Phase II DORA Study of Olaparib with or without Durvalumab as a Chemotherapy-Free Maintenance Strategy in Platinum-Pretreated Advanced Triple-Negative Breast Cancer

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ABSTRACT

Purpose: We explored the efficacy of PARP inhibition with or without programmed death ligand-1 (PD-L1) blockade as chemotherapy-free maintenance therapy for advanced triple-negative breast cancer (aTNBC) sensitive to platinum-based chemotherapy.

Patients and Methods: In the phase II non-comparative DORA trial (NCT03167619), patients with ongoing stable disease (SD) or complete/partial response (CR/PR) to first- or second-line platinum-based chemotherapy for TNBC (≤10% estrogen/progesterone receptor expression) were randomized 1:1 to receive olaparib 300 mg twice daily with or without durvalumab 1,500 mg on day 1 every 4 weeks. The primary objective was to compare progression-free survival (PFS) versus a historical control of continued platinum-based therapy.

Results: 45 patients were randomized (23 to olaparib alone, 22 to the combination; 3 with estrogen/progesterone receptor expression 1%–10%). At 9.8 months' median follow-up, median PFS from randomization was 4.0 [95% confidence interval (CI), 2.6–6.1] months with olaparib and 6.1 (95% CI, 3.7–10.1) months with the combination, both significantly longer than the historical control ($P = 0.0023$ and $P < 0.0001$, respectively). Clinical benefit rates (SD ≥24 weeks or CR/PR) were 44% (95% CI, 23%–66%) and 36% (95% CI, 17%–59%) in the monotherapy and combination arms, respectively. Sustained clinical benefit was seen irrespective of germline *BRCA* mutation or PD-L1 status, but tended to be associated with CR/PR to prior platinum, particularly in the olaparib-alone arm. No new safety signals were reported.

Conclusions: PFS was longer than expected with both regimens. A patient subset with wild-type *BRCA* platinum-sensitive aTNBC had durable disease control with chemotherapy-free maintenance.

Introduction

First-line standard therapy for advanced triple-negative breast cancer (aTNBC) generally comprises a backbone of taxane- or platinum-based chemotherapy. In the past 10 years, targeted treatment options for aTNBC have become standard of care in biomarker-selected populations following demonstration of significantly improved progression-free survival (PFS) and, in some cases, overall survival (OS) with the addition of immune checkpoint inhibitors (atezolizumab or pembrolizumab) to first-line chemotherapy in patients with programmed death ligand-1 (PD-L1)–positive aTNBC (1–3) and with PARP inhibitors (olaparib and talazoparib) instead of chemotherapy in patients with HER2-negative tumors associated with germline *BRCA* (g*BRCA*) pathogenic variants (4–7). Furthermore, the BROCADE3 trial demonstrated significant benefit from the addition of veliparib to platinum-based chemotherapy, with continuation of single-agent maintenance PARP inhibition if chemotherapy was discontinued (8). However, only approximately 40%–45% of patients presenting with aTNBC have PD-L1–positive tumors (1, 2), and approximately 11% have tumors harboring g*BRCA* mutations (9). For patients without these molecular markers, there remains a need for more effective treatment strategies.

Continuous chemotherapy via traditional systemic delivery or newer antibody–drug conjugates with targeted payload delivery is recommended in aTNBC, but toxicities are challenging for patients from a tolerability standpoint. Chemotherapy-free maintenance strategies are attractive if they can provide adequate disease control and superior quality of life. Experience in ovarian cancer, where PARP inhibitors are an established maintenance therapy after response to platinum-based chemotherapy, has demonstrated that a broader population of patients beyond those whose tumors harbor g*BRCA* mutations may benefit from maintenance PARP inhibition (10–14). Although benefit from treatment appears greatest in patients with

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Translational Relevance

PARP inhibition is an established maintenance strategy in some tumor types but evidence is limited in advanced triple-negative breast cancer (TNBC). The non-comparative randomized phase II DORA trial evaluated olaparib with or without the PD-L1 inhibitor durvalumab as a chemotherapy-free maintenance regimen. Sustained clinical benefit was seen irrespective of germline *BRCA* mutation or PD-L1 status but tended to be associated with response to prior platinum, particularly in the olaparib-alone arm. Maintenance PARP inhibition showed sustained disease control in a subset of patients with neither germline nor somatic *BRCA* mutations. These data provide new information on the role of maintenance therapy for advanced TNBC, offering the possibility of more tolerable long-term treatment avoiding some of the chemotherapy-related side effects of more aggressive regimens.

