

Applications of Olaparib and Durvalumab Combination Therapy for a Founder BRCA1 Mutation in the Chinese Han Population: A Literature Review

By Claire Li

AUTHOR BIOGRAPHY

Claire Li is a junior at Cupertino High School in Cupertino, CA. She is interested in researching human biology through a pathological lens and aims to study biochemistry in the future. By exploring the intersections among oncology, genetics, and biology, she hopes to use these findings to address social issues in healthcare and ensure the representation of diverse populations.

ABSTRACT

Mutations in BRCA1 and BRCA2, two genes that encode proteins vital to DNA repair processes, are associated with many cancers, including breast and ovarian cancer, as well as homologous recombination deficiency. BRCA mutations are linked with earlier diagnoses and can heavily influence prognosis, with mortality risks rising alongside age. Recently, in the Chinese Han population, a prevalent founder mutation, BRCA1:c.5470_5477del, was discovered in ovarian and breast cancer patients. For BRCA-mutated (BRCAm) ovarian and breast cancer cases, current therapies like chemotherapy and Poly (ADP-ribose) polymerase, or PARP, inhibitors exhibit benefits, with olaparib monotherapy being particularly notable. However, olaparib and durvalumab have shown superior results compared to olaparib alone in multiple trials, establishing the combination therapy as a promising alternative that promotes an immune response. Meanwhile, other emerging combination regimens have also shown favorable outcomes. This paper highlights a potential alternative to olaparib monotherapy for the treatment of founder mutation BRCA1:c.5470_5477del, and reviews current progress and prospective approaches for BRCAm ovarian and breast cancer.

Keywords: *cancer, germline BRCA1/2 mutations, BRCA1, PARP inhibitors, immunotherapy, durvalumab, olaparib, ovarian cancer, breast cancer, Chinese Han, founder mutation*

FALL 2026

INTRODUCTION

BRCA1 and BRCA2 are two genes that produce BRCA1 and BRCA2 proteins, respectively, that are vital for DNA damage response (DDR) at a cellular level (Moynahan et al., 1999; Moynahan et al., 2001). Within the homologous recombination repair pathway, these proteins oversee the noninvasive mending of DNA after double-strand breaks. However, genetic mutations can lead to nonfunctional BRCA1/2 genes that then encode for faulty BRCA proteins, rendering the homologous recombination repair pathway inoperable. This leads to homologous recombination deficiency (HRD), a phenotype characterized by a buildup of DNA double-strand breaks that occurs when less reliable repair pathways are alternatively utilized (Ashworth, 2008).

Known for inducing a heightened risk of breast cancer, ovarian cancer, and HRD via accumulating DNA damage, BRCA mutations can be fatal, especially with increasing age. The risk of death at 80 years old is 40 to 60% for BRCA1 alterations and 11 to 27% for BRCA2 alterations. BRCA mutation carriers are also associated with earlier cases of ovarian cancer (Michalzyck et al., 2025). A study conducted by Michalzyck et al. (2025) involving 101 individuals diagnosed with late-stage ovarian cancer shows that, among fifteen patients with BRCA1 mutations and ten patients with BRCA2 mutations, the average age of disease onset was 46.52 years old for BRCA1 patients and 63.83 years old for BRCA2 patients, which were both significantly lower than that of non-BRCAm patients.

To mitigate morbidity of BRCA-induced breast and ovarian cancer, especially in populations more susceptible to BRCA alterations, various treatments have been developed. This paper analyzes the possibilities of olaparib and durvalumab therapy for ovarian and breast cancer induced by the founder mutation BRCA1:c.5470_5477del, comparing its clinical results to olaparib monotherapy. From the results of various clinical trials, it concludes that the effectiveness of olaparib and durvalumab therapy is superior to that of olaparib alone. Furthermore, it recounts both current and future remedies to highlight recent advancements for BRCA-mutated ovarian and breast cancer.

METHODOLOGY

Academic sources were found through systematic searches in the Google Scholar and PubMed databases. Keywords utilized included a mixture of “ovarian cancer”, “breast cancer”, “olaparib”, “durvalumab”, “BRCA germline mutation”, “BRCA1:c.5470_5477del”, “BRCA1”, and “BRCA2”. Furthermore, primary experimental articles published recently (2020 to present) in peer-reviewed journals that provided detailed insight on statistics, potential therapeutic interventions, or mechanisms of either breast or ovarian cancer were prioritized.

