Open-label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer

Shaveta Vinayak, MD, MS; Sara M. Tolaney, MD, MPH; Lee Schwartzberg, MD; Monica Mita, MD; Georgia McCann, MD; Antoinette R. Tan, MD; Andrea E. Wahner-Hendrickson, MD; Andres Forero, MD; Carey Anders, MD; Gerburg M. Wulf, MD, PhD; Patrick Dillon, MD; Filipa Lynce, MD; Corrine Zarwan, MD; John K. Erban, MD; Yinghui Zhou, PhD; Nathan Buerстатte, BS, MPH; Julie R. Graham, PhD; Sujata Arora, MS; Bruce J. Dezube, MD; Melinda L. Telli, MD

IMPORTANCE Poly(adenosine diphosphate–ribose) polymerase inhibitor and anti–programmed death receptor-1 inhibitor monotherapy have shown limited clinical activity in patients with advanced triple-negative breast cancer (TNBC).

OBJECTIVE To evaluate the clinical activity (primary) and safety (secondary) of combination treatment with niraparib and pembrolizumab in patients with advanced or metastatic TNBC.

DESIGN, SETTING, AND PARTICIPANTS This open-label, single-arm, phase 2 study enrolled 55 eligible patients with advanced or metastatic TNBC irrespective of BRCA mutation status or programmed death-ligand 1 (PD-L1) expression at 34 US sites. Data were collected from January 3, 2017, through October 29, 2018, and analyzed from October 29, 2018, through February 27, 2019.

INTERVENTIONS Patients were administered 200 mg of oral niraparib once daily in combination with 200 mg of intravenous pembrolizumab on day 1 of each 21-day cycle.

MAIN OUTCOMES AND MEASURES The primary end point was objective response rate (ORR) per the Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary end points were safety, disease control rate (DCR; complete response plus partial response plus stable disease), duration of response (DOR), progression-free survival (PFS), and overall survival.

RESULTS Within the full study population of 55 women (median age, 54 years [range, 32-90 years]), 5 patients had confirmed complete responses, 5 had confirmed partial responses, 13 had stable disease, and 24 had progressive disease. In the efficacy-evaluable population (n=47), ORR included 10 patients (21%; 90% CI, 12%-33%) and DCR included 23 (49%; 90% CI, 36%-62%). Median DOR was not reached at the time of the data cutoff, with 7 patients still receiving treatment at the time of analysis. In 15 evaluable patients with tumor BRCA mutations, ORR included 7 patients (47%; 90% CI, 24%-70%), DCR included 12 (80%; 90% CI, 56%-94%), and median PFS was 8.3 months (95% CI, 2.1 months to not estimable). In 27 evaluable patients with BRCA wild-type tumors, ORR included 3 patients (11%; 90% CI, 3%-26%), DCR included 9 (33%; 90% CI, 19%-51%), and median PFS was 2.1 months (95% CI, 1.4-2.5 months). The most common treatment-related adverse events of grade 3 or higher were anemia (10 [18%]), thrombocytopenia (8 [15%]), and fatigue (4 [7%]). Immune-related adverse events were reported in 8 patients (15%) and were grade 3 in 2 patients (4%); no new safety signals were detected.

CONCLUSIONS AND RELEVANCE Combination niraparib plus pembrolizumab provides promising antitumor activity in patients with advanced or metastatic TNBC, with numerically higher response rates in those with tumor BRCA mutations. The combination therapy was safe with a tolerable safety profile, warranting further investigation.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT02657889

Published online June 13, 2019.

© 2019 American Medical Association. All rights reserved.
Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype that lacks estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (ERBB2/HER2 [formerly HER2 or HER2/neu]; OMIM 164870) expression. Triple-negative breast cancer carries a poorer prognosis than other subtypes, with 10-year survival rates of less than 50%. Targeted therapies are not currently available for non–BRCA-mutated TNBC, and chemotherapy remains the standard of care despite its limited benefit. In clinical trials, patients with advanced TNBC treated with single-agent taxane- or platinum-based chemotherapy had a median progression-free survival (PFS) of 4 to 6 months and a median overall survival of 11 to 17 months. Addition of anti–programmed death-ligand 1 (PD-L1) antibody atezolizumab to chemotherapy with albumin-bound paclitaxel in patients with untreated metastatic TNBC improved PFS and numerically improved overall survival vs albumin-bound paclitaxel alone.

