

Biomarker-driven therapies for patients with persistent/recurrent rare epithelial ovarian carcinomas: ENGOT-GYN2/GOG-3051/BOUQUET phase 2 study results

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Background

The most common type of epithelial ovarian cancer is high-grade serous ovarian carcinoma (HGSOC), which accounts for approximately 70% of cases.^{1,2} Rare epithelial ovarian histologies include low-grade serous ovarian carcinoma (LGSOC), low-grade (grade 1/2) endometrioid carcinoma, mucinous carcinoma, clear-cell carcinoma, carcinosarcoma, undifferentiated carcinoma, and mesonephric-like adenocarcinoma. Treatment guidelines for epithelial ovarian cancer have been established based largely on studies in HGSOC. Difficulties in improving treatment for patients with non-HGSOCs are exacerbated by their rarity (<6/100,000 people/year) and short life expectancy in the recurrent setting after platinum-based chemotherapy. The practical and logistical challenges of designing and conducting dedicated trials in specific histologic subtypes of rare ovarian cancers have hindered progress. From the patient perspective, this means that access to novel therapies and clinical trials of investigational agents is limited, representing an important factor contributing to treatment inequity and reducing the level of evidence for treatment decision-making. The ENGOT-GYN2/GOG-3051/BOUQUET platform study has provided a unique opportunity for women with rare epithelial ovarian tumors to participate in a prospective clinical trial and access novel therapies considered most likely to show activity according to the molecular profile of their disease.

Methods

Eligible patients had persistent or recurrent, histologically confirmed, measurable non-high-grade serous/non-high-grade endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (e.g., low-grade serous, clear-cell, mucinous, undifferentiated, or grade 1/2 endometrioid carcinoma, carcinosarcoma, malignant Brenner tumor, mesonephric-like adenocarcinoma), or small-cell carcinoma of the ovary hypercalcemic type. Patients had to have received 1–4 prior lines of non-hormonal systemic therapy, including at least one line of platinum-based chemotherapy. Eligible patients had platinum-resistant disease (i.e., disease progression during or within 6 months of last platinum therapy); however, patients with primary platinum-refractory disease (defined as progression during or within 4 weeks of the last dose of first-line platinum treatment) were not eligible. Patients were required to have Eastern Cooperative Oncology Group performance status 0 or 1 and to provide a tumor specimen for molecular assessment.

Patients were prescreened for eligibility, which included central testing of tumor samples using FoundationOne CDx next-generation sequencing (NGS) and central testing of estrogen receptor (ER) status by immunohistochemistry (IHC; CellCarta; VENTANA SP1 IHC assay). Use of existing FoundationOne CDx NGS and local ER test results was permitted for eligibility. Pathology eligibility was determined by central pathology review of tumor histology by external board-certified gynecologic pathologists.

If patients had more than one biomarker matching an open and enrolling arm, priority was given to the arm with the lower expected prevalence of the biomarker signature. Patients with tumors harboring a *BRAF*, *KRAS*, and/or *NRAS*-activating mutation and/or *NF1* loss-of-function alteration(s) were allocated to oral cobimetinib 60 mg/day on days 1–21 every 28 days. Patients with *ERBB2*-amplified and/or -mutated tumors were allocated to intravenous trastuzumab emtansine (T-DM1) 3.6 mg/kg on day 1 every 21 days. Patients with ER-positive tumors by IHC were allocated to oral giredestrant 30 mg/day with oral abemaciclib 150 mg twice daily, given every day in 28-day cycles. Patients with a biomarker profile that did not match any of the open and enrolling biomarker-driven treatment arms were allocated allocated to the non-matched arms included in the present report were treated with atezolizumab 1200 mg plus bevacizumab 15 mg/kg, both administered intravenously on day 1 every 21 days. All treatments were continued until unacceptable toxicity, consent withdrawal, or disease progression per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (or loss of clinical benefit as assessed by the investigator in patients receiving atezolizumab-containing therapy).

