bcac breast cancer aotearoa coalition

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Tangata tū pakari tonu

Update of July 2024 BCAC application for olaparib funding

5th January 2025

Attn: Priyanka Patel, Jared Solloway, Logan Heyes

Introduction

Breast Cancer Aotearoa Coalition has written this letter to:

- complement our July 2024 application for olaparib funding for gBRCA1/2pv early and metastatic breast cancer
- support the inclusion of gPALB2pv and sBRCA1/2m as requested in the Breast Special Interest Group's (BreastSIG) July 2024 olaparib application
- confirm that mainstreaming for breast cancer genetic testing has been agreed to and will be progressively rolled out across New Zealand in 2025 and to
- provide updated information relating to gBRCApv trials and funding decisions of note.

In our earlier olaparib application we noted that breast cancer treatment is individualised based on tumour characteristics, patient characteristics and treatment history. We highlighted that approximately 5% of unselected patients with breast cancer carry a germline BRCA pathogenic variant (pv).

This letter extends BCAC's July 2024 olaparib application to include gPALB2pv as noted in the Breast Special Interest Group's (BreastSIG) 2024 olaparib application and further extends it to include sBRCA1/2m (mutated) for metastatic breast cancer.

What is PALB2?

A relatively small proportion of breast cancers are caused by alterations in inherited genes that sharply increase the lifetime risk of developing breast cancer. PALB2 is receiving much attention. It is a potent breast cancer susceptibility gene related to the better known BRCA1/2 genes. PALB2 is similar to *BRCA1/2* in that it is involved in homologous recombination (HR) DNA repair, and *PALB2* pathogenic variants are associated with increased risk of breast cancer and reduced survival[1,2]. PARPis provide a therapeutic approach shown to be effective, particularly for patients with deficiencies in DNA repair mechanisms, and can benefit patients with germline *PALB2* pathogenic variants in addition to BRCA1/2.

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PALB2 stands for Partner And Localizer of BRCA2 — or "PAL" of BRCA2 — for short. The PALB2 gene normally codes for a protein that interacts with the protein made by the BRCA2 gene. It is sometimes called BRCA3. Together, the proteins make up part of the repair pathway that fixes DNA damage in cells. A pathogenic variant in any of these DNA repair genes prevents abnormal genes in cells from being fixed or eliminated, and those cells may grow uncontrollably to form tumours. PALB2 was originally identified in the laboratory of Dana Farber Professor David Livingston, and its clinical implications have since been studied by others at Dana-Farber Cancer Institute and others worldwide.

Prevalence and risk

A New Zealand study (Lattimore et al 2020[3]) identified that 13 of 367 (3.5%) breast cancer patients carried a pathogenic or likely pathogenic variant in *BRCA1*, *BRCA2, PALB2*, or *PTEN*. A significantly higher proportion of pathogenic variant carriers had grade 3 tumours (10/13) when compared to non-carriers (150/319, $P< 0.05$). On average, Māori were found to be slightly younger at diagnosis compared to non-Māori (57.6 versus 63.1 years) and a higher proportion of Māori were diagnosed with grade 3 tumours compared to non-Māori (60.9% vs 47.8%)

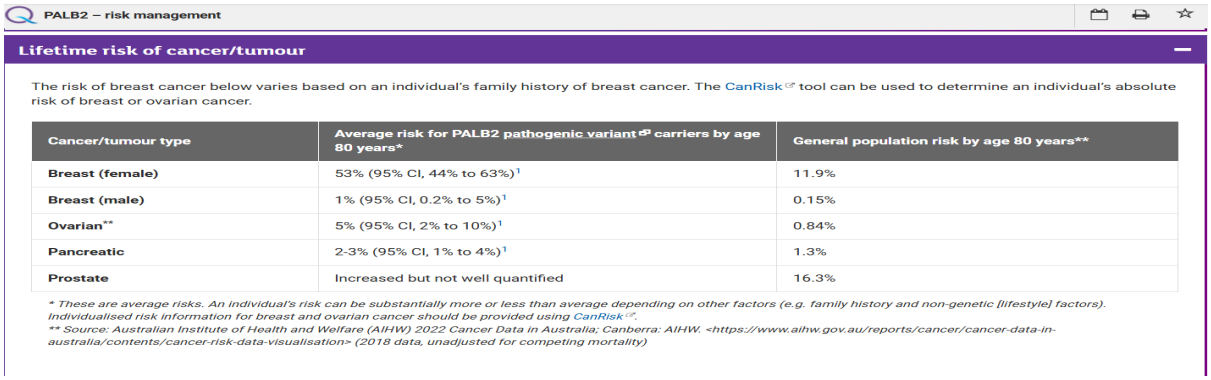
A larger study (Rezoug et al 2024[4]), between 2019 and 2022, across 3 hospital sites in Montreal Canada with 805 participants, found germline pathogenic variance prevalence was 7.3% and of those 5.3% had BRCA1/2 and PALB2 variants.