FALL 2026

Ovarian and Breast Cancer

Ovarian cancer (OC) is the deadliest female reproductive cancer (Michalzyck et al., 2025). Despite recent identification methods, patients are still commonly diagnosed belatedly in metastatic or advanced stages, causing a high mortality rate. Although the use of Serum CEA, CA199, AFP, and CA125 is widespread, no fully accurate singular biomarkers exist (Pan et al., 2025).

Meanwhile, breast cancer (BC) is another deadly cancer. In 2020, the GLOBOCAN database recorded 2.3 million new diagnoses and 670,000 deaths induced by BC. It is predicted that from 2022 to 2050, new diagnoses will increase by 38% and mortalities by 68% (Kim et al., 2025). One particular aggressive type, triple-negative breast cancer (TNBC), involves the absence of estrogen, human epidermal growth factor receptor 2, and progesterone. TNBC constitutes 15-20% of breast cancer cases (Almansour et al., 2022). Both BC and OC are conditions possibly caused by germline BRCA1 mutations.

BRCA1 Mutations in Breast and Ovarian Cancer

BRCA1 proteins can dictate histopathological traits and prognosis. In a study of 195 ovarian cancer patients in which tissue samples and data on prognosis over three years were collected, researchers found that the survival rate for patients lacking BRCA1 expression was substantially lower than for those who expressed BRCA1. When BRCA1 genes are mutated, nonfunctional BRCA1 proteins are produced, leading to reduced BRCA1 activity associated with cell degradation and ovarian cancer development and progression (Pan et al., 2025).

Whilst there is a lower risk for ovarian cancer in individuals of Chinese descent than Caucasian descent, it remains a prevalent cancer (Sung et al., 2021). According to a study by Cao et al. (2021), OC was identified in 55,342 female patients in China, which accounted for 17.6% of cases worldwide. Furthermore, it was responsible for 37,519 deaths, which accounted for 18.1% of cases worldwide. Another kin-cohort study by Yao et al. (2022) on 3984 individuals with breast cancer and their families showed that in a population where 98% were ethnically Chinese Han, female first-degree relatives of patients with BRCA1 mutations were at the greatest risk for ovarian cancer compared to those with BRCA2 mutations or no BRCA mutations. Additionally, the estimated total chance of OC in healthy Chinese females by age 70 was 38 times higher for BRCA1 carriers than for noncarriers, with the risk rising substantially at age 45. Thus, it is imperative to identify founder BRCA1 and BRCA2 mutations specific to the Chinese Han populations so that we may inform treatment approaches.

FALL 2026

A Founder Mutation for the Chinese Han: BRCA1:c.5470_5477del

In the Chinese Han population, a BRCA1 founder deletion mutation in exon 22 was recently identified (Meng et al., 2020). In a study by Meng et al. (2020) of 9,505 Chinese Han breast cancer patients, BRCA1:c.5470_5477del was classified as a founder mutation in the Chinese Han population. 471 individuals were found to be germline BRCA1/2 carriers, and 25 recurrent pathogenic variants were identified, with the most common mutation being BRCA1:c.5470_5477del, detected in 30 patients from 29 unrelated families, and 27 of 29 unrelated individuals bore an identical haplotype. People with a BRCA1:c.5470_5477del mutation also had a substantially worse prognosis than noncarriers. Another study by Li et al. (2021) of 530 Henanese patients with OC found that BRCA1:c.5470_5477del was a founder mutation. 28.3% of patients had pathogenic BRCA variants, with 117 with BRCA1 mutations, 33 with BRCA2 mutations, and one with both. 13.9% of germline BRCAm (gBRCAm) cases had founder mutations, with BRCA1:c.5470_5477del being the most prevalent alteration in eight cases. While having a founder mutation did not influence Progression-Free Survival (PFS), all BRCA1 pathogenic variants were linked with early onset of ovarian cancer.

Current Therapies

To combat BRCA-induced malignancies, several remedies like chemotherapy, often with platinum-based agents, have been proposed. In addition to platinum-based chemotherapy, PARP inhibitors (PARPi) have also become widespread treatment methods (Tan et al., 2026).

Chemotherapy is considered a conventional therapy for BRCAm breast and ovarian cancer. (Tan et al., 2026). However, the INFORM trial by Tung et al. (2020) compared neoadjuvant single-agent cisplatin with doxorubicin-cyclophosphamide (AC) regimens in 117 gBRCAm HER2-negative breast cancer patients and found both to be similarly favorable. Due to BRCA mutations, participants were linked to greater rates of platinum-based chemotherapy (Michalzyck et al., 2025); despite this, the INFORM trial reported that pathogenic complete response (pCR) rate in cisplatin recipients was only 12% higher than in the AC group. Overall, the treatments showed no substantial differences in anti-tumor properties or residual disease, but greater baseline TILs, a BRCAm BC biomarker, were associated with improved response to either therapy. The results positioned AC as a promising alternative to platinum-based chemotherapy.

