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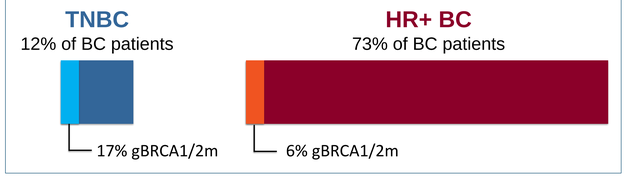
Randomized open-label multicenter phase 2 trial comparing first-line olaparib versus CDK4/6 inhibitor plus endocrine therapy in patients with gBRCAmut-associated HR+/HER2- advanced breast cancer [BR21-08, OPERA trial]

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Background

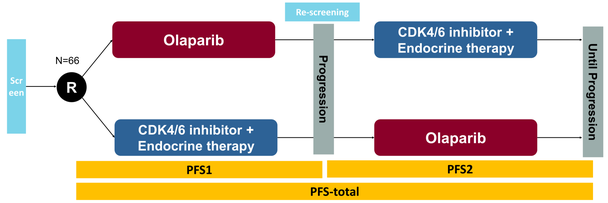
- CDK4/6 inhibitors combined with endocrine therapy are the current first-line standard for HR+/HER2– advanced breast cancer.
- Germline BRCA1/2 mutations occur in about 6% of HR+/HER2– cases[1], highlighting the need to consider germline status when choosing therapy.
- PARP inhibitors such as olaparib and talazoparib show efficacy in HER2-negative subtypes, including TNBC and HR+/HER2–.
- **The optimal sequencing between PARP inhibitors and CDK4/6i + ET remains uncertain**, especially regarding their comparative role as initial treatment in gBRCAm tumors.



Methods

- **Open-label, multicenter, randomized phase II study** (BR21-08, OPERA) in patients with recurrent or metastatic **HR+/HER2– ABC harboring germline BRCA1/2 mutations** and no prior systemic therapy for advanced disease.
- Patients were randomized to **olaparib (300 mg twice daily) or investigator's choice of CDK4/6 inhibitor plus endocrine** therapy.
- Upon progression, cross-over to the alternate regimen was permitted.
- The primary endpoint was progression-free survival on first-line therapy **(PFS1).**
- Assuming a hazard ratio of 0.375, 66 patients were required to achieve 90% power with a two-sided alpha of 0.05.

Study Design



Clinical Characteristics

Clinical Characteristics	N=9
Age, years, median (range)	50 (35 ~ 63)
Menopausal status	
Pre-menopausal	1
Post-menopausal	8
gBRCA status	
gBRCA1 mutation	1
gBRCA2 mutation	8
Family history of breast cancer	
None	3
First-degree	3
Second-degree	3
Previous treatment in EBC	
None (De novo stage 4)	1
AC	2
AC followed by Taxane	2
CMF	2
AD	1
Paclitaxel + Carboplatin	1

gBRCA, germline BRCA; AC, Adriamycin + Cyclophosphamide; CMF, cyclophosphamide + methotrexate + fluorouracil; AT, Adriamycin + Docetaxel

Efficacy analysis

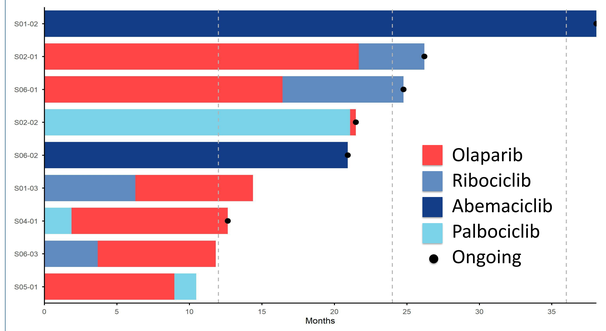


Fig. 1. Swimmer plot. With a median follow-up of 25.5 months, **median PFS1 was 16.4 months in the olaparib arm and 13.6 months in the control arm**. Two patients on abemaciclib remain on first-line therapy. Among seven patients who received second-line treatment, those switched from CDK4/6i + ET to olaparib had a median PFS2 of 8.1 months, and those switched from olaparib to CDK4/6i + ET had 4.5 months.

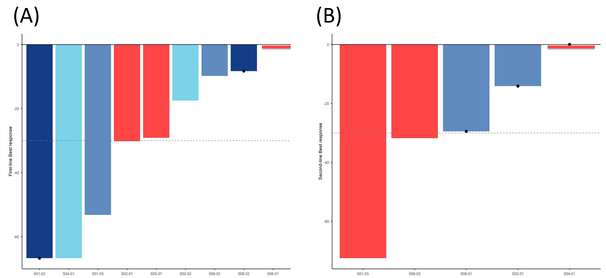


Fig 2. Waterfall plot. (A) First-line ORR: 50% in control (1 CR, 2 PR) vs. 33% in olaparib arm (1 PR). (B) Second-line: Two patients on olaparib achieved PR; CDK4/6i + ET ongoing.

Safety analysis

Olaparib	All	≥ G3
Nausea	3	0
Anemia	1	0
Fativue	1	0
Mucositis	1	0
Constiplation	1	0
Dyspepsia	1	0
GERD	1	0
Atypical pneumonia	1	0

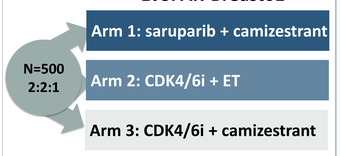
CDK4/6i + Endocrine tx	All	≥ G3
Neutropenia	10	7
Nausea	3	0
Diarrhea	3	0
Anorexia	2	0
Abdominal pain	2	0
Urticaria	2	0
Fatigue	1	0
LFT elevation	1	0
Fever	1	0
Flu like symptoms	1	0
Weight loss	1	0
Muscle spasm	1	0
Dyspepsia	1	0

Conclusion

- **First-line olaparib showed numerically longer PFS and a more favorable safety profile compared with CDK4/6i plus ET in patients with gBRCAm HR+/HER2– advanced breast cancer.**
- Given the limited sample size, results should be interpreted with caution.
- The relative efficacy of PARP inhibition versus CDK4/6i plus ET in patients with gBRCAm or PALB2 mutations is being further investigated in the ongoing **EvoPAR-Breast01 study**.

Key Eligibillity
- Advanced breast cancer with either locally advanced disease not amendable to curative treatment or metastatic disease
- First line HR-positive HER2-negative advanced breast cancer
- BRCA1 or BRCA2 or PALB2 mutation (germline or somatic)

EvoPAR-Breast01



Stratification factors
- Liver metastasis vs non-liver metastasis vs non-visceral metastasis
- TFI < 12 months vs TFI ≥ 12 months or de novo metastatic
- Prior PARP inhibitor or platinum chemotherapy (yes vs no)

[1]Aleskandarany M, et al. Breast Cancer Res Treat. 2015;150:81-90

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