The risk of breast cancer is significantly enhanced when an individual carries a disease-predisposing or pathogenic variant in high-risk cancer susceptibility genes, such as *BRCA1*, *BRCA2 and PALB2* which, respectively, confer a 72%, 69%, 53% absolute risk of breast cancer[5,6,7].

Identification of disease-associated genetic changes in breast cancer susceptibility genes, including *BRCA1*, *BRCA2* and *PALB2*, not only has actionable implications for carriers, but also for family members who are found to carry these high-risk variants. Identification of high-risk variants influences clinical decisions around patient treatment, including surgical options (i.e. choosing to have a total mastectomy instead of a wide local excision), while PARP inhibitors and cisplatin are key chemotherapeutic options for the treatment of cancers in these patients

EviQ Guidelines

The eviQ regional guidelines indicate an average breast cancer risk for PALB2 variant carriers of 53% by age 80 years compared with the population risk of 11.9%[6].



PALB2 – risk management

Lifetime risk of cancer/tumour

The risk of breast cancer below varies based on an individual's family history of breast cancer. The CanRisk tool can be used to determine an individual's absolute risk of breast or ovarian cancer.

Cancer/tumour type	Average risk for PALB2 pathogenic variant carriers by age 80 years*	General population risk by age 80 years**
Breast (female)	53% (95% CI, 44% to 63%)[1]	11.9%
Breast (male)	1% (95% CI, 0.2% to 5%)[1]	0.15%
Ovarian**	5% (95% CI, 2% to 10%)[1]	0.84%
Pancreatic	2-3% (95% CI, 1% to 4%)[1]	1.3%
Prostate	Increased but not well quantified	16.3%

** These are average risks. An individual's risk can be substantially more or less than average depending on other factors (e.g. family history and non-genetic [lifestyle] factors). Individualised risk information for breast and ovarian cancer should be provided using CanRisk.*
*** Source: Australian Institute of Health and Welfare (AIHW) 2022 Cancer Data in Australia; Canberra: AIHW. <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-risk-data-visualisation> (2018 data, unadjusted for competing mortality)*

Updated NCCN Guidelines

In November 2024, the National Comprehensive Cancer Network (NCCN) updated their oncology guidelines (version 2, 2025), introducing expanded NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) to incorporate advances in the understanding of hereditary cancer risk in breast, ovarian, pancreatic, and prostate cancers. The new guidelines followed the recent publication of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
These updated Guidelines indicate that PALB2 (GENE-A (Section 6 - 11) Primary Breast Cancer confers an absolute breast cancer risk of 32%–53%[7].

Who should be tested for PALB2?

The panel of genes available for individuals who are offered genetic screening through Genetic Health Service New Zealand (GHSNZ) expanded in 2015 from *BRCA7* and *BRCA8*, to include *PALB8* and *TP❶❾*, as well as specific risk-associated variants in *CHEK8* and *ATM*. Screening of *PTEN* and *CDH7* is offered if separate gene-specific criteria are met. Anyone tested prior to 2015 will not have been tested for PALB2.

