Supplementary Online Content

Konstantinopoulos PA, Waggoner S, Vidal GA, et al. Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma. *JAMA Oncol.* Published online June 13, 2019. doi:10.1001/jamaoncol.2019.1048

This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods

Phase 1 Patients

Patients were enrolled with either advanced or metastatic TNBC or advanced, recurrent epithelial (any serous, endometrioid, mucinous, or clear cell) ovarian, fallopian tube, or primary peritoneal cancer (collectively referred to as OC). OC patients must have had a response lasting at least 6 months to first-line platinum-based therapy but were considered to have either "acquired" platinum-resistant disease following subsequent platinum therapy per investigator's assessment at the time of enrollment, or were not eligible for further platinum-containing treatment based on toxicity or allergy. OC patients may have received up to 5 lines of cytotoxic therapy; (neo)adjuvant therapy, small molecules (eg, tyrosine kinase inhibitors), hormonal agents, and bevacizumab were not counted as separate lines of therapy.

Phase 2 Patients

The phase 2 OC part of the study further evaluated the RP2D and dosing schedule in patients with advanced, recurrent epithelial high-grade serous or endometrioid OC who had experienced a response lasting at least 6 months to first-line platinum-based therapy but were considered to have platinum-resistant disease as in phase 1. Patients may have received up to 4 lines of cytotoxic therapy; neoadjuvant, adjuvant, and the combination of both were considered to be one line of therapy. Small molecules, hormonal agents, and bevacizumab were not counted as lines of therapy. Patients with primary platinum-refractory OC or those who had received prior treatment with a PARPi, anti-PD-1, or anti-PD-L1/2 were not eligible.

DLTs

DLTs were defined as grade ≥3 treatment-related nonhematologic adverse events or any grade ≥3 treatment-related hematologic adverse event lasting ≥7 days or associated with bleeding (thrombocytopenia), infection or febrile illness (neutropenia) or requiring blood transfusion (thrombocytopenia or anemia). If 2 of the 6 initially enrolled patients in a cohort experienced hematologic DLTs, a lower dose level was opened. If the 2 observed DLTs included one hematologic DLT and one nonhematologic DLT or 2 nonhematologic DLTs, dose level 1 cohort was expanded up to approximately 12 patients to better characterize the safety of the combination treatment.

Biomarker Testing

Tumor *BRCA* mutation (t*BRCA*) and HRD status were evaluated using the Myriad Genetics (Salt Lake City, UT, USA) research assay. Germline *BRCA* (g*BRCA*) results from local testing performed by individual sites were collected when available. PD-L1 expression was evaluated by Merck & Co., Inc (Kenilworth, NJ, USA); PD-L1 status was determined using a CPS 1 provisional cutoff by immunohistochemistry (IHC) using an investigational version of the PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA, USA). The CPS is the number of positively stained tumor and immune cells relative to total tumor cells.

Phase 1 Results

Of the 14 patients in phase 1, 7 patients received 200 mg niraparib once daily in combination with 200 mg pembrolizumab once every 21 days (dose level 1), and 7 patients received 300 mg niraparib once daily in combination with 200 mg pembrolizumab once every 21 days (dose level 2). At dose level 1, grade ≥3 treatment-related adverse events were reported in 3 of 7 patients, with DLTs occurring in 1 patient (grade 3 anemia, grade 4 thrombocytopenia, and grade 4 neutropenia) (**eTable 1**). At dose level 2, grade ≥3 treatment-related adverse events were reported in 7 of seven patients, with a DLT occurring in 1 patient (grade 4 thrombocytopenia) and a DLT equivalent occurring in a second patient (grade 4 thrombocytopenia on cycle 2 day 1). No treatment-related deaths were reported.

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eTable 1. Grade ≥3 Treatment-Related Adverse Events in Phase 1*

Adverse Event, n (%)	Dose Level 1† n=7	Dose Level 2‡ n=7	Total N=14
Anemia	2 (29)	3 (43)	5 (36)
Thrombocytopenia	1 (14)	4 (57)	5 (36)
Neutropenia	1 (14)	1 (14)	2 (14)
Pancytopenia	0	1 (14)	1 (7)
Colitis	1 (14)	0	1 (7)
Decreased appetite	1 (14)	0	1 (7)
Hyperglycemia	1 (14)	0	1 (7)
Fatigue	1 (14)	0	1 (7)
Nausea	0	1 (14)	1 (7)
Stomatitis	1 (14)	0	1 (7)

Data are n (%).
*Causality by drug was not assessed; adverse events may have been related to niraparib, pembrolizumab, or both.
†Dose level 1: niraparib 200 mg oral once daily + pembrolizumab 200 mg intravenous once every 21 days.
‡Dose level 2: niraparib 300 mg oral once daily + pembrolizumab 200 mg intravenous once every 21 days.

