MOONSTONE/GOG-3032: Interim Analysis of a Phase 2 Study of Niraparib + Dostarlimab in Patients With Platinum-Resistant Ovarian Cancer

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Background

Ovarian cancer has the highest mortality of all gynecologic cancers.[1] Although initial response to surgery and first-line platinum-based chemotherapy is favorable, up to 70% of patients relapse and the majority of tumors become platinum-resistant.[2,3]

Patients with platinum-resistant ovarian cancer have a high unmet need for effective anti-cancer therapies; few treatment options are available, especially for those without a *BRCA* mutation (*BRCA*m).[4,5]

Niraparib is a poly (ADP-ribose) polymerase inhibitor (PARPi) approved for:

- Maintenance treatment after first-line treatment or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (OC) in adult patients who have had a complete or partial response to platinum-based chemotherapy (USA and EU).[6,7]
- Treatment of adult patients with advanced, homologous recombination deficiency (HRD)-positive OC who have received ≥3 prior chemotherapy regimens (USA).[6]

Dostarlimab is an anti-programmed death 1 (PD-1) humanized monoclonal antibody that binds with high affinity to the PD-1 receptor, effectively blocking interaction with the PD-1 ligands (PD-L1 and PD-L2), and shows activity in patients with solid tumors, including those who have progressed after a platinum-based regimen.[8,9]

PARPi + anti-PD-1/PD-L1 combinations may have synergistic antitumor effect, regardless of *BRCA*m status.[10,11]

- TOPACIO reported an objective response rate (ORR: 18%) and disease control rate (DCR: 65%) with niraparib in combination with the PD-1 inhibitor pembrolizumab in patients with OC of any *BRCA* status.[12]

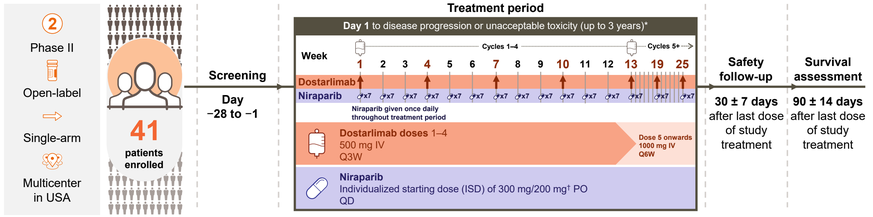
MOONSTONE (GSK study 213353; NCT03955471) is a Phase II open-label, single-arm study that evaluated efficacy and safety of niraparib in combination with dostarlimab in patients with advanced platinum-resistant OC (PROC) without a known *BRCA*m who received prior bevacizumab. Here we present an interim analysis (data cutoff October 6, 2021).

Aim

To evaluate the efficacy and safety of niraparib + dostarlimab in patients with advanced, relapsed, high-grade, PROC without a known *BRCA*m who progressed and had received prior bevacizumab.

Methods

Study design



Study population

Key inclusion criteria

- Female, ≥18 years of age.
- Recurrent high-grade serous, endometrioid, or clear cell ovarian, fallopian tube, or primary peritoneal cancer.
- Have received 1−3 lines of prior therapy with platinum, taxane, and bevacizumab.
- Have had disease progression <6 months from the last administered platinum therapy (as evidenced by radiographic progression per RECIST v.1.1[13]).
- Measurable disease (according to RECIST version v.1.1[13]).
- ECOG performance status of 0 or 1.
- Adequate organ function.

Key exclusion criteria

- Prior treatment with a PARPi, anti-PD-1, anti–PD-(L)1 or anti–PD-L2 agent.
- Known deleterious or suspicious deleterious mutations in *BRCA1/2*.
- Disease progression within 3 months (as evidenced by radiographic progression per RECIST v.1.1[13]) of first-line platinum therapy.

Study objectives and endpoints

Primary endpoint‡

ORR assessed by investigator:

- In the overall population.
- In the subset of patients with vCPS ≥5%.

Key secondary endpoints‡

DoR OS
PFS DCR
ORR assessed by an independent review committee.
Safety and tolerability of combination treatment.

Exploratory endpoints

Efficacy in patients with confirmed *BRCA* wild-type tumors.‡, §
Duration of disease control in patients with best overall response of SD, PR, or CR.
HRQoL as measured by FOSI.
Disease-related and treatment-related biomarkers of response, including:

- Measures of homologous recombination repair pathway defects.
- Optimal PD-L1 levels for efficacy.

CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FOSI, Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; vCPS, visually-estimated combined positive score; QD, daily. *Other reasons for discontinuation include withdrawal of consent, investigator's decision, or death. Patients who discontinue one of the treatments due to adverse events will be able to continue treatment with the second agent until disease progression or unacceptable toxicity. †ISD of 300 mg in patients with a screening actual body weight ≥77 kg and platelet count ≥150,000/µL or 200 mg in patients with screening actual body weight <77 kg or platelet count <150,000/µL. ‡ Time-to-event efficacy analyses were performed using Kaplan-Meier methods and tumor response was evaluated using RECIST v1.1[13]. §Definitive germline *BRCA* mutation status per tumor sample obtained during study. Adverse events (AEs) could be volunteered spontaneously by the study subject or discovered by study staff during physical examination or by asking open, nonleading questions; AEs were coded using the Medical Dictionary for Regulatory Activities and summarized. Futility was prespecified as ≤5 responses in the first 40 patients, therefore, the predictive probability of early termination was 79% with true ORR of 10%.

Results

Patient population

At interim analysis (data cutoff October 6, 2021), 41 patients were enrolled in the study.

Median patient age was 65 years (range, 35–77); most patients received 2 prior lines of therapy and most had primary resistance to platinum therapy (**Table 1**).

- Most patients had PD-L1 vCPS <5%.

Table 1. Demographics, baseline, and clinical characteristics

Characteristic, n (%)	Overall population N=41
Age, median (range)	65 (35–77)
Sex, female	41 (100)
Race	
White	32 (78)
Black or African American	3 (7.8)
Asian	2 (4.9)
Native American	1 (2.4)
Unknown	3 (7.3)
ECOG status	
0	26 (63.4)
1	15 (36.6)
g*BRCA* status*	
g*BRCA*wt	39 (95.1)
Unknown	2 (4.9)
PD-L1 status†	
vCPS ≥5%	13 (31.7)
vCPS <5%	25 (61.0)
Unknown	3 (7.3)
Prior lines of therapy	
1	8 (19.5)
2	22 (53.7)
3	11 (26.8)
Response to first line of platinum therapy	
Platinum-resistant (28 < PFI < 190 days)	26 (63.4)
Platinum-sensitive (PFI ≥ 190 days)	15 (36.6)

ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval; vCPS, visually-estimated Combined Positive Score. *Centralized g*BRCA* status was determined using Myriad *BRCA* Analysis test on blood samples. †PD-L1 status was determined using the PD-L1 immunohistochemistry test (Ventana SP263) on tumor samples; vCPS score is based on a composite of PD-L1 expression on tumor and immune cells. PD-L1 status was missing for 3 patents (2 quantity not sufficient and 1 had a sample >2 years out of the stability testing for PD-L1 testing).

Efficacy

At interim analysis, ORR was 7.3% (PR in 3 out of 41 patients) in the overall population (**Table 2**).

- Median PFS was 2.1 months (range, 2.0–2.2) in the overall population.

In the 3 patients with PR, DoR was 3, 3.8* and 9.2* months. Best overall responses are summarized in **Figure 1**.

PD-L1 status did not predict response in this patient population (**Table 2**).

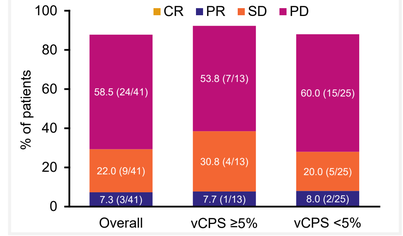
*Censored per protocol censoring rules.

Table 2. Efficacy overview

Efficacy, n (%) [95% CI]*	Overall N=41	PD-L1 status	
		vCPS ≥5% n=13	vCPS <5% n=25
ORR (CR + PR)	3 (7.3) [1.5–19.9]	1 (7.7) [0.2–36.0]	2 (8.0) [1.0–26.0]
DCR (CR + PR + SD)	12 (29.3) [16.1–45.5]	5 (38.5) [13.9–68.4]	7 (28.0) [12.1–49.4]
Median PFS, months (95% CI)	2.1 (2.0–2.2)	2.2 (1.6–not evaluable)	2.1 (1.8–2.2)

CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.
*Clopper-Pearson method

Figure 1. Best overall responses



Safety

Safety data are summarized in **Table 3**.

The most common treatment-related adverse events (TRAEs) were nausea, fatigue, vomiting, and anemia (**Table 4**).

Table 3. Safety overview

Event n (%)	Overall population N=41
Any TEAE	41 (100)
Any TRAE	39 (95.1)
Any grade ≥3 TEAE	31 (75.6)
Any serious TEAE	21 (51.2)
Any TEAE leading to study drug interruption/reduction/delay	29 (70.7)
TEAE leading to niraparib interruption	28 (68.3)
TEAE leading to niraparib dose reduction	13 (31.7)
TEAE leading to dostarlimab interruption	0 (0)
TEAE leading to dostarlimab delay	14 (34.1)
Fatal TEAEs	0 (0)