g*BRCA* mutations, patients without g*BRCA* mutations also derive benefit. Homologous recombination deficiency (HRD), frequently caused by loss-of-function mutations in the *BRCA* genes, is a defect in the mechanism used to repair double-stranded DNA breaks. HRD is characterized by sensitivity to PARP inhibitors and/or platinum salts. A substantial proportion of sporadic TNBC tumors without g*BRCA* mutations have HRD (15), which may play a role in predicting sensitivity to DNA-damaging agents and PARP inhibitors in early-stage TNBC (16–19). However, the clinical utility of testing for HRD is unclear in aTNBC (20, 21) and technical challenges, genomic scarring, and reversion mutations highlight the limitations of many existing HRD testing approaches. In *BRCA*-like TNBC, the addition of veliparib to cisplatin significantly improved PFS in the randomized phase II S1416 trial but no significant benefit was seen in the cohort with non-*BRCA*-like TNBC (22).

We hypothesized that sensitivity to previous platinum-containing therapy may help to identify a subgroup of patients with aTNBC likely to benefit from maintenance PARP inhibition. Furthermore, we hypothesized that dual blockade of PARP and PD-L1 may be synergistic in aTNBC. PARP inhibitors can enhance the immune response via activation of genes in the cyclic GMP–AMP synthase–stimulator of IFN pathway and upregulation of immune checkpoints (23). In the clinical setting, the combination of olaparib and the anti–PD-L1 agent durvalumab demonstrated activity in g*BRCA*-mutated metastatic breast cancer (mBC) in the MEDIOLA study, without overlapping toxicities (24). In addition, combining olaparib and durvalumab with standard neoadjuvant weekly paclitaxel increased the pathologic response rate compared with paclitaxel alone in HER2-negative and triple-negative early breast cancers in the I-SPY2 trial (25).

The DORA trial was designed to evaluate a chemotherapy-free maintenance regimen of olaparib, with or without durvalumab, in patients with aTNBC showing ongoing clinical benefit from platinum therapy.

Patients and Methods

Study design, patient population, randomization, and treatment

DORA (NCT03167619) was a non-comparative multicenter randomized phase II trial conducted at five sites in the Republic of Korea, the US, and Singapore.

Eligible patients had histologically confirmed triple-negative or estrogen/progesterone receptor-low (≤10% tumor cells positive) disease that was inoperable locally advanced or metastatic and not amenable to curative resection. Before randomization on the DORA trial, patients had to have ongoing investigator-determined stable disease (SD) or complete/partial response (CR/PR) after at least three 3- or 6-weekly cycles (including bi-weekly or days 1 and 8 every 21 days) of first- or second-line platinum-based chemotherapy (monotherapy or combination therapy). Additional eligibility criteria included age ≥21 years and adequate hematologic, renal, and hepatic function. Patients previously treated with a PARP inhibitor were ineligible. Following the FDA accelerated approval of atezolizumab in combination with first-line nab-paclitaxel for PD-L1–positive aTNBC, and with inclusion of immunotherapy in clinical trials conducted in early TNBC, the protocol was amended in March 2020 to allow prior immune checkpoint inhibitors in any setting, except if patients had required discontinuation of a PD-1, PD-L1, or CTLA-4 inhibitor because of treatment-related toxicities, or if patients had previously experienced an immune-related grade 3 or 4 adverse event. No washout period or treatment-free interval was specified as it was expected that patients would have received the minimum period of induction platinum-based chemotherapy before randomization in this trial.

The aim of randomization was to reduce bias due to patient selection in either treatment arm. The trial was not designed to determine the relative efficacy of the two treatment arms or to determine potential differences between them; comparison of the two treatment arms was an exploratory objective. Randomization was stratified by site and treatment line (first- vs. second-line therapy for aTNBC). Eligible patients were allocated in a 1:1 ratio to receive olaparib maintenance therapy either alone or in combination with durvalumab using stratified permuted block randomization. In both treatment arms, platinum-based chemotherapy was discontinued after randomization, and maintenance therapy was to begin within 4 weeks after the last dose of chemotherapy. Maintenance therapy was administered in 28-day cycles comprising oral olaparib 300-mg tablets twice daily every day in the single-agent arm and the same regimen in combination with intravenous durvalumab 1,500 mg on day 1 every 28 days in the combination arm. Maintenance therapy was continued until objective disease progression according to RECIST version 1.1, providing the investigator still considered the patient to be benefiting from treatment.