Programmed death receptor-1 (PD-1) limits autoimmunity by inhibiting effector T lymphocytes and is activated by the immunosuppressive PD-L1. Tumor cell–expressed PD-L1/2 ligands can bind PD-1 receptors to inactivate T cells, thus evading immune system-mediated destruction. Expression of PD-L1 positively correlates with the presence of tumor-infiltrating lymphocytes, and expression of both is higher in TNBC tumors than in other breast cancer subtypes. Response rates to anti–PD-1 and anti–PD-L1 antibodies alone range from 5% to 23%, with higher rates observed when these are used as first-line therapy and among patients with PD-L1-positive tumors. Although these clinical activities are modest at best, the few patients who respond have shown long durations of response and survival.

Poly(adenosine diphosphate–ribose) polymerase (PARP) enzymes act to detect and repair DNA damage, and blocking this process with PARP inhibitors leads to cell death through synthetic lethality, particularly in cells already deficient in homologous recombination repair (HRR). Tumor mutations in BRCA1 (OMIM 113705) and BRCA2 (OMIM 600185) (t(BRCAmut) cause defects in HRR and are estimated to be present in 20% to 25% of patients with basal-like TNBC. In the registrational phase 3 trial of the PARP inhibitor olaparib, the subgroup of patients with germline BRCAmut TNBC had an objective response rate (ORR) of 55% and experienced a benefit in PFS compared with patients receiving the physician’s choice of treatment. In the registrational phase 3 trial of talazoparib tosoylate, patients with germline BRCA mutation TNBC had an ORR of 62% and a PFS of 5.8 months. Monotherapy with PARP inhibitors has not shown activity outside patients with BRCA mutations. In a phase 2 study of olaparib, no responses to olaparib occurred among 21 patients with TNBC irrespective of BRCA mutation status, and PFS was only 54 days. Monotherapy with PARP inhibitors has not been well studied in tumors with DNA repair defects other than BRCA.

Preclinical models have shown that PARP inhibitors and anti–PD-1 antibodies show synergistic antitumor activity irrespective of BRCA mutation status and PD-L1 expression. The TOPACIO/KEYNOTE-162 (Niraparib in Combination With Pembrolizumab in Patients With Triple-Negative Breast Cancer or Ovarian Cancer) trial evaluated the hypothesis that combination treatment of niraparib plus pembrolizumab would be a safe and effective therapy for patients with advanced or metastatic TNBC.
Per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), patients who achieved a complete response or a partial response had the response confirmed. Details of biomarker testing are provided in eMethods in Supplement 2.

Outcomes
The primary objective of the phase 2 TNBC cohort study was to assess the clinical activity of combination treatment with niraparib and pembrolizumab using the primary end point of ORR, as assessed by the investigators per RECIST 1.1. Secondary end points included the duration of response (DOR) per RECIST 1.1; disease control rate (DCR), defined as the proportion of patients achieving a complete response, a partial response, or stable disease as per RECIST 1.1; PFS; and overall survival. Full definitions of outcome measures, including exploratory objectives and safety variables, are in eMethods in Supplement 2.

