8-1-2021

A randomized, double-blind, placebo-controlled, phase II study to assess the efficacy/safety of farletuzumab in combination with carboplatin plus paclitaxel or carboplatin plus pegylated liposomal doxorubicin (PLD) in women with low CA-125 platinum-sensitive ovarian cancer

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Recommended Citation

Herzog T, Pignata S, Ghamande S, Rubio MJ, Fujiwara K, Vulsteke C, Armstrong D, Sehouli J, Coleman R, Gabra H, Scambia G, Monk B, Arija JA, Ushijima K, Hanna R, Zamagni C, Wenham R, Gonzalez-Martin A, Slomovitz B, Jia Y, Ramsay L, Tewari K, Weil S, and Vergote I. A randomized, double-blind, placebo-controlled, phase II study to assess the efficacy/safety of farletuzumab in combination with carboplatin plus paclitaxel or carboplatin plus pegylated liposomal doxorubicin (PLD) in women with low CA-125 platinum-sensitive ovarian cancer. Gynecologic Oncology 2021; 162:S38-S39.

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nonmutant) and 980 were evaluable for gLOH (46% were HRD, 54% HRP). Median TMB was similarly low in *BRCA1/2*m and *BRCA1/2* nonmutant (3.78 vs 2.52 Mut/Mb, respectively), and HRD and HRP (3.78 vs 2.52 Mut/Mb, respectively) tumors. Only 3% (29/1024) of evaluable tumors had TMB ≥10 Mut/Mb and 0.3% (3/1022) were MSI-high (1 mixed, 1 undifferentiated, 1 other). All high-grade serous cases were MS-stable. PFS prognosis (assessed in the placebo + CPB arm) was improved in patients with *BRCA1/2*m (hazard ratio [HR] 0.62, 95% CI 0.46–0.84) and HRD (HR 0.63, 95% CI 0.49–0.80) tumors. There was a suggested association between PD-L1+ and HRD (HRD prevalence: 40% vs 25% in PD-L1+ vs PD-L1– subgroups, respectively; exploratory Fisher's exact test p=0.0001) but not with *BRCA1/2*m (*BRCA1/2*m prevalence: 21% vs 14%, respectively; exploratory Fisher exact test p=0.064). Adding atezolizumab to CPB did not improve PFS, irrespective of *BRCA1/2* or HRD status (table). In the PD-L1+ population, HRs were similar in *BRCA1/2*m and *BRCA1/2* nonmutant subgroups, and in HRD and HRP subgroups. In the PD-L1– population, atezolizumab did not improve PFS.

Population	Median PFS, months		Unstratified PFS
	Atezolizumab + CPB	Placebo + CPB	HR (95% CI)
Intent to treat (n=1301)	19.5	18.4	0.92 (0.79–1.07)
*BRCA1/2*m (n=234)	21.8	21.1	0.87 (0.59–1.29)
BRCA1/2 nonmutant (n=816)	18.7	16.7	0.85 (0.70–1.02)
HRD (n=446)	20.8	20.7	0.92 (0.70–1.21)
HRP (n=534)	18.0	15.3	0.82 (0.66–1.02)
PD-L1+ (n=784)	20.8	18.5	0.81 (0.66–1.00)
*BRCA1/2*m (n=162)	25.8	21.4	0.75 (0.45–1.25)
BRCA1/2 nonmutant (n=509)	20.7	16.4	0.75 (0.59–0.96)
HRD (n=317)	24.8	21.3	0.69 (0.49–0.97)
HRP (n=311)	18.4	16.1	0.81 (0.60–1.09)
PD-L1– (n=517)	17.4	18.3	1.06 (0.84–1.33)
*BRCA1/2*m (n=72)	18.1	19.7	1.16 (0.61–2.20)
BRCA1/2 nonmutant (n=307)	16.0	16.7	0.99 (0.74–1.32)
HRD (n=129)	17.4	20.7	1.76 (1.10–2.82)
HRP (n=223)	17.0	15.2	0.82 (0.58–1.14)

Conclusions: We showed that the majority of ovarian tumors have low TMB scores regardless of *BRCA1/2* or HRD. Neither *BRCA1/2*m nor HRD was associated with greater clinical benefit from adding atezolizumab to CPB. PD-L1 status was more reliably associated with numerically longer PFS with atezolizumab + CPB. This is the first randomized double-blind trial in ovarian cancer to demonstrate that genomic instability triggered by *BRCA1/2*m or HRD does not improve sensitivity to immune checkpoint inhibitors.