Objectives and outcomes

The primary objective was to determine investigator-assessed PFS of the two regimens. PFS was defined as the interval between randomization and first reported disease progression (according to RECIST version 1.1) or death from any cause within 30 days of the last dose of study treatment. Secondary endpoints included OS (defined as the interval between randomization and death from any cause), clinical benefit rate (defined as SD for ≥24 weeks or CR/PR according to RECIST version 1.1), tolerability, and safety. Objective response rate was a predefined secondary endpoint but, in line with published trials of maintenance PARP inhibition (10–12), this endpoint was not considered to be relevant in the maintenance setting given the possible confounding effect of prior platinum response. Exploratory objectives included characterization of the molecular epidemiology of biomarkers in aTNBC through next-generation sequencing (NGS), exploration of the tumor microenvironment, and analysis of epigenetic changes (to be reported separately).

Sample size determination and statistical analysis

Median PFS from the time of randomization (after platinum-based induction therapy) was assumed to be approximately 2 months

without maintenance therapy (26). An improvement to 4 months with maintenance therapy would be considered clinically meaningful. To test the null hypothesis of median PFS of 2 months against an alternative hypothesis of median PFS of 4 months with investigational maintenance therapy, assuming exponential PFS distribution and with 90% power at a 2-sided 5% significance level, 25 patients were required in each treatment arm. Allowing for a 20% drop-out rate, the planned sample was 60 patients overall.

Study assessments

Before randomization, tissue samples (archival or fresh) were collected from all patients. Tumors were sequenced using the NGS Tempus xT assay version 4 (Tempus Laboratories, Inc.), which is a custom testing panel consisting of 648 genes with single-nucleotide variants, indels, and translocation measured by hybrid capture NGS. g*BRCA* mutation testing was not mandatory, but the total number of patients known to be carriers of g*BRCA* mutations was limited to 10. PD-L1 status was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies), with combined positive score (CPS) ≥10 defined as PD-L1 positive.

Tumors were evaluated according to RECIST version 1.1 at baseline and every 8 weeks thereafter. Safety was assessed on an ongoing basis, with adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

The trial was conducted in compliance with Good Clinical Practice guidelines (International Conference on Harmonisation E6: Good Clinical Practice or Singapore Guideline for Good Clinical Practice) and applicable national and local regulatory requirements, and in accordance with the ethical principles of the Declaration of Helsinki. The protocol, any amendments, and all patient materials were approved by the Institutional Review Board or Ethics Committee at each participating site before initiation of the trial. All patients provided written informed consent before undergoing any study-specific procedures.

Data availability

Data availability is subject to local rules and regulations. Clinical trial and sequencing data presented in this article are not publicly available because subjects did not provide consent for their data to be made available. Every reasonable effort will, however, be made to promptly satisfy scientifically valid requests. Requests for data should be made to the corresponding author together with a detailed study plan and a commitment not to use the data and their derivatives for commercial purposes. The proposal will require approval by the SingHealth Centralized Institutional Review Board, National Cancer Centre Singapore and the Principal Investigators of the study. Requesting researchers will be required to sign a data access agreement with the relevant parties.

Table 1. Baseline characteristics[a].

Characteristic	Olaparib alone (*n* = 23)	Olaparib plus durvalumab (*n* = 22)
Median (range) age, years	48 (35–77)	51.5 (25–72)
Age, years		
≤65	19 (83)	21 (95)
>65	4 (17)	1 (5)
Race		
Asian	16 (70)	18 (82)
White	5 (22)	4 (18)
Other/missing	2 (9)	0
ECOG performance status		
0	16 (70)	13 (59)
1	7 (30)	8 (36)
2	0	1 (5)
Most recent platinum regimen		
1st line	18 (78)	19 (86)
2nd line	5 (22)	3 (14)
Median (range) duration of prior platinum, months	2.9 (1.4–5.9)	2.7 (1.4–22.3)
Best response to prior platinum		
CR/PR	14 (61)	13 (59)
SD	9 (39)	9 (41)
Germline *BRCA* status		
Deleterious mutation	1 (4)[b]	7 (32)[c]
No mutation detected/variant of unknown significance	13 (57)	6 (27)
Not tested[d]	9 (39)	9 (41)
Tumor cells positive for estrogen receptor		
<1%	21 (91)	21 (95)
≥1%–≤10%	2 (9)	0
Missing	0	1 (5)
Tumor cells positive for progesterone receptor		
<1%	23 (100)	0
≥1%–≤10%	0	1 (5)
DFI from initial diagnosis to advanced/metastatic TNBC		
De novo	7 (30)	4 (18)
≤1 year	3 (13)	2 (9)
>1 year	13 (57)	16 (73)
Median (range) interval between metastatic diagnosis and randomization, months	5.3 (2.7–61.2)	4.9 (2.5–14.6)

Note: Data are *n* (%) unless otherwise specified.
Abbreviations: CR/PR, complete response/partial response; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; SD, stable disease; TNBC, triple-negative breast cancer.
[a]Please see the full table in the Supplementary Table S2.
[b]*BRCA2*.
[c]All *BRCA1*.
[d]*BRCA* testing is less readily available at Asian sites.