Statistical Analysis
Data were analyzed from October 29, 2018, to February 27, 2019. Demographics, baseline characteristics, and safety results were summarized descriptively. Efficacy was evaluated by determining confirmed ORR using RECIST 1.1. Response end points were evaluated using the full analysis set, defined as all patients who received any amount of the study treatment, as well as the efficacy-evaluable analysis set, which included points were evaluated using the full analysis set, defined as by determining confirmed ORR using RECIST 1.1. Response end points were evaluated using the full analysis set, defined as all patients who received any amount of the study treatment, as well as the efficacy-evaluable analysis set, which included all patients who received any amount of the study treatment and who had at least 1 evaluable postbaseline tumor assessment. Point estimates and 2-sided 90% CIs were provided for the analysis of ORR and DCR. For time-to-event end points, the median and corresponding 2-sided 95% CIs were obtained using Kaplan-Meier methods. Safety was evaluated in all patients who received any amount of the study treatment. Exploratory subgroup analyses were performed by biomarker status (BRCA, HRR, and PD-L1) using descriptive methods; no inferential analyses were performed on any subgroup. All statistics were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Patients
From January 3 through October 4, 2017, 55 women with TNBC were enrolled in phase 2 and received the initial dose of the study drugs (Figure 1). At the time of the October 29, 2018, data cut-off, 7 patients were receiving treatment. Overall, 48 patients had discontinued treatment, 37 because of radiologic disease progression, 2 because of clinical disease progression, and 9 because of adverse events. The median age in the TNBC cohort was 54 years (range, 32-90 years). Patients had received a median of 1 prior line of therapy (range, 0-3) in the metastatic setting, with 14 of 55 (25%) receiving 2 prior lines. Forty-three patients (78%) received previous adjuvant or neoadjuvant therapy that was not counted as a prior line of therapy (eTable 1 in Supplement 2). Among the 31 patients who received platinum-based chemotherapy at any time, 16 patients had a platinum chemotherapy-free interval (time from last platinum-based chemotherapy dose to progression) of no more than 8 weeks, and 15 patients had a platinum-free interval longer than 8 weeks. The biomarker status of enrolled patients is listed in eTable 2 in Supplement 2. The median duration of follow-up at the time of data cutoff was 14.8 months (range, 0.7-25.0 months).

Efficacy
In the full analysis population (n = 55), 5 patients had confirmed complete responses, 5 had confirmed partial responses, 13 had stable disease, and 24 had disease progression. Of the 8 patients who did not have an evaluable postbaseline scan, 1 discontinued owing to clinical progression that was not confirmed by scan, and the remaining 7 discontinued study treatment early owing to an adverse event regardless of causality. Three of the patients with stable disease had a partial response that was not confirmed by a subsequent scan. In the efficacy-evaluable population (n = 47), the confirmed ORR included 10 patients (21%; 90% CI, 12%-33%) with a complete response in 5 patients (11%), and the DCR included 23 (49%; 90% CI, 36%-62%) (Table 1).

In patients with a confirmed complete or partial response, the median DOR had not been reached at the time of data cutoff (eFigure in Supplement 2). Duration of response ranged from 4.6 to 15.9 months, with 7 responders still receiving treatment at the time of the data cutoff (Figure 2A-B). Of the 10 responders, 3 patients (all with ongoing treatment) had a response duration longer than 1 year; 4 patients (all with ongoing treatment)
had a response duration of 9 to 12 months; and 2 additional patients (none with ongoing treatment) had a response duration of 6 to 9 months (Figure 2B). Four of 13 patients with stable disease continued without progression for more than 6 months. In all treated patients, the median PFS was 2.3 months (95% CI, 2.1-3.9 months), with 6- and 12-month PFS estimated to be 28% and 14%, respectively. The overall survival data were not mature at the time of this analysis.

Exploratory univariate analyses were conducted in biomarker-defined evaluable populations according to BRCA or HRR mutation status or PD-L1 status (eTable 2 in Supplement 2). Fifteen of the 47 patients (32%) in the evaluable population had tBRCAmut, 27 (57%) had tBRCA wild type (tBRCAwt), and the remaining 5 had unknown tBRCA status. Of the 15 patients with tBRCAmut, 8 mutations were germline, 2 were somatic, and 5 had unknown germline/somatic status. Of the 5
patients with unknown \( tBRCA \) status, 2 had germline \( BRCA_{wt} \) mutations and 3 had unknown germline \( BRCA \) status. Overall, 28 patients (60%) had PD-L1-positive disease (combined proportion score \( \geq 1 \)), 13 (28%), PD-L1-negative disease; and 6 (13%), unknown. Positivity for PD-L1 was higher in the \( tBRCA \) population compared with the \( BRCA_{wt} \) population (15 of 27 [56%]).

