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# DORA: A phase II, multicenter, international study of olaparib with or without durvalumab as a chemotherapy-free maintenance strategy in platinum-pretreated advanced triple-negative breast cancer (TNBC)

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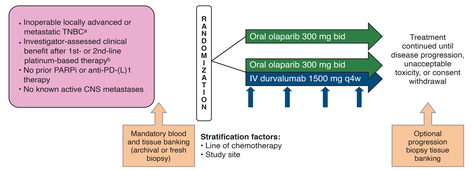
## Background

- A substantial proportion of sporadic TNBC tumors without germline *BRCA* (g*BRCA*) mutations have homologous recombination deficiencies (HRDs)[1]; however, optimal biomarkers have not yet been defined.
- Maintenance polyADP ribose polymerase (PARP) inhibition (PARPi) is standard of care in platinum-sensitive high-grade serous ovarian cancer,[2] but there is a paucity of data in TNBC.[3]
- PARPi can enhance immune response via cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway activation and upregulation of immune checkpoints.[4]
- The combination of olaparib and the anti-PD-L1 agent durvalumab (O+D) demonstrated activity in g*BRCA*-mutated metastatic breast cancer in the MEDIOLA study, without overlapping toxicities.[5]
- We hypothesized that sensitivity to previous platinum-containing therapy may help to identify a subgroup of patients likely to benefit from maintenance PARPi and PD-L1 blockade, irrespective of *BRCA* mutation status.
- The DORA trial was designed to evaluate a chemotherapy-free maintenance regimen of olaparib, with or without durvalumab, in patients with advanced TNBC who derived clinical benefit from platinum therapy.

## Study design

- DORA (NCT03167619) is a non-comparative randomized phase II trial (Figure 1).
- The primary endpoint was progression-free survival (PFS).
  - In the primary analysis, median PFS was derived from the estimated hazard assuming an exponential PFS distribution, and compared with a historical control hazard corresponding to a median PFS of 2 months.
- Secondary endpoints included overall survival (OS), safety, and tolerability.
- Tumors were evaluated by RECIST (version 1.1) at baseline and every 8 weeks thereafter.
- Tumors were sequenced using the next-generation sequencing (NGS) Tempus xT assay (Tempus Labs, Inc., Chicago, IL).
- PD-L1 status was assessed using the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies) with combined positive score (CPS) ≥10 defined as PD-L1 positive.

**Figure 1. DORA maintenance trial design**




bid = twice daily; IV = intravenous; q4w = every 4 weeks. [a]Enrollment of known g*BRCA* carriers was limited to 10 patients. [b]At least three 3-weekly cycles or at least six weekly cycles.

## Results

### Patient population and treatment exposure

- Between February 4, 2019, and December 24, 2020, 45 patients from five sites in Korea, the USA, and Singapore were randomized.
  - 8 patients had known deleterious *BRCA* mutations (Table 1).
- At the data cut-off date (June 30, 2021), median follow-up was 9.8 months (range 2.1–26.1 months).
- The median number of olaparib cycles was 5 (range 2–19) in the olaparib arm and 5.5 (range 1–24) in the O+D combination arm; the median number of durvalumab cycles was 4 (range 1–24).

### Efficacy

- In the primary analysis, PFS in both treatment groups was longer than historical control (Table 2).
- 20% of patients were still on treatment at the data cutoff date.
- Treatment outcomes according to prior platinum sensitivity, *BRCA* mutation status, and PD-L1 status are shown in Figure 2.
- Among the patients with durable (>6 months) clinical benefit:
  - 7 of 8 in the olaparib arm had CR/PR to prior platinum and only 2 had a known *BRCA* mutation (both tumor *BRCA1*)
  - 5 of 9 in the O+D combination arm had CR/PR to prior platinum and 4 had SD; 3 had *BRCA1* mutations, 2 had PD-L1-positive tumors, and 4 had neither.