Results

Patient population and treatment exposure

Between February 4, 2019 and December 24, 2020, 45 patients were randomly assigned to maintenance therapy: 23 to olaparib alone and 22 to olaparib plus durvalumab combination therapy. Baseline characteristics and the representativeness of study participants are shown in **Table 1** and Supplementary Tables S1 and S2. Eight patients had known g*BRCA* mutations as a medical history (1 with *BRCA2* pathogenic variant in the single-agent arm, 7 with *BRCA1* pathogenic variants in the combination arm). Most patients (76%) were Asian and approximately 60% had CR/PR to previous platinum therapy.

At the data cutoff date (June 30, 2021), median follow-up was 9.8 months (range, 2.1–26.1 months; median 13.6 months in the single-agent group and 8.8 months in the combination group). The median number of olaparib cycles was 5 (range, 2–19) in the olaparib-alone arm and 5.5 (range, 1–24) in the combination arm (**Table 2**). The median number of durvalumab cycles was 4 (range, 1–24). At the data cutoff date, 20% of patients were still on treatment. Among those who had discontinued study treatment permanently, the reason was disease progression in all but 1 patient, in whom combination treatment was discontinued by the investigator for non-compliance with the study procedure before the first tumor assessment.

Table 2. Treatment exposure.

Treatment exposure	Olaparib alone ($n = 23$)	Olaparib plus durvalumab ($n = 22$)
Olaparib		
Median (range) of olaparib cycles	5 (2–19)	5.5 (1–24)
Patients with olaparib dose interruption	18 (78)	18 (82)
Due to AE	9 (39)	10 (45)
Lasting ≥3 days	8 (35)	9 (41)
Lasting ≥14 days	3 (13)	1 (5)
Patients with olaparib dose reduction[a]	4 (17)	2 (9)
Due to AE	3 (13)	2 (9)
Due to physician decision	2 (9)	0
Patients with olaparib permanently discontinued	20 (87)	16 (73)
Olaparib treatment ongoing	3 (13)	6 (27)
Durvalumab		
Median (range) of durvalumab cycles	—	4 (1–24)
Patients with ≥1 durvalumab cycle omitted	—	2 (9)
Patients with durvalumab permanently discontinued	—	16 (73)
Durvalumab treatment ongoing	—	6 (27)

Note: Data are *n* (%) unless otherwise specified.
Abbreviation: AE, adverse event.
[a]More than one reason possible.

PFS

By the data cutoff date, PFS events had been recorded in 20 patients (87%) in the olaparib-alone arm and 15 (68%) in the combination arm. In all patients, the first PFS event was disease progression. In the primary PFS analysis, PFS in both treatment groups was longer than for the historical control. Median PFS was 4.0 months [95% confidence interval (CI), 2.6–6.1] with olaparib alone ($P = 0.0023$ vs. historical control) and 6.1 months (95% CI, 3.7–10.1) with the combination ($P < 0.0001$ vs. historical control). Kaplan–Meier estimates of 1-year PFS rates were 10% (95% CI, 2%–27%) with olaparib alone and 33% (95% CI, 15%–53%) with the combination (**Fig. 1**).

In subgroup analyses of the primary endpoint, PFS was longer in patients with CR/PR than with SD to prior platinum-based chemotherapy. In the olaparib arm, median PFS was 5.4 (95% CI, 3.0–9.7) months in patients with CR/PR to prior platinum and 2.2 (95% CI, 1.2–4.3) months in patients with SD to prior platinum. Corresponding values in the combination arm were 7.6 (95% CI, 3.8–15.1) months and 4.4 (95% CI, 2.1–9.3) months, respectively. Exploratory analyses in the subgroup of 37 patients treated in the first-line setting showed median PFS of 4.1 (95% CI, 2.5–6.7) months with olaparib and 7.0 (95% CI, 4.0–12.3) months with the combination.

Focusing on *BRCA* status, in the single-agent olaparib arm, only 1 patient had a known g*BRCA* mutation, but maintenance PARP inhibition showed sustained disease control in some patients with neither germline nor somatic *BRCA* mutations (**Fig. 1**). For example, one 50-year-old female diagnosed with *de novo* metastatic TNBC (pleura, liver, peritoneal, cutaneous nodules, bone, and lymph nodes) in June 2019, who had wild-type (WT) g*BRCA* with tumor expressing PD-L1 on 2% of immune cells, achieved a PR for 4 months on weekly paclitaxel and carboplatin. She was randomized to single-agent olaparib in the DORA trial, and still had an ongoing response 2 years later after 26 cycles of maintenance olaparib (**Fig. 2**).