EviQ Australasian Guidelines[6] recommend testing for Individuals with breast cancer who meet one of the following eviQ criteria:

- a pathogenic variant probability of ≥10% using the Manchester score or CanRisk (validated pathogenic variant prediction tools)
- diagnosed age ≤40 years
- bilateral breast cancer or 2 or more synchronous or asynchronous breast cancers with first cancer diagnosed age ≤50 years
- triple negative breast cancer (TNBC) diagnosed age ≤60 years or at any age if the patient would potentially be eligible for adjuvant therapy with a PARP inhibitor
- hormone receptor positive, HER2 negative, early breast cancer with one or more high risk features (grade 3, lymph node positive, size >20mm), diagnosed at any age if the patient would potentially be eligible for adjuvant therapy with a PARP inhibitor
- male breast cancer diagnosed at any age
- testing criteria for one or more other genes included in the panel
- with recurrent or advanced disease where a finding of a mutation in BRCA1, BRCA2 or PALB2 could affect treatment options.

Testing is also offered to those with or without breast cancer who have a family history of breast, ovarian, pancreatic or advanced prostate cancer. People who had genetic testing before 2015 will need to have expanded testing to include more genes

conferring risk of breast and ovarian cancer, at least. People who have been tested on panels of multiple genes after 2015 almost certainly will have had PALB2 included in the list, and results provided in their report.

Evidence for PARPis in patients with germline PALB2 variants and BRCA1/2 somatic mutations if a germline BRCA is absent

TBCRC-048, a phase 2 trial published in 2024[8], following an earlier trial in 2020[9], and ongoing investigations[10,11,12,13,] are demonstrating benefits of olaparib to an expanded patient group (gPALB2pv and sBRCA1/2m). The effectiveness of olaparib was evaluated in 54 patients with metastatic breast cancer with either a germline mutation in an HR-related gene other than *BRCA1/2* or a somatic mutation in an HR-related gene, including *BRCA1/2*, if a germline *BRCA* mutation was absent[5]. Among the patients with germline *PALB2* mutations, **82% showed a response**, and **all demonstrated clinical benefit**. The notable ORR (75%) with olaparib in this second cohort of women with MBC and g*PALB2*pv was again demonstrated. Olaparib activity in MBC patients with s*BRCA*m was also confirmed[8].

As highlighted in Appendix 1, median PFS was **13.3 months** for patients with germline *PALB2* variants and **6.3 months for those with somatic *BRCA1/2* mutations**.

Patients with a single *ATM* or *CHEK2* mutation did not respond, confirming the importance of the particular mutated HR-related gene. Of note, more than **75% of patients were hormone receptor–positive**, emphasising the fact that molecular testing should not be limited to patients with triple-negative breast cancer.

Recent studies have sought to determine whether PARPis have a role in the adjuvant treatment of germline *PALB2* mutation carriers. This expanded population of patients with breast cancer showed benefit from PARPis. There is also value in offering patients a noncytotoxic based line of therapy such as PARPis, especially in patients with deteriorating performance status.

At the San Antonio Breast Cancer Symposium 2024 a presentation by Tolaney reporting data from Nadine Tung 2024, (with a May 2024 cut off) indicated that of 24 PALB2 patients, 1 had a complete response (4%) and 17 (71%) had a partial response, 5 had stable disease and 1 progressive disease (ORR 75% (18/24, 80%-CI: 60%-86%) (CBR 18 weeks 83% (20/24, 90% - CI:66%-94%). Median PFS 9.6 months (90% CI: 8.3-12.4) Median DOR: 7 months (90% CI: 5.5-11). It was also noted that responses were seen in HER2+ 3/3, TNBC 2/2 and ER+/Her2-neg (13/19)[24].

For sBRCA1/2, N=30, 1 patient showed a complete response 3%, 10 a partial response (33%), 13 had stable disease (43%) and 6 had progressive disease (20%) (ORR 37% (11/30,80% -CI: 25%-50%). Median PFS 7.2 months (90% -CI:3.9-13.6) and Median DOR 12.4 months (90% CI:4.3 not reached)[24]. A copy of this SABCS 2024 satellite presentation by Sara Tolaney, has been attached.

Olaparib is not the only PARPi shown to have activity in patients with germline *PALB2* mutations. A recent single-centre phase 2 trial confirmed the efficacy of talazoparib in patients with advanced HER2-negative breast cancer and HR gene mutations[14,15,16].