The response rate was numerically higher in patients with \( tBRCA \) than in those without confirmed \( tBRCA \). The ORR included 7 of 15 patients with \( tBRCA \) (47%; 90% CI, 24%-70%), and the DCR, 12 of 15 (80%; 90% CI, 56%-94%), with 2 confirmed complete responses, 5 confirmed partial responses, and 5 with stable disease (Figure 2A-B and Table 2). Of the 2 patients with somatic \( tBRCA \), 1 had a complete response and 1 had a partial response. One patient with \( tBRCA \) and stable disease that continued without progression for longer than 6 months and 6 patients with a complete or a partial response continued to receive treatment at the data cutoff date. The median PFS in patients with \( tBRCA \) was 8.3 months (95% CI, 2.1 months to not estimable) (Figure 2C).

Among the 27 patients with \( tBRCA \) status, the ORR included 3 (11%; 90% CI, 3%-26%) and the DCR included 9 (33%; 90% CI, 19%-51%), with 3 complete responses and 6 with stable disease. Two patients with \( BRCA_{wt} \) status and stable disease continued without progression for longer than 6 months; 1 patient continued to receive treatment at the time of the data cutoff (Figure 2B). Median PFS in patients with \( BRCA_{wt} \) was 2.1 months (95% CI, 1.4-2.5 months). Mutations in the HRR pathway genes other than \( BRCA \) were observed in 5 patients, for whom the ORR included 1 (20%; 95% CI, 1%-66%) and DCR included 4 (80%; 95% CI, 34%-99%). For the 20 patients with \( BRCA1/2 \) or other HRR mutations (15 \( tBRCA \) and 5 other HRR mutations), the ORR included 8 patients (40%; 90% CI, 22%-61%), and the DCR included 16 (80%; 90% CI, 60%-93%) (Table 2). eTable 3 in Supplement 2 has additional information about specific HRR gene mutations and responses.

The response rate was also numerically higher in patients with PD-L1-positive disease than in those with PD-L1-negative disease. Among 28 patients with PD-L1-positive tumors, 9 were included in the ORR of 32% (90% CI, 18%-49%) compared with 1 of 13 patients in the ORR of 8% (90% CI, 0.4%-32%) with PD-L1-negative tumors. Best treatment responses for individual evaluable patients are shown in Figure 2A. The ORR was numerically greater in patients receiving no more than 1 line of previous treatment vs 2 or more lines and in patients without prior platinum-based chemotherapy use; in patients with prior platinum-based chemotherapy, the ORR was numerically greater in those patients with a platinum chemotherapy-free interval (days from the last platinum-based dose to disease progression) greater than 56 days. However, the number of patients was small and the CIs overlapped for these subgroup analyses (eTable 4 in Supplement 2). Response rates by prior platinum-based chemotherapy use and biomarker status (\( tBRCA \) and \( HRR \) mutation and PD-L1 expression) are shown in eTable 5 in Supplement 2.

### Safety

All patients with TNBC who received the study treatment (\( N = 55 \)) were evaluable for safety outcomes. Treatment-related adverse events of any grade were reported in 51 patients (93%), the most common of which were nausea (30 [55%]), fatigue (24 [44%]), anemia (19 [35%]), thrombocytopenia (14 [25%]), and constipation (13 [24%]) (Table 3). In general, nausea was controlled using standard antiemetics. The most common treatment-related adverse events of grade 3 or greater were anemia (10 [18%]), thrombocytopenia (8 [15%]), and fatigue (4 [7%]). Seven patients received platelet transfusion(s) for thrombocytopenia, and 15 received red blood cell transfusion(s) for anemia. In addition, adverse events of grade 3 or greater that were most common in laboratory findings included decreased platelet count (6 [11%]), decreased neutrophil count (4 [7%]), and decreased lymphocyte count (4 [7%]). Treatment-related serious adverse events were reported in 11 patients (20%); only thrombocytopenia (3 patients) and pyrexia (2 patients) were reported in more than 1 patient. The most common adverse events leading to treatment discontinuation were increased levels of alkaline phosphatase, bilirubin, alanine aminotransferase, and aspartate aminotransferase and fatigue. One death resulted from acute respiratory distress syndrome, deemed by the investigator to be possibly related to treatment.