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63 - Focused Plenary

A randomized, double-blind, placebo-controlled, phase II study to assess the efficacy/safety of farletuzumab in combination with carboplatin plus paclitaxel or carboplatin plus pegylated liposomal doxorubicin (PLD) in women with low CA-125 platinum-sensitive ovarian cancer

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Objectives: The primary objective of this study (MORAb-003-011/ENGOT-ov27) was to determine if farletuzumab (FAR) had superior efficacy compared with placebo (PLB) in improving progression-free survival (PFS) when added to carboplatin (carbo)/paclitaxel (pacli) or carbo/PLD, in subjects with platinum-sensitive ovarian cancer in first relapse (platinum-free interval: 6-36 months) with low cancer antigen 125 (CA-125). CA-125 inhibits target cell killing via antibody-dependent cellular cytotoxicity, thereby reducing the efficacy of immunotherapeutic antibodies. Subgroup analysis in a prior randomized Phase III study±FAR suggested that subjects with CA-125 levels ≤3 x upper limit of normal (ULN), showed superior PFS (hazard risk [HR] = 0.49) and overall survival (OS, HR = 0.44) compared with PLB.

Methods: Eligibility included age ≥18 years old, CA-125 ≤3 x ULN (105 U/mL), high-grade serous epithelial ovarian cancer, and previous treatment with debulking surgery and first-line platinum-based chemotherapy. Subjects received 6 cycles with either carbo/pacli every 3 weeks or carbo/PLD in combination with either FAR [5 mg/kg weekly] or PLB in a 2:1 ratio. Maintenance treatment with FAR (5 mg/kg weekly) or PLB was given until disease progression. Tumor assessments were every 6 weeks during the Combination Treatment Phase and every 9 weeks during the Maintenance Treatment Phase. The study was designed to detect a PFS HR of 0.667 (33.3% risk reduction) with FAR compared with PLB with approximately 85% power and a 1-sided type I error rate of 0.10. The comparison of PFS between treatment groups was based on the log-rank test. The HR was estimated based on Cox's proportional-hazards model.

Results: A total of 214 subjects were randomized and enrolled, 142 with FAR+chemotherapy (FAR-CT) and 72 with placebo+chemotherapy (PLB-CT). The median PFS in the Intent-to-Treat [ITT] Population was not significantly different between treatment groups; 11.7 months (95% confidence interval [CI]: 10.2, 13.6) versus 10.8 months (95% CI: 9.5, 13.2) for FAR-CT and PLB-CT, respectively (HR = 0.89; 80% CI: 0.71, 1.11). An interim analysis of OS showed no significant difference between treatment groups. The overall response rate (ORR) was 69.6% in 96 subjects treated with FAR-CT versus 73.5% in 50 subjects treated with PLB-CT (p=0.53). No significant differences between treatment groups were observed for any other efficacy parameters. The safety profile of the 2 treatment groups was similar except for an increase in interstitial lung disease among the FAR cohort. Interstitial lung disease occurred in 7 of 141 (5.0%) subjects treated with FAR-CT

(1 with Grade 1, 4 with Grade 2, and 2 with Grade 3) and none in subjects treated with PLB-CT.

Parameter	FAR-CT	PLB-CT
Median PFS (95% CI)	11.7 months (10.2, 13.6)	10.8 months (9.5, 13.2)
ORR; n/N (%)	96/138 (69.6)	50/68 (73.5)
Deaths as a result of an adverse event within 30 days of last dose of drug; n/N (%)	1/141 (1)	1/70 (1)
Serious adverse events; n/N (%)	42/141 (29.8)	17/70 (24.3)
Interstitial lung disease events; n/N (%)	7/141 (5.0)	0

Conclusions: The combination of FAR-CT did not show signals of superior efficacy compared with PLB-CT in improving PFS or other efficacy parameters in subjects with platinum-sensitive recurrent ovarian cancer in first relapse who had low CA-125 levels. No new safety concerns were identified with the combination of FAR-CT. Since FAR binds to the folate receptor alpha, a novel antibody-drug conjugate has been developed and clinical studies are ongoing to assess the safety/efficacy of this modification.
Clinical Trial Registry: NCT02289950.