Treatment outcomes according to prior platinum sensitivity, *BRCA* mutation status, and PD-L1 status are shown at the patient level in **Fig. 1**. Among patients with durable (>6 months) clinical benefit, 7 of 8 in the olaparib-alone arm had CR/PR to prior platinum, none of the 8 had known g*BRCA* mutation *a priori*, and 2 were identified to have tumor *BRCA1* mutations. In the olaparib plus durvalumab combination arm, 5 of 9 patients with durable clinical benefit had CR/PR to prior platinum and 4 had SD; 3 of the 9 had known g*BRCA* mutations (all *BRCA1*), 2 had PD-L1–positive tumors (both WT *BRCA*), and 2 did not have sufficient tumor samples for NGS.

Secondary efficacy endpoints

The clinical benefit rate was 44% (95% CI, 23%–66%) with olaparib alone and 36% (95% CI, 17%–59%) with olaparib plus durvalumab. Overall response rate is shown in Supplementary Table S3 together with details of best overall response.

By the data cutoff date, after deaths in 11 patients (48%) in the olaparib arm and 8 (36%) in the combination arm, median OS was 21.7 months with olaparib alone and 18.3 months with the combination regimen (**Fig. 3**).

Safety

The most common adverse events (reported in >30% of patients) were nausea, fatigue, and anemia in the olaparib-alone arm and nausea, decreased appetite, anemia, vomiting, and cough in the olaparib plus durvalumab combination arm (**Fig. 4**). Grade 3/4 adverse events were reported in 9 patients (39%) in the olaparib arm and 8 patients (36%) in the combination arm. Three patients (14%) in the combination arm experienced immune-related adverse events. Generally, adverse events were manageable with dose interruptions or reductions. In the olaparib-alone arm, 1 patient (4%) discontinued olaparib because of tumor-associated fever (not considered treatment related). In the olaparib plus durvalumab combination arm, 2 patients (9%) discontinued durvalumab because of pneumonitis and thyroiditis (one case each) but none discontinued olaparib.

There were no treatment-related deaths during the study and no new safety signals were reported.

Targeted panel sequencing

Archival tumor samples were available for 42 of the 45 enrolled patients, of which 6 were of insufficient DNA quality or quantity to complete sequencing. The most frequent genetic alterations were in the *TP53* gene (67%), followed by *BRCA1* (20%), *PIK3CA* (13%), and *RB1* (9%; Supplementary Fig. S1). Specific to homologous recombination-related genes, we identified alterations in *BRCA1* in 9 tumor samples, *PALB2* in 2 samples, and *BRCA2* in 1 sample.

Discussion

The DORA trial evaluated a novel, chemotherapy-free maintenance approach for patients with aTNBC after induction platinum-containing therapy. The primary objective of DORA was met in both treatment arms with a median PFS that was statistically significantly superior to the historical control reference. The median PFS with first-line chemotherapy regimens in aTNBC is 3–6 months, including in the most recent KEYNOTE-355 clinical trial, in which patients unselected for PD-L1 who received platinum- or taxane-based chemotherapy with placebo achieved a median PFS of 5.6 months (2). Given the 2- to 3-month platinum induction required for entry into the DORA trial, an added PFS of 4 months or more with a maintenance strategy was considered to be clinically meaningful. More than one third of patients achieved disease control for ≥6 months. Furthermore, maintenance therapy ongoing in 20% of patients at data cutoff date and study closure