Immune-related adverse events were those known to be associated with anti-PD-1 inhibitors.34 The immune-related

### Table 2. Response Rates in Biomarker-Defined, Efficacy-Evaluable Population

<table>
<thead>
<tr>
<th>Biomarker Status</th>
<th>No.</th>
<th>ORR, No. (%) [90% CI]</th>
<th>DCR, No. (%) [90% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( tBRCA )</td>
<td>15</td>
<td>7 (47) [24-70]</td>
<td>12 (80) [56-94]</td>
</tr>
<tr>
<td>( BRCA_{wt} )</td>
<td>27</td>
<td>3 (11) [3-26]</td>
<td>9 (33) [19-51]</td>
</tr>
<tr>
<td>( tBRCA ) unknown</td>
<td>5</td>
<td>0 (0) [0-45]</td>
<td>2 (40) [8-81]</td>
</tr>
<tr>
<td><strong>HRR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( HRR_{mut} )</td>
<td>20</td>
<td>8 (40) [22-61]</td>
<td>16 (80) [60-93]</td>
</tr>
<tr>
<td>( HRR_{wt} )</td>
<td>22</td>
<td>2 (9) [2-26]</td>
<td>6 (27) [13-47]</td>
</tr>
<tr>
<td>( HRR ) unknown</td>
<td>5</td>
<td>0 (0) [0-45]</td>
<td>1 (20) [1-66]</td>
</tr>
<tr>
<td><strong>PD-L1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>28</td>
<td>9 (32) [18-49]</td>
<td>14 (50) [33-67]</td>
</tr>
<tr>
<td>Negative</td>
<td>13</td>
<td>1 (8) [0.4-32]</td>
<td>6 (46) [22-71]</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>0 (0) [0-39]</td>
<td>3 (50) [15-85]</td>
</tr>
</tbody>
</table>

Abbreviations: DCR, disease control rate; HRR, homologous recombination repair; mut, mutation; ORR, objective response rate; PD-L1, programmed death-ligand 1; \( tBRCA \), tumor \( BRCA \); wt, wild type.

*Measured in \( BRCA1/2 \) and 16 other DNA repair genes.
adverse events deemed to be associated with treatment by the investigators occurred in 8 patients (15%); the only such event reported in more than 1 patient was hypothyroidism (47%) (Table 3). Two patients (4%) had grade 3 immune-related adverse events associated with the study treatment. One patient had grade 3 adrenal insufficiency, which resolved after treatment with corticosteroids and interruption of pembrolizumab therapy, and 1 patient had polymyalgia rheumatica, which resolved after treatment with corticosteroids, interruption of niraparib therapy, and discontinuation of pembrolizumab therapy. No treatment-associated grade 4 or 5 immune-related adverse events occurred, and no niraparib treatment discontinuations occurred because of immune-related adverse events.

### Discussion

TOPACIO is the first study, to our knowledge, to report the safety and efficacy of combining PARP inhibitors and immunoncology checkpoint therapy in patients with metastatic or advanced TNBC with or without BRCA mutation. Among enrolled patients, 78% had received prior adjuvant or neoadjuvant chemotherapy; two-thirds of the patients had received chemotherapy in the metastatic setting, of whom half had received platinum-based chemotherapy. Although the prespecified statistical criterion for the primary objective was not met (null <15%), combination treatment with niraparib and an anti–PD-1 antibody provided promising, durable clinical benefit. Disease control was achieved in half of the evaluable patients, and nearly one-quarter of evaluable patients experienced an objective response, with the median DOR not yet reached. Niraparib plus pembrolizumab provided responses of meaningful durability; of the 10 patients with treatment responses, 7 were still receiving treatment at the time of the data cutoff, and remarkably, 8 patients continued to receive treatment for 1 year or longer. These findings suggest that PARP inhibitors plus PD-1 blockade may provide clinically relevant improvements in DOR.