**Table 1. Baseline characteristics (ITT population)**

| Characteristic | Olaparib alone (n=23) | O+D combination (n=22) |
|---|---|---|
| Median (range) age, years | 48 (35–77) | 51.5 (25–72) |
| Most recent platinum, n (%) | | |
| 1st line | 18 (78) | 19 (86) |
| 2nd line | 5 (22) | 3 (14) |
| Prior platinum regimen, n (%) | | |
| Carboplatin | 16 (70) | 10 (45) |
| Cisplatin | 7 (30) | 12 (55) |
| Single agent | 2 (9) | 6 (27) |
| Doublet with taxane | 14 (61) | 9 (41) |
| Doublet with gemcitabine | 7 (30) | 7 (32) |
| g*BRCA* status, n (%) | | |
| Deleterious mutation | 1 (4)[a] | 7 (32)[b] |
| No mutation detected/variant of unknown significance | 13 (57) | 6 (27) |
| Not tested[c] | 9 (39) | 9 (41) |
| DFI from initial diagnosis to advanced/metastatic TNBC, n (%) | | |
| De novo | 7 (30) | 4 (18) |
| ≤1 year | 3 (13) | 2 (9) |
| >1 year | 13 (57) | 16 (73) |

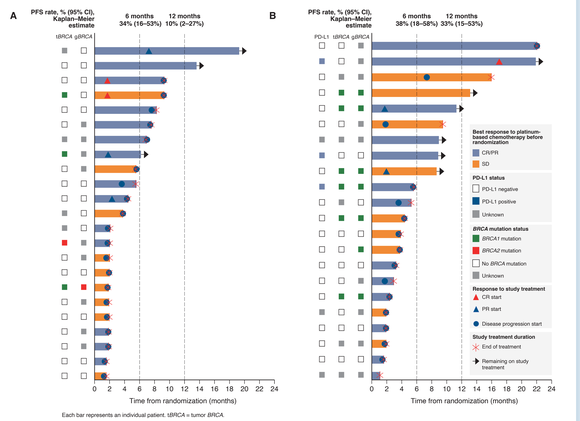
[a]*BRCA2*. [b]All *BRCA1*. [c]*BRCA* testing is less readily available at Asian sites. DFI = disease-free interval; ITT = intent-to-treat.

**Table 2. Primary PFS and subgroup analyses**

| Median PFS, 95% CI | Olaparib alone (n=23) | O+D combination (n=22) |
|---|---|---|
| All patients | 4.0 (2.6–6.1) | 6.1 (3.7–10.1) |
| $\chi^2$ p-value vs historical control | 0.0023 | <0.0001 |
| Subgroups according to prior platinum sensitivity | | |
| CR/PR to prior platinum | 5.4 (3.0–9.7) | 7.6 (3.8–15.1) |
| SD to prior platinum | 2.2 (1.2–4.3) | 4.4 (2.1–9.3) |

CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease.

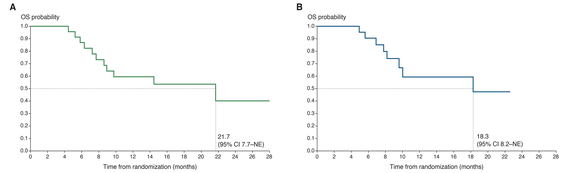
**Figure 2. Treatment exposure and response according to tumor characteristics: (A) Olaparib alone; (B) O+D combination therapy**




Each bar represents an individual patient. t*BRCA* = tumor *BRCA*.

- In the single-agent olaparib arm, only one patient had a g*BRCA* mutation, but maintenance PARPi showed sustained disease control in patients with neither germline nor somatic *BRCA* mutations (Figure 2 and Box 1).
- In the O+D combination arm, median PFS appeared longer in patients with vs without g*BRCA* mutation (8.2 vs 2.9 months, respectively).
- Median OS was 21.7 months with olaparib alone and 18.3 months with O+D combination therapy (Figure 3).

**Figure 3. OS for: (A) Olaparib alone and (B) O+D combination therapy**




NE = not estimable.