The use of PARPi in germline *PALB2* mutations is also supported by recently published case reports demonstrating exceptional responses to PARPi in patients harbouring germline *PALB2* mutations, even in cases with poor performance status and visceral crises[17,18]. Although limited in numbers, real-world analysis of the Flatiron Health Foundation Clinico-Genomic Database has also reported a benefit with olaparib in 4 patients with germline *PALB2* mutations and 9 patients with somatic *BRCA1/2* mutations[19].

The current evidence is limited by the low number of patients with germline *PALB2* mutations available for inclusion in studies but nonetheless is adequate in strength and consistency to support the use of PARPis in this clinical setting, as these patients are at high risk and are likely to have a meaningful clinical response.

Given the evidence, Breast Cancer Aotearoa Coalition supports BreastSIG's submission to extend the use of olaparib to gPALB2pv carriers. We also support inclusion of sBRCA1/2 **somatic** mutations in those eligible for PARPi treatment, as benefits have been demonstrated, and clinical management would be identical to that for germline BRCAm cancers[8].

Discussion among leading US-based clinicians at ASCO in 2024 on data presented on the use of PARPi to treat PALB2m breast cancer

Hope Rugo: (Professor of Medicine and the Director of the Breast Oncology Clinical Trials program at the University of California and an investigator of SPORE (Specialized Program of Research Excellence in Breast Cancer) in the Bay Area "this is remarkable data in a small number of patients with an excellent response *clearly indicating that PALB2* should be treated as a *BRCA2 and* for the somatic mutations a lower response, but still impressive for somatic mutations of *BRCA1/2*[18]."

Joyce O'Shaughnessy: (Breast Oncology Texas, Co-Chair of Breast Cancer Research, Chair of Breast Cancer Prevention Research at Baylor-Sammons Cancer Center and for The US Oncology Network and member of the Scientific Advisory Board for US Oncology Research Network.) "this data corroborates initial findings with germline *PALB2*. A very, very nice-looking waterfall plot, really, it's a home run, it's a major home run. And then the somatic *BRCA1/2* patients, it was a 37% response rate. Durability was there too about a year-ish, maybe a little longer. So very, very nice. And not really dependent on the allele fraction of the *BRCA1* or *BRCA2*[18]."

Sarah Tolaney: (Chief, Division of Breast Oncology, Susan F. Smith Center for Women's Cancers
Associate Director, Susan F. Smith Center for Women's Cancers, Senior Physician, Associate Professor of Medicine, Harvard Medical School) "a 50% response in

somatic BRCA and about 80% in germline PALB2 in that original presentation. And as you noted, these numbers are not that different. This validates that. We did start prescribing olaparib in these two patient populations in the metastatic setting once we had seen those data[18]."

O'Shaughnessy: Yes. Yeah. These are high-risk women. So yeah, I do think it's important[18].

Mainstreaming of genetic testing in New Zealand will progressively become available for breast cancer patients in 2025 leading to more equitable care

The Breast Cancer Aotearoa Coalition learned at a Familial Breast and Ovarian Cancer Group (FBOCG) meeting held on 14 November 2024 that mainstreaming of genetic testing for a set of breast cancer heritable variants had been agreed to by Health New Zealand management for patients that currently meet testing criteria. This was confirmed by Emma Felix (Senior Genetic Counsellor /Mainstreaming Lead Genetic Health Service NZ (GHSNZ)) on 4 December 2024.

Emma has led a mainstreaming pilot and roll out of genetic testing for ovarian cancer alongside Michelle Wilson, Auckland-based medical oncologist, regional and academic research lead. At the FBOCG meeting, Michelle Wilson stressed that cure is a possibility for ovarian cancer with upfront treatment.

Emma emphasised the need to predict, prevent, diagnose and treat patients more precisely, leading to health and economic benefits. Mainstreaming will enable timely, equitable access for all, as currently there is a significant wait (11-14 months) before GHSNZ can provide testing for patients in need. This leads to well-informed patients able to afford private care accessing private genetic counselling and therapy while others must wait a year or more for testing and longer for treatment, increasing inequity.