Of particular importance is that the combination treatment demonstrated clinical activity in patients irrespective of BRCA mutation or PD-L1 status, although the clinical activity is more pronounced in patients with tBRCAmut compared with those with PD-L1-positive tumors. The 21% ORR in all evaluable patients is numerically higher than the single-digit ORRs reported for anti–PD-1 and anti–PD-L1 agents in similar patient populations.17,18 This increase in response rate does not appear to be completely driven by stronger activity in the population with tBRCAmut because we observed 3 complete responses in patients with tBRCAwt status, and 2 of the 3 had no mutation in other HRR pathway genes.

The 47% ORR observed in patients with tBRCAmut treated with the niraparib plus pembrolizumab combination is similar to the ORR reported for olaparib monotherapy in patients with germline BRCAmt TNBC. However, the median PFS of 8.3 months in these patients in the present study was nearly 3 months longer than that observed for olaparib (5.6 months)23 or talazoparib (5.8 months)25 in patients with germline BRCAmut TNBC. The observation that PD-L1 was more frequently expressed in patients with tBRCAmut compared with tBRCAwt is consistent with previous publications in other cancer types.35,36 Breast cancers in patients with BRCA mutations lack effective DNA repair and are genomically unstable with a high mutational load, and treatment may rely on immune checkpoint inhibition via the PD-1/PD-L1 pathway to avoid immune destruction.37 The benefit from immunotherapy, given as monotherapy or combination therapy, can also manifest itself via long response durations or prolonged periods of stable disease. Median DOR was not reached at the time of data cutoff (range, 4.6-15.9 months), whereas for talazoparib, the median DOR was 4.3 months in patients with TNBC.28 Of the 10 responders, 2 patients (both with ongoing treatment) had a response duration longer than 1 year; 4 patients (all with ongoing treatment) had a response duration of 9 to 12 months; and 3 additional patients (1 with ongoing treatment) had a response duration of 6 to 9 months. Furthermore, 8 patients continued to receive treatment for longer than 1 year. Two patients with tBRCAwt disease, 1 with tBRCAmut disease, and 1 with BRCA status unknown and stable disease continued to receive treatment without progression for longer than 6 months.

Although patients without prior platinum-based chemotherapy had numerically higher response rates than those with prior platinum-based chemotherapy, the CIs overlap. This finding is consistent with a previous trial of talazoparib in patients with breast cancer,38 which suggested higher response rates in patients without prior platinum-based chemotherapy.

No new safety signals were identified with the combination of niraparib plus pembrolizumab compared with monotherapy. The frequency of nausea is consistent with previous studies of niraparib.39,40 Indeed, nausea is one of the most frequently reported adverse events associated with PARP inhibitors in patients with breast cancers.41 Most events of grade 3 or greater were hematologic and consistent with the class effects of PARP

### Table 3. Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. (%) of Patients by Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade (N = 55)</td>
</tr>
<tr>
<td>Any treatment-related</td>
<td>51 (93)</td>
</tr>
<tr>
<td>Treatment-related occurring in &gt;10% of patients</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (55)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (44)</td>
</tr>
<tr>
<td>Anemia</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (24)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Prespecified treatment-related and immune-related</td>
<td>8 (15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. (%) of Patients by Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade (N = 55)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
inhibitors; these were treated with transfusion as clinically indicated. We found no increase in the incidence of immune-related adverse events compared with that observed with niraparib treatment in the registrational trial, indicating that the addition of the checkpoint inhibitor pembrolizumab was not associated with immune-related tolerability of niraparib.

Limitations

This phase 2 study had a single-arm, open-label design and as such lacked a comparator arm. Therefore, the findings presented herein will need to be validated in a larger clinical trial. In addition, although the findings regarding patients with BRCA1 disease and those with HRR mutations are noteworthy, owing to lack of randomization and small patient numbers, we cannot draw strong conclusions on the role of synergy between niraparib and pembrolizumab vs either agent as monotherapy.