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eTable 2. Patient Baseline Characteristics

Characteristic	Phase 1 Ovarian Cancer Patients n=9	Phase 2 Ovarian Cancer Patients n=53	Combined Phase 1 and 2 Ovarian Cancer Patients N=62
Age, median (range), years	62.0 (48–72)	60.0 (46–83)	60.0 (46–83)
ECOG PS, n (%)			
0	7 (78)	37 (70)	44 (71)
1	2 (22)	16 (30)	18 (29)
Prior lines of therapy, median (range)	2 (1–3)	3 (1–5)	3 (1–5)
Prior bevacizumab, n (%)	6 (67)	33 (62)	39 (63)
Prior chemotherapies, n (%)[a]			
Anthracycline	5 (56)	35 (66)	40 (65)
Cyclophosphamide	1 (11)	4 (8)	5 (8)
Gemcitabine	4 (44)	25 (47)	29 (47)
Paclitaxel	9 (100)	52 (98)	61 (98)
Platinum	9 (100)	53 (100)	62 (100)
Topotecan	1 (11)	2 (4)	3 (5)
Platinum status, n (%)			
Not applicable[b]	4 (44)	11 (21)	15 (24)
Resistant	4 (44)	26 (49)	30 (48)
Refractory	1 (11)	16 (30)	17 (27)
t*BRCA* status, n (%)			
BRCA1 mutation	1 (11)	8 (15)	9 (15)
BRCA2 mutation	1 (11)	1 (2)	2 (3)
BRCA wildtype	7 (78)	42 (79)	49 (79)
Unknown	0	2 (4)	2 (3)
HRD status, n (%)			
HRD	4 (44)	18 (34)	22 (35)
Non-HRD	4 (44)	29 (55)	33 (53)
Unknown	1 (11)	6 (11)	7 (11)
PD-L1 status, n (%)[c]			
Positive	4 (44)	31 (58)	35 (56)
Negative	5 (56)	16 (30)	21 (34)
Unknown	0	6 (11)	6 (10)

Data are n (%).
ECOG PS=Eastern Cooperative Oncology Group Performance Status; HRD=homologous recombination deficiency; PD-L1=programmed cell death receptor ligand 1; t*BRCA*=tumor *BRCA*; TNBC=triple-negative breast cancer.
[a]Prior chemotherapies only include chemotherapies used in >1 patient, therapies used in only 1 patient are not listed.
[b]Patients with platinum-free interval ≥180 days but unable to receive further platinum (due to toxicity or allergic reaction).
[c]PD-L1 positivity was based on CPS 1 provisional cutoff by immunohistochemistry.

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eTABLE 3. Treatment-Related Adverse Events (TRAEs) Occurring in ≥10% of Phase 2 Ovarian Cancer Patients and All irTRAEs[a]

Adverse Event, no. (%)	Any Grade N=53	Grade ≥3 N=53
Treatment-Related Adverse Events		
Fatigue	28 (53)	2 (4)
Nausea	22 (42)	2 (4)
Anemia	19 (36)	11 (21)
Constipation	19 (36)	1 (2)
Thrombocytopenia	14 (26)	5 (9)
Decreased appetite	12 (23)	1 (2)
Vomiting	11 (21)	2 (4)
Headache	8 (15)	1 (2)
Diarrhea	8 (15)	1 (2)
Insomnia	7 (13)	0
Dyspnea	6 (11)	1 (2)
Rash	6 (11)	0
Weight decreased	6 (11)	1 (2)
Prespecified irTRAEs		
Any immune-related TRAE	10 (19)	3 (6)
Hypothyroidism	7 (13)	1 (2)
Hyperglycemia	1 (2)	1 (2)
Autoimmune dermatitis	1 (2)	1 (2)
Infusion-related reaction	1 (2)	0
Thyroiditis	1 (2)	0

Data are no. (%).
[a]Causality by drug was not assessed; adverse events may have been related to niraparib, pembrolizumab, or both.

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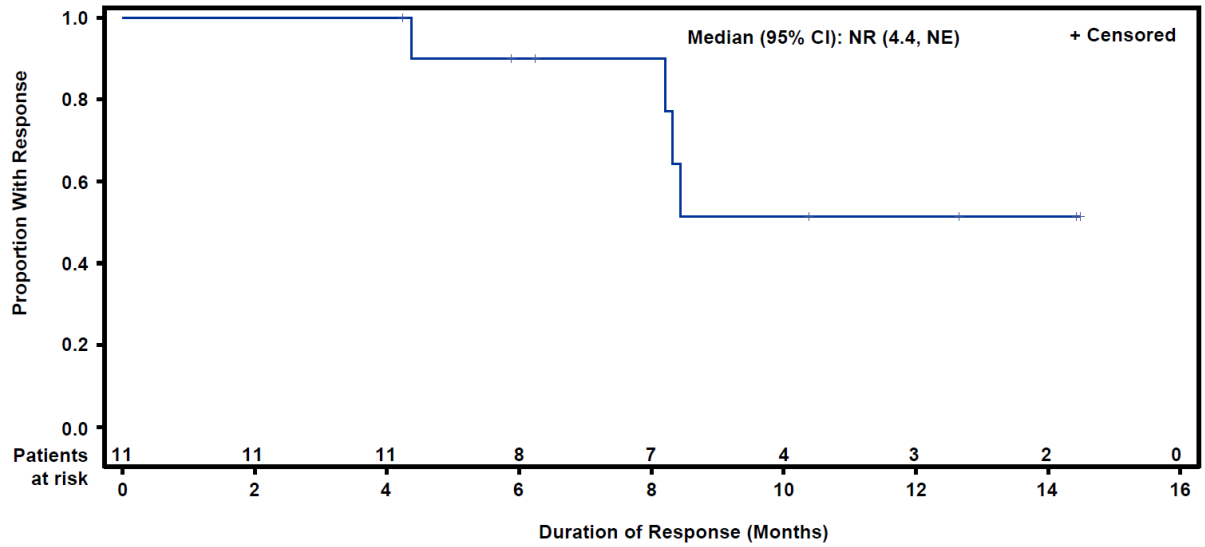
eFigure. Duration of Response



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