Another option is niraparib, a PARPi approved by the FDA as maintenance therapy for platinum-sensitive recurrent ovarian cancer (PSROC) cases regardless of BRCA mutation status. In a phase III trial, Wu et al. (2021) randomly assigned 265 Chinese individuals with PSROC to oral niraparib or placebo groups. In the experiment, 50 BRCA1 patients comprised 76.9% of the niraparib group, and 28 BRCA1 patients comprised 80% of the placebo group. Wu et al. (2021) found that niraparib was overall favorable for

non-BRCA and BRCA patients. Compared to the placebo group, those receiving niraparib were 68% less likely for cancer progression or death, and had a greater median PFS at 18.3 months, in contrast to 5.4 months. Additionally, niraparib maintenance treatment induced a significantly greater median Chemotherapy-Free Interval and Time to First Subsequent Therapy than the placebo, demonstrating its long-term benefit of delaying ovarian cancer progression.

Rucaparib maintenance therapy is a potential option as well. In the Phase III trial ATHENA, Monk et al. (2022) administered PARPi to 538 recently diagnosed OC patients, finding that after 2 years of continued treatment, rucaparib was remarkably beneficial for BRCAm patients. Subjects were randomly assigned so that 21.3% of the rucaparib cohort and 21.6% of the placebo cohort had BRCA mutations. Rucaparib demonstrated better results, with 45.1% of the rucaparib group being progression-free after 24 months compared to 25.4% of placebo patients. Individuals with HRD, which constituted 40% of both groups, had a significantly longer median PFS of 28.7 months with rucaparib, compared with 11.3 months in the placebo group. Monk et al. (2022) concluded that rucaparib was a promising, relatively non-toxic therapy for the general ovarian cancer patient population.

The PAOLA-1 study utilized monoclonal antibody bevacizumab and PARPi olaparib as primary maintenance therapy for 806 advanced ovarian cancer patients across two years, where Ray-Coquard et al. (2023) concluded it was substantially beneficial for BRCA1/2 cases. Individuals were randomized into bevacizumab and placebo or olaparib and bevacizumab cohorts. After five years, a higher proportion of patients in the olaparib and bevacizumab group were alive, with 73.2% of BRCAm individuals in the olaparib group alive compared to 53.8% in the placebo group. The HRD-positive group exhibited 38% lower death with the olaparib regimen, mainly because BRCAm patients responded significantly and were recurrence-free.

Olaparib Monotherapy

Olaparib is a targeted PARP inhibitor often utilized to treat BRCA-mutated ovarian and breast cancer, especially because BRCA mutations have heightened response to PARPis (Zhou et al., 2025).

In a double-blind trial by Tutt et al. (2021), 1836 HER-2 negative breast cancer patients with BRCA1/2 mutations, including 72.3% with BRCA1 genetic alterations, were randomly assigned to oral olaparib or placebo groups for one year. Most had prior chemotherapy exposure, and 82.2% were also diagnosed with triple-negative breast cancer. Results demonstrated moderate benefits from olaparib monotherapy: the 3-year disease-free survival was 87.5% in the olaparib group compared to 77.1% in the placebo group. Nevertheless, 25.0% of olaparib patients, as opposed to 5.2% of placebo patients, decreased treatment dosage. Tutt et al. (2021) also concluded that adjuvant olaparib decreased the possibility of recurrence and progression

for early high-risk breast cancer patients, and observed favorable results when post-localized olaparib was combined with adjuvant or neoadjuvant chemotherapy.

When DiSilvestro et al. (2022) followed up on a maintenance olaparib therapy trial for 391 BRCA-mutated AOC patients after 7 years, they found no statistically significant increase in overall survival (OS). This trial randomly assigned individuals to placebo or olaparib groups and administered treatment over two years or until disease progression. The placebo cohort tended to have shorter therapies, and 44.3% of that group had received olaparib at the time of the checkup. Considering that 67.0% of the olaparib group were alive in contrast to 46.5% of the placebo group, DiSilvestro et al. (2022) supported the prioritization of first-line PARPi maintenance therapy for BRCAM advanced ovarian or breast cancer.