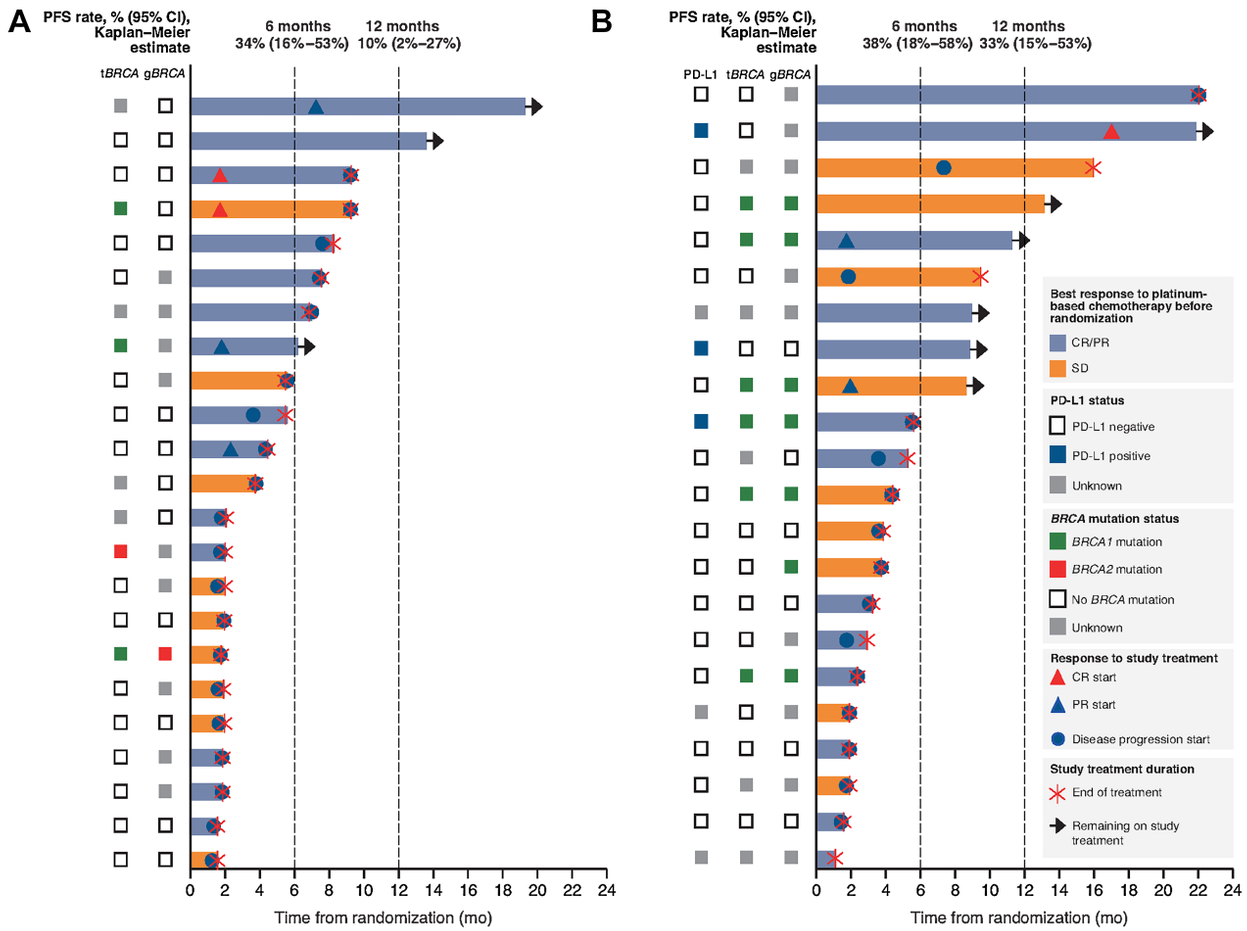


Figure 1.
Treatment exposure and response according to tumor characteristics. **A,** Olaparib alone. **B,** Olaparib plus durvalumab. One patient in the olaparib plus durvalumab arm had a germline pathogenic variant in *BRCA1* confirmed by the site but reported as a *BRCA1* variant of unknown significance and pathogenic *PALB2* variant on tumor testing. Each bar represents an individual patient. t*BRCA*, tumor *BRCA*.

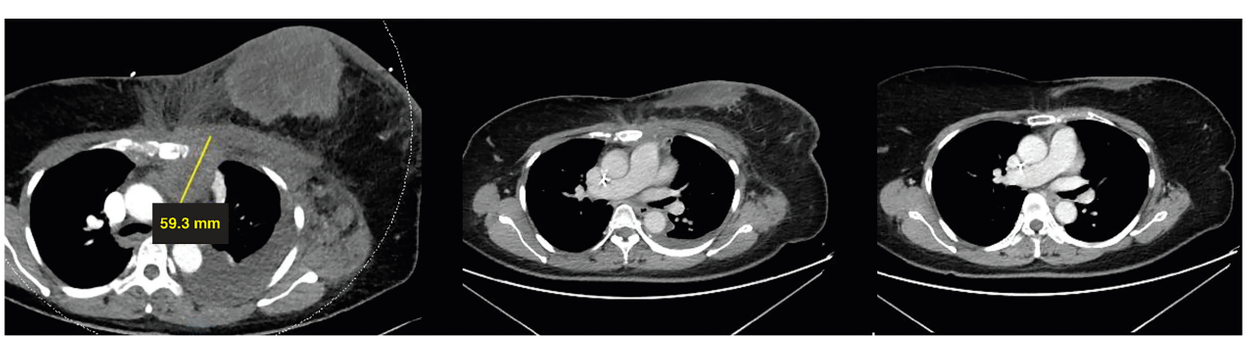


Figure 2.
Case study: maintenance olaparib in wild-type germline *BRCA* metastatic triple-negative breast cancer. PR, partial response.