Mainstreaming will be led across three hubs (Northern, Central and Southern) by oncologists and surgeons across the country, to increase access and remove barriers to testing. An added benefit is that it will facilitate identification of at-risk families (preventative medicine), provide rapid test timeframes, integration of genomics into healthcare and provide benefits to patients of a reduction in costs related to genetics referral and appointment.

Ovarian cancer mainstream genetic testing is happening across the country with the exception of the mid-central region, currently unable to proceed due to staffing issues with complete roll-out in 2025. This means there is a group of capable breast and ovarian oncologists and surgeons who wish to lead and initiate a similar service for breast cancer patients in 2025. Oncologists returning to New Zealand from overseas also have experience of mainstreamed genetic testing. Oncologists in New Zealand have been prescribing olaparib since 2019 for ovarian cancer, so have experience with this medicine. Several have also used it in breast cancer under Pharmac's Exceptional Circumstances NPPA programme and for patients able to pay for this treatment in a

private clinic. There are existing and developing resources to guide, educate and assist patients and clinicians in the use of germline testing. These are available online via GHSNZ. Mainstream testing is currently offering a service within the required timeframe, with test repatriation, which does not happen when tests are completed offshore, aligning with New Zealand's data sovereignty aspirations. GHSNZ has committed to providing urgent clinic back up as required and ongoing support.

Updates of note since BCAC's 2024 olaparib application

Updated results from OlympiA

At San Antonio Breast Cancer Symposium (SABCS) 2024 General Session 1, Judy Garber, Chair and Chief of the Division of Cancer Genetics and Prevention at Dana-Farber Cancer Institute and a Professor of Medicine at Harvard Medical School presented the latest OlympiA third prespecified analysis at 10 years. This was 10 years from the first patient recruited to the study, with median follow up of 6.1 years (max. 9.6 years), an additional 2.6 years follow up since the previous analysis. This analysis showed that at 6.1 years median follow up, 12 months of olaparib after neoadjuvant chemotherapy, surgery and radiation therapy if indicated, continues to demonstrate clinically meaningful improvements in Invasive Disease-Free Survival (IDFS), Distant Disease-Free Survival (DDFS), and Overall Survival (OS) in patients with a germline BRCA pathogenic variant (gBRCApv) high risk HER2-negative primary breast cancer. The olaparib benefit was consistent across all subgroups, including for patients with high-risk ER and or PgR positive disease. Fewer primary malignancies were observed in the olaparib arm. No new safety signals were observed with longer follow up, and there is no evidence of increased risk of MDS or AML.

These data continue to support adjuvant olaparib as standard of care for patients with gBRCApv high risk HER2-negative primary breast cancer and therefore highlight the importance of gBRCApv testing for treatment planning. Blinded follow up for the final analysis continues until June 2029[22,23]. A copy of this SABCS presentation and a related AACR news release summarising updated results have been attached.

Funding of olaparib for EBC and MBC in Australia

- Australia announced a decision to fund olaparib for eBRCA HER2-negative breast cancer after neo or adjuvant chemotherapy from July 2024, based on results from the Olympia A clinical trial, with an ESMO rating of A[19].
- From 1 January 2025 eligible Australians with an inherited form of metastatic breast cancer may access Lynparza®[1] (olaparib) following a broadening of its Pharmaceutical Benefits Scheme (PBS) listing. It is the first oral therapy available on the PBS for eligible HER2-negative (human epidermal growth factor receptor 2 negative) metastatic breast cancer patients with faulty DNA repair genes, i.e. BRCA genes. The PBS listing of Lynparza® now includes the treatment of patients with HER2-negative metastatic breast cancer with a confirmed g*BRCA*1 (germline *BRCA*1) or g*BRCA*2 (germline *BRCA*2) pathogenic or likely pathogenic gene variant who have previously been treated with chemotherapy in the

neoadjuvant, adjuvant or metastatic setting. As part of this PBS listing, it has also announced germline BRCA testing will be reimbursed for all metastatic breast cancer patients, and not just those with a high hereditary risk, to determine their eligibility for Lynparza®[20].