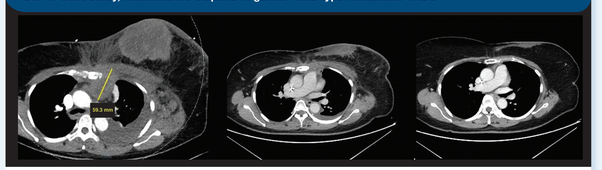
## Safety

- The most common adverse events (AEs; reported in >30% of patients) were:
  - Nausea, fatigue, and anemia in the olaparib-alone arm
  - Nausea, decreased appetite, anemia, vomiting, and cough in the O+D combination arm.
- Grade 3/4 AEs were reported in 9 patients (39%) in the olaparib arm and 8 patients (36%) in the O+D combination arm.
- Generally, AEs 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 O+D combination arm, 2 patients (9%) discontinued durvalumab because of pneumonitis and thyroiditis (one case each) but none discontinued olaparib.
- No new safety signals were reported.

## Conclusions

- The DORA trial evaluated a novel, chemotherapy-free maintenance approach for patients with advanced TNBC after induction platinum-containing therapy.
- The primary objective of DORA was met in both treatment arms: PFS was statistically significantly superior to the historical control reference.
- A subset of patients with non-g*BRCA*-altered advanced TNBC who previously derived clinical benefit from platinum-based chemotherapy had durable disease control with the chemotherapy-free maintenance strategy of olaparib ± durvalumab.
  - Small patient numbers in planned subgroup analyses according to *BRCA* mutation status or platinum response preclude firm conclusions but encouraging signals were seen in true platinum responders
  - Maintenance therapy was ongoing in 20% of patients at data cut-off and study closure.
- These findings suggest that existing biomarkers may miss a significant proportion of patients who could benefit from a maintenance PARPi strategy and support the hypothesis that prior platinum response may serve as a biomarker for benefit from maintenance PARPi therapy, with or without immunotherapy.[7]

**Box 1. Case study, maintenance olaparib in g*BRCA* wild-type metastatic TNBC[8]**




**Jun 2019**
Baseline before paclitaxel + carboplatin induction chemotherapy

**Nov 2019**
PR on platinum-based chemotherapy
Start of maintenance olaparib in DORA trial

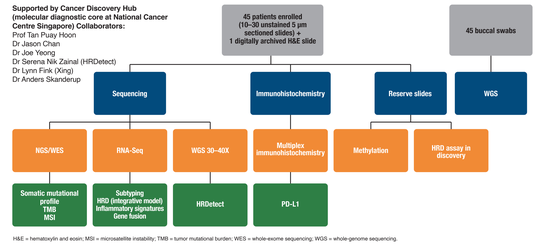
**Dec 2021**
Cycle 26 of DORA trial
Ongoing response to maintenance olaparib

- 50-year-old female, g*BRCA* wild type, PD-L1 expression on 2% of immune cells
- **Jun 2019:** Diagnosed with de novo metastatic TNBC (pleura, liver, peritoneal, cutaneous nodules, bone, lymph nodes)
- **Jul 2019–Nov 2019:** Weekly paclitaxel + carboplatin → good PR
- **Nov 2019:** Randomized to olaparib monotherapy in the DORA trial

## Future directions

- Extensive correlative analysis is ongoing, including assessment of *BRCA1/RAD51C* promoter methylation and mutational signatures (Figure 4).
- Further evaluation of this approach is ongoing in the phase II/III KEYLYNK-009 trial (NCT04191135).

**Figure 4. Ongoing translational research**




H&E = hematoxylin and eosin; MSI = microsatellite instability; TMB = tumor mutational burden; WES = whole-exome sequencing; WGS = whole-genome sequencing.

## Acknowledgments and references

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1. Sharma P, et al. Ann Oncol 2018;29:654–60.
2. Tew WP, et al. J Clin Oncol 2022 Sep 23 [Epub ahead of print].
3. Han HS, et al. Ann Oncol 2022;33:299–309.
4. Bound NT, et al. Front Genet 2022;13:886170.
5. Domchek SM, et al. Lancet Oncol 2020;21:1155–64.
6. Wang Z, et al. Sci Rep 2019;9:1853.
7. Marchetti C, et al. J Clin Oncol 2022 Oct 6 [Epub ahead of print].
8. Tan TJ, et al. J Clin Oncol Precis Oncol 2022 Nov 3 [Epub ahead of print].