Conclusions

These data suggest that the combination of a PARP inhibitor and an anti–PD-1 antibody has a tolerable safety profile in patients with advanced or metastatic TNBC and promising antitumor activity, irrespective of BRCA mutation status. To confirm the findings of this trial, further clinical development of niraparib in combination with PD-1 inhibition in larger-scale studies is under consideration.

ARTICLE INFORMATION

Accepted for Publication: March 9, 2019.
Published Online: June 13, 2019.
Open Access: This article is published under the JN-OA license and is free to read on the day of publication.

Author Affiliations: Case Comprehensive Cancer Center, University Hospitals, Case Western Reserve University, Cleveland, Ohio (Vinayak); currently affiliated with Fred Hutchinson Cancer Research Center, Division of Oncology, University of Washington School of Medicine, Seattle, Washington (McCann); the Department of Medical Oncology, Center of Breast Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Tolaney); the Division of Hematology/Oncology, The Weizmann Institute of Science, Rehovot, Israel (Zelig); the Division of Hematology and Medical Oncology, Cedars-Sinai Medical Center, Los Angeles, California (Mita); the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio (McCann); Levine Cancer Institute, Atrium Health, Charlotte, North Carolina (Tan); the Department of Medical Oncology, Mayo Clinic Rochester, Rochester, Minnesota (Wahner-Hendrickson); the Department of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, Alabama (Ferero); Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill (Anders); the Department of Medicine, University of North Carolina at Chapel Hill (Anders); the Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts (Wulf); the Division of Hematology/Oncology, University of Virginia, Charlottesville (Dillon); Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, Washington, DC (Lynce); the Department of Hematology and Oncology, Lahey Hospital and Medical Center, Burlington, Massachusetts (Zaran); the Department of Medicine/Hematology/Oncology, Tufts Medical Center, Boston, Massachusetts (Erb); TESARO: A GSK Company, Waltham, Massachusetts (Zhou, Buerstae, Graham, Arora, Dezube); the Department of Medical Oncology, Stanford University School of Medicine, Stanford, California (Telli).

Author Contributions: Dr Vinayak and Ms Arora had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Vinayak, Zhou, Arora, Dezube, Telli. Acquisition, analysis, or interpretation of data: Vinayak, Tolaney, Schwartzberg, Mita, McCann, Tan, Wahner Hendrickson, Ferero, Anders, Wulf, Dillon, Lynce, Zaran, Erban, Zhou, Buerstae, Graham, Dezube, Telli. Drafting of the manuscript: Vinayak, Zhou, Graham, Arora, Dezube. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Arora, Dezube. Obtained funding: Dezube. Administrative, technical, or material support: Schwartzberg, Mita, Dillon, Buerstae, Graham, Dezube. Supervision: Vinayak, Tan, Lynce, Zaran, Dezube.

