in a prospective clinical trial.

5. Conclusions

In the ENGOT-ov50/GOG-3029/INNOVATE-3 study, which included a broad PROC patient population, TTFields+PTX did not improve OS compared with PTX; however, an exploratory post-hoc analysis suggests the addition of TTFields therapy improved survival in PROC patients who were PLD-naive. There were no new safety signals and no additive systemic toxicities with TTFields therapy.

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Non-confidential analyzed data will be made available 3 years after the date of publication upon reasonable request from qualified researchers to Nicolas Leupin, Chief Medical Officer, Novocure (nleupin@novocure.com).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115306.

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