Furthermore, a trial by Liu et al. (2025) with 272 PSROC patients administered olaparib and found that at data cutoff, 90% of participants discontinued therapy due to disease progression, and 37.5% had passed away. Most subjects also underwent platinum-based chemotherapy afterward. However, the one-year OS rate was particularly high in BRCAM groups, at 94.6% for mutated individuals compared to 89.4% for HRD-positive non-mutated or 71.9% for HRD-negative individuals. Overall, olaparib was promising for BRCAM groups, even exhibiting a superior OS to that of two or fewer chemotherapy lines. Finally, Liu et al. (2025) observed that a higher proportion of BRCAM patients received prolonged treatment for over 18 months, as only 16.2% of the HRD and wild-type cohorts versus 31% of the BRCAM cohort qualified. Also, those with germline and somatic BRCA mutations experienced longer PFS and higher response rates than those in the non-BRCAM HRD-positive or HRD-negative groups. Olaparib monotherapy has therefore shown mixed results, prompting exploration of combination regimens as a beneficial alternative.

Olaparib and Durvalumab Combination Therapy

While olaparib monotherapy benefits BRCAM ovarian and breast cancer patients somewhat significantly, treatment resistance inhibits the prospects of prolonged cancer-free periods in subjects (Dilmac et al., 2023; Kulkarni et al., 2025). However, a regimen of combination therapy with olaparib and durvalumab, an anti-PD-L1 inhibitor and immunotherapy, could be a promising solution for disease recurrence and improved therapeutic results.

Olaparib and durvalumab treatment is associated with tumor reduction and disease regression. In a trial by Fujii et al. (2025) involving 15 recurrent TNBC patients treated with durvalumab (1500mg iv q4w) and oral olaparib (300mg twice daily), three patients with germline BRCA mutations benefited substantially compared to 12 BRCA wild-type patients. Notably, two of three subjects in the gBRCAM group had BRCA1 deletion mutations, and the entire group experienced partial remission. The median PFS was also considerably shorter in

the BRCA wild-type group, at 16.7%, compared with 66.7% in the mutation cohort. Furthermore, median OS and overall survival rate were significantly lower as well.

According to a study by Drew et al. (2024), MEDIOLA, 114 patients with platinum-sensitive recurrent ovarian cancer received olaparib and durvalumab combination therapy with or without a monoclonal antibody drug called bevacizumab; notably, all 51 gBRCAm patients were given olaparib and durvalumab only. Accordingly, this cohort responded exceptionally well to treatment, with an objective response rate (ORR) of 92.2%, and 22 patients (43.1%) exhibiting a complete response. In comparison, the non-gBRCAm doublet with the durvalumab and olaparib combination therapy had an ORR of 34.4%, highlighting the substantial benefits these agents bring to individuals with BRCA mutations in particular.

Scientists first proposed PARPi and immune checkpoint inhibitor combination therapy after discovering that olaparib augments immune responses. In particular, a study by Staniszewska et al. (2022) utilized RNA sequencing in conjunction with in vivo experiments to demonstrate synergy between PARPis and anti-PD-1/PD-L1 or anti-CTLA-4 therapies. In vivo trials linked the combination therapy to an anti-tumor effect: in cell lines, olaparib alone induced a 58% reduction in growth rate, whereas combination therapy achieved 106%. Olaparib also induced phenomena associated with a heightened immune response to cancer, such as higher numbers of tumor-invasive CD8⁺ T and NK cells—effects only seen in BR5 BRCA1-mutated cells and not in MC-38 BRCA wild-type cells. Other benefits, like greater immune reaction pathway activation and upregulation of the tumor-cell intrinsic immune response pathway, were induced by olaparib in BRCAm cells. Overall, Staniszewska et al. (2022) concluded that due to increased immune response and anticancer benefits, administering olaparib and ICBs—especially anti-PD-L1 treatments like durvalumab—together is a promising remedy for BRCAm cancer.

A trial by Westin et al. (2024) named DUO-E compared durvalumab with or without olaparib as maintenance therapy following combination therapy with durvalumab and carboplatin or paclitaxel. 718 participants with late-stage endometrial cancer were randomly assigned to a control, durvalumab monotherapy, or durvalumab and olaparib therapy group. Notably, Asians constituted around 30% of each cohort. Westin et al. (2024) found that within the Intention-to-Treat (ITT) population, the durvalumab and olaparib group had a 45% lower risk of progression or death than the control cohort, as well as greater OS and PFS than in other cohorts. Furthermore, patients with PD-L1 positivity—linked with BRCA mutations—favored combination therapy the most. The median PFS was 20.8 months for durvalumab and olaparib together compared to 11.3 months for durvalumab only and 9.5 months for the control group. No significant differences were found in PD-L1-negative participants. Results from DUO-E indicate the benefits of including PARPis together with immunotherapy as first-line treatment.