Conflict of Interest Disclosures: Dr Vinayak reported receiving clinical trial funding from TESARO; serving on an advisory board for TESARO; and serving on an advisory board for OncoSec Medical (uncompensated). Dr Tolaney reported receiving institutional research funding from Novartis, Genentech, Eli Lilly and Company, Pfizer, Merck & Co, Exelixis, Eisai Co, Inc, Bristol-Myers Squibb, AstraZeneca, Cyclacel Pharmaceuticals, Inc, and Nektar and serving as an advisor/consultant to Novartis, Eli Lilly and Company, Pfizer, Merck & Co, AstraZeneca, Eisai Co, Inc, Puma Biotechnology, Genentech, Immunomedics, Nektar, TESARO, and NanoString Technologies. Dr Schwartzberg reported receiving institutional grants from Astenogen, GlaxoSmithKline, Spectrum Pharmaceuticals, Medivation, Bayer, Genentech, Pfizer, Sanofi, Bristol-Myers Squibb, Novartis, and MedImmune; serving as a consultant to Helsinn, Pfizer, Amgen, NanoString Technologies, Napo Pharmaceuticals, Inc, Taiho Pharmaceutical, Genentech/Roche, Bristol-Myers Squibb, Genomic Health, Myriad Genetics, and AstraZeneca; and receiving nonprofit financial support from AbbVie, AstraZeneca, Helsinn, Merck & Co, Novartis, Bayer, Celgene, Eli Lilly and Company, Bristol-Myers Squibb, Genentech, and Pfizer. Dr Tan reported receiving clinical trial funding from TESARO, and institutional grants from Merck & Co. Dr Ferero reported receiving speaker fees from Seattle Genetics and institutional grants from TESARO, Seattle Genetics, Pfizer, Novartis, Genentech, Incyte Corp, TRACON Pharmaceuticals, Inc, Forty Seven, Inc, and Afinited NV. Dr Anders reported receiving clinical trial funding and funding for preclinical work from TESARO; receiving research support from Novartis, Merrimack Pharmaceuticals, Puma Biotechnology, Eli Lilly and Company, Merck & Co, Seattle Genetics, Nektar, and GI Therapeutics, Inc; serving as an uncompensated advisor to Novartis, Merrimack Pharmaceuticals, Puma Biotechnology, Eli Lilly and Company, Seattle Genetics, Nektar, and Genentech; and receiving royalties from UpToDate and Jones and Bartlett Learning. Dr Wulf reported receiving grants from Stand Up to Cancer, Mary Kay Ash Foundation, Ovarian Cancer Research Foundation, Breast Cancer Alliance, Breast Cancer Research Foundation, the National Institutes of Health, and Merck & Co and having a patent licensed to Cell Signaling and R&D Systems. Dr Dillon reported receiving clinical trial funding from TESARO, and Merck & Co. Dr Lynce reported receiving grants from Bristol-Myers Squibb, Pfizer, and Regeneron Pharmaceuticals, Inc, and serving on an advisory board for AstraZeneca. Dr Zaran reported financial relationships with Perceptive Informatics and Revere Pharmaceuticals. Dr Erban reported receiving research support from TESARO, MacroGenics, Inc, and Hoosier Cancer Research Network and serving on an advisory board for TESARO. Dr Zhou, Graham, and Dezube, Ms Arora, and Mr Buerstae are employees of TESARO. Dr Telli reported receiving institutional funding from Genentech, Pfizer, Merck & Co, AstraZeneca, Vertex Pharmaceuticals, PharmaMar, Medivation, and OncoSec Medical; serving as an advisor to Genentech, Aduro Biotech, Celldex, Pfizer, Merck & Co, Immunomedics, AstraZeneca, Vertex, and PharmaMar; and serving on a Data Safety and Monitoring Committee for GI Therapeutics, Inc. No other disclosures were reported.

Funding/Support: This study was supported by TESARO: A GSK Company, and Merck & Co.

Role of the Funder/Sponsor: The funding sources had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The funders collaborated with the investigators in designing the trial, provided the study drug, coordinated the management of the study sites, funded the statistical analysis, and provided medical writing support. Authors employed by TESARO in coordination with all authors, were involved in preparation, review, approval, and decision to submit the manuscript.
Niraparib Combined With Pembrolizumab for Advanced or Metastatic Triple-Negative Breast Cancer

Meeting Presentation: This paper was presented in part at the American Society of Clinical Oncology Annual Meeting, June 4, 2018, Chicago, Illinois and at the San Antonio Breast Cancer Symposium 2018, December 6, 2018, San Antonio, Texas.

Additional Contributions: The authors thank the patients and their families for their participation in this study, as well as the study teams at each of the study sites. Geoffrey Shapiro, MD, PhD, Dana-Farber Cancer Institute, was involved in the design of the study and Deepali Gupta, BS, TESARO, was the lead statistical programmer; Chuan Zhu, BS, TESARO, the lead data manager; and Cynthia Rouser, CDM, TESARO, data manager. Medical writing and editing, funded by TESARO, was coordinated by Ashjuit Tagde, PhD, TESARO, and provided by Nicole Renner, PhD, Jeremy Kennard, PhD, and Dena McWain, BA, Ashfield Healthcare Communications; and Adrienne M. Schreiber, BA, TESARO. All acknowledged individuals provided input as part of their regular employment, and no compensation was received beyond normal salary and benefits.

REFERENCES