Table 4. TRAEs occurring in >10% of patients

Adverse event n (%)	Related to either niraparib or dostarlimab	Related to niraparib	Related to dostarlimab
Nausea	23 (56.1)	21 (51.2)	11 (26.8)
Fatigue	14 (34.1)	13 (31.7)	13 (31.7)
Vomiting	13 (31.7)	13 (31.7)	7 (17.1)
Anemia	13 (31.7)	13 (31.7)	7 (17.1)
Platelet count decreased	11 (26.8)	11 (26.8)	0 (0)
Thrombocytopenia	8 (19.5)	8 (19.5)	0 (0)
Constipation	7 (17.1)	7 (17.1)	2 (4.9)
Diarrhea	6 (14.6)	5 (12.2)	6 (14.6)
Aspartate aminotransferase increased	6 (14.6)	4 (9.8)	4 (9.8)
Blood creatinine increased	6 (14.6)	5 (12.2)	1 (2.4)
Decreased appetite	6 (14.6)	5 (12.2)	3 (7.3)
Abdominal pain	5 (12.2)	5 (12.2)	1 (2.4)
Dyspnea	5 (12.2)	3 (7.3)	4 (9.8)
Hypertension	5 (12.2)	5 (12.2)	0 (0)
Insomnia	5 (12.2)	5 (12.2)	0 (0)

Conclusions

The ORR observed with niraparib in combination with dostarlimab did not reach the threshold for second-stage accrual, highlighting that PROC is difficult to treat and there remains an unmet need for effective treatments for patients with PROC and no known *BRCA*m, and prior bevacizumab treatment.

Although DCR was 29.3%, futility was declared based on low ORR.

PD-L1 status did not predict response, highlighting the need for robust biomarkers to predict response in PROC.

The safety of the combination was similar to the safety profile of each agent as monotherapy.

Disclosures

LMR reports personal fees from GSK/Tesaro for consultancy unrelated to this study; **DMO** reports grant funding (to the institution); personal fees for an advisory board; support for manuscript preparation from GSK/Tesaro; **BJM** reports consulting/advisory role and honoraria for AbbVie, ChemoCare, ChemoID, Eisai, Geistlich Pharma, Incyte, Mateon Therapeutics, Merck, Myriad Pharmaceuticals, Perthera, Precision Oncology, Samumed, Takeda, and VBL Therapeutics; consulting/advisory role, honoraria, and research funding (to the institution) from Advaxis, Amgen, Immunogen, NuCana BioMed and Pfizer; consulting/advisory role, speakers bureau, honoraria, and research funding (to the institution) from AstraZeneca, Roche/Genentech and Tesaro; consulting/advisory role, speakers bureau and honoraria from Clovis Oncology; speakers bureau, honoraria and research funding (to the institution) from Janssen; consulting/advisory role for Cerulean Pharma, OncoMed, and OncoSec; a leadership role for US Oncology; honoraria from Agenus, Conjupro Biotherapeutics, Genmab, Immunomedics, OncoQuest, and Puma Biotechnology; research funding (to the institution) from Array BioPharma, Lilly, Morphotek, Novartis, and Regeneron; **RLC** reports consulting, grant and honoraria/reimbursement from AstraZeneca, Clovis Oncology, Janssen, Merck, and Roche/Genentech; consulting and honoraria/reimbursement from Arrivive, Eisai, Novocure, Oncomed/Mateo, OncoQuest, OncoSec, and Tesaro/GSK; consulting and grant from AbbVie, grant from Genmab and V-Foundation; **SG** reports a consulting/advisory role for AstraZeneca, Immunogen, Rigel, and Sermonix Pharmaceuticals; research funding (to the institution) from AbbVie, AstraZeneca, Genentech/Roche, Iovance Biotherapeutics, Pfizer, PharmaMar, and Tesaro; hold patents, royalties or other intellectual property with Sermonix Pharmaceuticals; **SA** reports research funding from AstraZeneca; **LD** Reports consulting/advisory role for Genentech/Roche, Merck, Inovio Pharmaceuticals, CUE Biopharma; institutional research funding from GSK, Millennium, Bristol-Myers Squibb, Aeterna Zentaris, Novartis, Abbvie, Tesaro, Cerulean Pharma, Aduro Biotech, Advaxis, Syndax, Pfizer, Merck, Genentech/Roche, Cerulean Pharma, Morab, Morphotek, Syndax, Ludwig Institute for Cancer Research, Leap Therapeutics; **HD** reports a consulting/advisory role for Eisai and Merck; **RWH** reports speaker's bureau from AstraZeneca, Clovis, and GSK; **MH** reports advisory board participation for Clovis Oncology and Janssen; grant funding from Lilly and Merck; **HSC** has nothing to disclose; **NGC** reports participation in advisory boards from AstraZeneca, GSK, Toray, Tarveda Therapeutics, Aadi; **ACEN** is an employee and stockholder in Natera Inc.; **REO** reports personal fees for advisory boards from Tesaro and GSK; and reports non-paid membership of steering committees for the PRIMA and DUO-O studies; **SW** reports a consulting/advisory role for Regeneron; **ZW**, **EZ** and **VS** are employees of and stockholders in GSK; **PAK** reports personal fees for advisory board participation from AstraZeneca, Merck, and Pfizer.

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