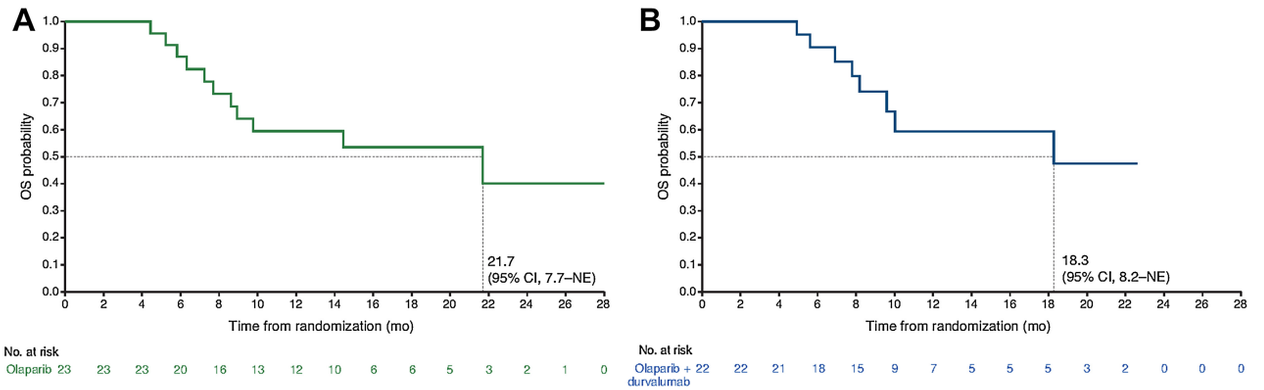


Figure 3.
Overall survival (OS). **A,** Olaparib alone. **B,** Olaparib plus durvalumab. NE, not estimable.

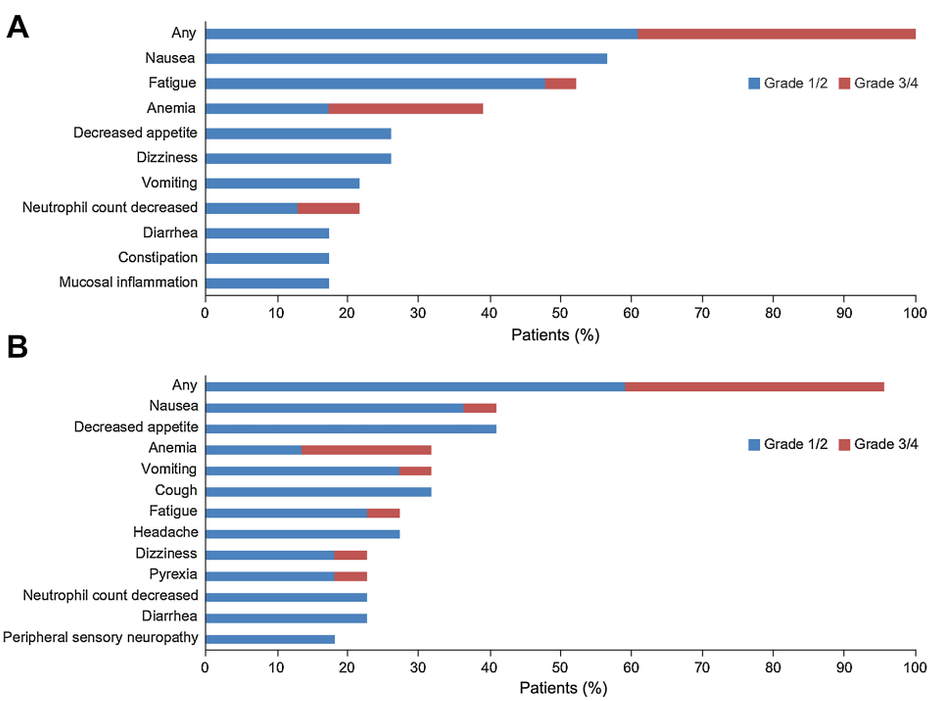
indicates sustained tumor control with the chemotherapy-free regimens evaluated in DORA. Together with the good safety profile, these findings suggest that maintenance olaparib with or without durvalumab deserves further investigation in platinum-responsive aTNBC, offering patients a favorable balance of disease control and tolerability.

Potential clinical and genomic biomarkers of prolonged disease control with this strategy were evaluated. Small patient numbers in planned subgroup analyses according to *BRCA* mutation status or platinum response preclude firm conclusions; however, encouraging signals were seen in true responders with CR/PR to the prior platinum regimen.