Results

Given the important influence of histology on clinical outcome, the largest histologic subgroup (LGSOC) was explored further in post hoc analyses. In the cobimetinib arm, the cORR in 15 patients with LGSOC was 40% and median PFS was 24.9 months (95% CI: 10.9–27.9 months) (Table 4 and Extended Data Fig. 5). The subgroup of responding patients appeared to be enriched with *BRAF*- compared with *KRAS*-mutated tumors (Fig. 1a). Two (15%) of 13 patients with LGSOC treated with giredestrant–abemaciclib had a confirmed PR, and median PFS was 11.0 months. Median PFS was 17.3 months with atezolizumab–bevacizumab in non-matched patients with LGSOC, despite a low cORR (13%). In seven ABC-treated non-matched patients with LGSOC, there was a higher cORR (43%) but shorter median PFS (9.9 months).

Regimen	Cobimetinib (n = 29)	T-DM1 (n = 21)	Giredestrant + abemaciclib (n = 20)	Atezolizumab + bevacizumab (n = 21)	Atezolizumab + bevacizumab + cyclophosphamide (n = 20)
Grade 3/4 AE, n (%)	19 (66)	10 (48)	14 (70)	11 (52)	9 (45)
Grade 3	17 (59)	7 (33)	12 (60)	10 (48)	9 (45)
Grade 4	2 (7)	3 (14)	2 (10)	1 (5)	0
Grade 5 AE, n (%)	1 (3) ^a	0	0	0	0
Serious AE, n (%)	9 (31)	10 (48)	6 (30)	10 (48)	5 (25)
Related to treatment	4 (14)	6 (29)	Any 4 (20) Gire 2 (10) Aberna 4 (20) Both 2 (10)	Any 6 (29) Atezo 4 (19) Bev 4 (19) Both 2 (10)	0

Regimen	Cobimetinib (n = 29) ^a	T-DM1 (n = 21)	Giredestrant + abemaciclib (n = 20)
Median (range) duration of follow-up, months	7.4 (0–35)	5.3 (0–15)	9.5 (1–12)
Best overall response	(n = 28)	(n = 21)	(n = 20)
Confirmed ORR, n/N (%) [95% CI] [†]	7/28 (25) [11–45]	1/21 (5) [0–24]	1/20 (5) [0–25]
CR	1 (4) [0–18]	0 [0–16]	0 [0–17]
PR	6 (21) [8–41]	1 (5) [0–24]	1 (5) [0–25]
SD	11 (39)	9 (43)	12 (60)
PD	8 (29)	7 (33)	2 (10)
Not evaluable	0	1 (5)	1 (5)
Missing	2 (7)	3 (14)	4 (20)
DCR, n/N (%) [95% CI]	14/28 (50) [31–69]	7 (33) [15–57]	10/20 (50) [27–
Median DoR, months (95% CI) [range]	21.3 (6.0–NE) [3 ^b –29 [†]]	9.1 (NE) [9.1–	NE (NE) [3–3 ^b]
PFS events, n/N (%)	21/28 (75)	17/21 (81)	11/20 (55)
Median PFS, months (95% CI)	5.4 (2.1–10.9)	2.8 (2.0–4.7)	10.1 (5.4–NE)
6-month PFS rate, % (95% CI)	50 (31–69)	23 (4–42)	58 (33–82)
OS events, n (%)	14/28 (50)	13 (62)	5 (25)
Median OS, months (95% CI)	11.6 (7.4–NE)	6.4 (4.8–14.8)	NE (10.0–NE)
6-month OS rate, % (95% CI)	74 (58–91)	63 (41–85)	84 (67–100)

Conclusion

ENGOT-GYN2/GOG-3051/BOUQUET was an ambitious multi-arm, biomarker-guided study in patients with rare epithelial ovarian cancers, identifying signals of antitumor activity with targeted therapy in small subgroups before expanding the sample size in subgroups of interest. The trial evolved into an 11-arm umbrella trial as new investigational agents targeting many of the canonical cancer pathways became available. Notable anticancer activity was observed with cobimetinib in patients with MAPK pathway alterations, particularly in patients with LGSOC, highlighting the importance of considering both mutational profiles and histology when selecting targeted therapies. For non-biomarker-selected patients, bevacizumab–atezolizumab combination regimens showed encouraging outcomes compared with standard-of-care chemotherapy.