An olaparib and durvalumab combination regimen has shown favorability in BRCAm cancers other than ovarian or breast cancer as well. In a trial of 48 patients with late-stage solid cancers and homologous recombination repair mutations, Thavaneswaran et al. (2023) divided participants into two groups to investigate the effects of olaparib and durvalumab combination therapy across 15 months. Cohort one included four BRCA1m individuals. The therapy was deemed relatively non-toxic and moderately beneficial. Durvalumab and combination therapy have shown significant results, but recent advancements and trials are solidifying other regimens as potential alternatives.

Emerging Therapies

Although significant progress for treating BRCA1 mutations, such as BRCA1:c.5470_5477del, has been made with olaparib and durvalumab combination therapy, other emerging combination therapies show clinical promise too. A study by Freyer et al. (2024) with 74 advanced ovarian cancer (AOC) patients demonstrated that oral olaparib, bevacizumab, and durvalumab inhibited cancer progression in 69.8% of subjects over three months. This combination was optimal for platinum-resistant recurrent AOC. Eight subjects had gBRCA1 mutations, whilst five had gBRCA2 alterations; however, despite a 74% disease control rate, 43.8% remained progression-free after six months, which was lower than the results of similar trials. Nonetheless, the therapy remains promising in theory. Since bevacizumab can alter tumor environments and prevent DNA damage caused by HRD in a hypoxic environment, patients display increased sensitivity and response to PARPi like olaparib. Further synergy is present between PARPi and anti-PD-L1 inhibitors like durvalumab: PARPi increase harmful PARP complexes, which activate antigens and death signals to trigger an immune reaction and raise sensitivity to immunotherapy.

Another treatment method combines PARP inhibitor olaparib with AKT inhibitor capivasertib, an ATP-competitive inhibitor of all AKT isoforms. In a study by Yap et al. (2020), where 25 of 64 patients with various cancers harbored BRCA mutations, 16 of 22 BRCAm patients with a RECIST-measurable condition improved from this regimen. Notably, this study included 20 germline cases. Of 25 individuals with advanced ovarian cancer, 11 improved, including seven with BRCA1/2 mutations; of 18 individuals with advanced breast cancer, eight improved. Additionally, five of 13 with previous PARPi therapy also improved, demonstrating capivasertib and olaparib together as a potential solution to combating PARPi resistance, which is a prevalent obstacle in BRCA1/2-mutated high-grade serous OC. Overall, capivasertib and olaparib make an effective and somewhat safe therapy for refractory OC and BC.

A third promising treatment targeting homologous recombination repair mutations, such as BRCA1/2, combines the antibody-drug conjugate (ADC) rucaparib with PARPi sacituzumab govitecan (SG), a SN-38 conjugate for Trop-2. In the SEASTAR trial, Yap et al. (2022) noted that pairing PARP inhibitors with

FALL 2026

ADCs improved treatment precision and reduced toxicity. Six patients, including two with BRCA1/2 mutations, were split into two cohorts and given different rucaparib and SG regimens. All individuals were subjected to at least 12 weeks of therapy, during which three patients exhibited a partial response. While some side effects exist, rucaparib and SG together can target BRCAm cancers as they combat progressive solid tumors regardless of previous PARPi exposure. To optimize treatment efficacy, although combining durvalumab and olaparib is a viable alternative to conventional treatments like olaparib alone, novel therapies drive advancements and present as potential alternatives to treat BRCAm OC and BC.

CONCLUSION

In conclusion, olaparib and durvalumab combination therapy is promising for patients with breast and ovarian cancer due to BRCA mutations such as BRCA1:c.5470_5477del, a recently discovered germline founder mutation in the Chinese Han population. Although hereditary BRCA alterations can heighten the chances of ovarian and breast cancer—both potentially fatal—administering a PARP inhibitor like olaparib in conjunction with durvalumab immunotherapy is associated with increased survivability compared to olaparib monotherapy, establishing the dual regimen as a likely alternative. However, more research is required to truly assess the efficacy of durvalumab with olaparib for BRCA1:c.5470_5477del specifically. Despite challenges and uncertainty, emerging combination therapies show potential as reliable remedies for BRCAm ovarian and breast cancers.

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