In terms of the contribution of durvalumab, it is not possible to interpret the relative efficacy of the two regimens, as the trial was not designed to compare the two experimental regimens and there were marked imbalances between treatment arms with regard to *BRCA* mutation status (not only the presence/absence of *BRCA* mutations, but also the type of *BRCA* mutation). Furthermore, no conclusions can be made on the true synergistic impact of PD-L1 inhibition on PARP inhibition. However, a recently reported randomized phase II trial in patients with *BRCA*-mutated advanced breast cancer showed no benefit from the addition of the PD-L1 inhibitor atezolizumab to olaparib, either in the overall population or in the aTNBC subgroup (27).

Maintenance PARP inhibition is standard of care in platinum-sensitive high-grade serous ovarian cancer (28) but there is a paucity of data in TNBC (29). Maintenance regimens are rarely used in aTNBC, but offer the possibility of more tolerable long-term treatment avoiding some of the chemotherapy-related side effects of more aggressive regimens, as is standard in the first-line treatment of HER2-positive advanced breast cancer. Several trials in breast cancer have evaluated "switch maintenance" strategies, in which patients receive an intensive induction therapy and then, after response, switch to an alternative,

Figure 4.
Most common adverse events (AE; grade ≥3 in any patient or any grade in ≥15% of patients). **A,** Olaparib alone. **B,** Olaparib plus durvalumab. Additional grade 3/4 AEs in the olaparib-alone arm comprised lymphocyte count decreased, cough, hypophosphatemia, and neutropenia, each in 1 patient (4%). Additional grade 3/4 AEs in the olaparib plus durvalumab combination arm comprised non-cardiac chest pain, neutropenia, pneumonia, upper abdominal pain, amylase increased, white blood cell count decreased, and lipase increased, each in only 1 patient (5%).



more tolerable non-cross-resistant regimen. For example, in HER2-negative mBC, the IMELDA phase III trial demonstrated PFS and OS benefit from a switch to capecitabine and bevacizumab maintenance treatment versus bevacizumab alone after induction therapy with docetaxel and bevacizumab (30). In *BRCA*-mutated HER2-negative mBC, subgroup analyses of the randomized phase III BROCADE3 trial mentioned above (8) suggested a benefit from maintenance veliparib after stopping chemotherapy (29), although the trial was not designed to compare maintenance versus no maintenance therapy. Finally, the randomized phase II SAFIR-02 BREAST IMMUNO trial compared switch maintenance therapy to durvalumab versus continuation of chemotherapy after induction chemotherapy for HER2-negative mBC. Neither PFS nor OS was improved with the switch maintenance strategy, but an exploratory analysis suggested improved OS with durvalumab in the subgroup of patients with TNBC (31).

The main limitations of the present trial are the relatively small sample size and the lack of a standard control arm, which prevents assessment of the relative contribution of each drug. Designing and conducting a trial in the pure maintenance setting for TNBC is challenging not only because of the evolving standards of care, but also because the few maintenance regimens evaluated in clinical trials (30, 32) have not been adopted uniformly across healthcare systems. For patients with PD-L1–positive aTNBC, the combination of pembrolizumab and chemotherapy demonstrated median PFS of almost 10 months in the KEYNOTE-522 trial (2). However, access to these regimens and the testing capabilities required to select eligible patients varies between countries. Furthermore, most patients with aTNBC have PD-L1–negative tumors [only 3 (16%) of 19 patients in DORA with known PD-L1 status had CPS ≥10]. Therefore, alternative maintenance strategies, particularly those offering the convenience of oral instead of intravenous administration, are worthy of consideration.

An important strength is the observation that, although existing biomarkers may miss a significant proportion of patients who could benefit from a maintenance PARP inhibitor strategy, prior platinum response may serve as a biomarker for benefit from maintenance PARP inhibitor therapy, with or without immunotherapy (33). Information on response to early platinum cycles is readily available and may help in patient selection for maintenance therapy. The opportunity to taper chemotherapy to a more tolerable chemotherapy-free maintenance regimen may be attractive to patients, enabling them to avoid prolonged toxicity from platinum-containing therapy. Further evaluation of this approach is ongoing in the phase II/III KEYLYNK-009 trial (NCT04191135) evaluating olaparib plus pembrolizumab maintenance therapy after first-line chemotherapy plus pembrolizumab for TNBC. Extensive ongoing analyses of the DORA trial aim to explore methylation status, markers of resistance, and other potential associations with clinical benefit to inform future research of this promising strategy.

Authors' Disclosures

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Authors' Contributions

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Note

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