64 - Focused Plenary
Randomized phase II trial of durvalumab (anti-PDL1) and tremelimumab (anti-CTLA4) administered in combination versus sequentially for the treatment of recurrent platinum-resistant non-clear cell ovarian cancer (NCT03026062)

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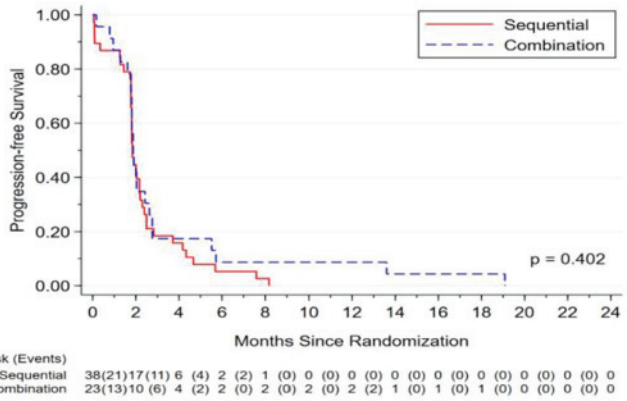
Objectives: Single agent immune checkpoint blockade (ICB) has demonstrated response rates of 5-15% in patients with recurrent high-grade ovarian cancer (HGOC), with another 15-40% of patients achieving stable disease. Combination ICB using ipilimumab and nivolumab resulted in improved response rates in a mixed population with platinum resistant and sensitive disease. The objective of the current trial was to evaluate sequential versus combination CTLA4 and PDL1 blockade strategies for extending progression free survival (PFS) in patients with platinum resistant/refractory HGOC.
Methods: Patients were required to have pathologically confirmed platinum resistant or refractory epithelial ovarian cancer, no prior immunotherapy, and PS= 0-1 for enrollment. The current abstract includes data only on subjects with high grade serous ovarian cancer (HGSOC), as enrollment of patients with clear cell histology is still ongoing. The primary endpoint was PFS and response was assessed using modified RECIST v1.1. Unlimited numbers of prior regimens were allowed. Patients were adaptively randomized to sequential arm: tremelimumab (3mg/kg q4 weeks x 4 doses) followed by durvalumab (1.5g IV q4 weeks for up to 9 doses) upon progression, or the combination arm: tremelimumab (1mg/kg IV plus durvalumab 1.5g IV q4wk for up to 4 doses followed by durvalumab monotherapy for up to 9 doses). For the Bayesian adaptive randomization, the probability of being assigned to an arm was proportional to the likelihood the arm had better PFS, such that patients were more likely to be randomized to the more effective arm.
Results: A total of 61 subjects were adaptively randomized to sequential treatment (n=38) or combination therapy (n=23). 46 (79%) patients had wild-type breast cancer gene (*BRCA*). Median prior lines of therapy was 4 (range: 1-10). There was no difference in median PFS in the sequential arm (1.84 months ; 95% CI: 1.77 – 2.17)) compared with the combination arm (1.87 months; 95% CI: 1.77 – 2.43), p=0.402. Similarly, median OS in the sequential and combination arms were 10.61 months (5.95 – 15.34) and 7.26 (4.24 – 15.57), respectively (p=0.810). In the sequential arm no objective responses were observed, although 12 patients (31.6%) exhibited stable disease. In the combination arm, 2 patients had partial response (8.7%) while one additional patient (4.4%) had stable disease. The adverse event profile was consistent with that previously reported for immune checkpoint therapy.



Conclusions: There was no difference in the median PFS between the combination and sequential durvalumab plus tremelimumab treatment strategy arms in a heavily pretreated population of patients with platinum resistant/refractory HGOC. Response rates were comparable to prior reports, though the combination regimen did not add significant benefit as has been previously described with combination of ipilimumab/nivolumab. Further exploration into subpopulations that may have increased benefit from ICB is warranted.

65 - Focused Plenary
KGOG 3046/TRU-D: a phase II study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy in patients with advanced-stage epithelial ovarian cancer

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Objectives: We hypothesized that adding durvalumab and tremelimumab to chemotherapy in advanced-stage epithelial ovarian cancer (aEOC) would increase progression-free survival (PFS) with minimal effects on safety. KGOG 3046 (NCT03899610) is a single-arm phase 2 study evaluating the combination of dual immune checkpoint inhibition and neoadjuvant chemotherapy (NAC) for the upfront treatment of aEOC.
Methods: Patients with FIGO stage IIIC-IV EOC were offered three cycles of durvalumab (1500 mg), tremelimumab (75 mg) with chemotherapy for NAC followed by interval debulking surgery (IDS). After surgery, three cycles of durvalumab (1120 mg) and adjuvant chemotherapy followed by durvalumab maintenance (1120 mg [total 12 cycles]) were administered. During treatment, serial biopsies were performed at pre-treatment, IDS, and progression to identify immune biomarkers and changes in the tumor microenvironment. The primary endpoint was a 12 months PFS rate. Interim analysis was performed to evaluate outcomes after NAC (RECIST after NAC, R0 rate