Clinical benefit of olaparib shown in gBRCA1/2m HER2 positive MBC

OPHELIA (NCT03931551), a single-arm, open-label, phase 2 clinical trial, enrolled patients aged ≥18 years diagnosed with HER2-positive MBC with germinal deleterious mutations in BRCA1 or BRCA2 who had received at least one prior systemic regimen for advanced disease. 68 patients received olaparib plus trastuzumab until disease progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was investigator-assessed clinical benefit rate for at least 24 weeks as per RECIST v.1.1. Key secondary endpoints included overall response rate (ORR) and safety profile. This phase II trial showed that olaparib plus trastuzumab led to an objective response rate of 60% and a clinical benefit rate of 80%. The combination was well-tolerated, with most of the adverse events being grade 1 to 2. Although the trial was terminated prematurely because of slow accrual, olaparib plus trastuzumab showed promising efficacy and a good safety profile in patients with HER2 positive advanced breast cancer with germline BRCA1/2 mutations20.

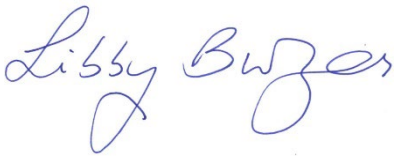
Conclusion

Breast Cancer Aotearoa Coalition has provided the above information to extend the requested eligibility criteria in our July 2024 application for olaparib funding and in support of BreastSIG's application indicating benefit to be gained from including gPALB2pv patients in the patient group that should be given access to Olaparib and further extends it to somatic BRCA1/2m patients. Testing for gBRCA1/2pv and gPALB2pv would be completed in an Auckland laboratory while somatic BRCA1/2 testing would be completed in Wellington.

We encourage Pharmac to consider this new information alongside our earlier application and look forward to learning when it will go before a Pharmac Committee.

Ngā mihi,

Fay Sowerby, BCAC Secretary



Libby Burgess, BCAC Chair

References

1. Rahman N, Seal S, Thompson D, et al; Breast Cancer Susceptibility Collaboration (UK). PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet*. 2007;39(2):165-167.
2. Cybulsky C, Kluźniak W, Huzarski T, et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. *Lancet Oncol*. 2015;16(6):638-644.
3. Lattimore, V., Parsons, M.T., Spurdle, A.B. *et al.* Under-ascertainment of breast cancer susceptibility gene carriers in a cohort of New Zealand female breast cancer patients. *Breast Cancer Res Treat* **185**, 583–590 (2021). https://doi.org/10.1007/s10549-020-05986-8
4. Rezoug Z, Totten SP, Szlachtycz D, et al. Universal Genetic Testing for Newly Diagnosed Invasive Breast Cancer. *JAMA Netw Open.* 2024;7(9):e2431427. doi:10.1001/jamanetworkopen.2024.31427
5. Kuchenbaecker KB, Olsson H (2017) at al., Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 317(23):2402–2416. https://doi.org/10.1001/jama.2017.7112
6. https://www.eviq.org.au/cancer-genetics/adult/genetic-testing-using-cancer-gene-panels/3413-breast-cancer-panel-testing#reference-6ba69de5-778a-4927-bbc4-17bf4ab73dfc
7. expanded NCCN Clinical Practice Guidelines in Oncology
8. Nadine M. Tung et al., TBCRC 048 (olaparib expanded) expansion cohorts: Phase 2 study of olaparib monotherapy in patients (pts) with metastatic breast cancer (MBC) with germline (g) mutations in PALB2 or somatic (s) mutations in BRCA1 or BRCA2. *JCO* **42**, 1021-1021(2024).DOI:10.1200/JCO.2024.42.16_suppl.1021
9. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol*. 2020;38(36):4274-4282.
10. Kuemmel S, Harrach H, Schmutzler RK, et al. Olaparib for metastatic breast cancer in a patient with a germline *PALB2* variant. *NPJ Breast Cancer*. 2020;6(1):31.
11. Cheng JM, Canzoniero J, Lee S, Soni S, Mangini N, Santa-Maria CA. Exceptional responses to PARP inhibitors in patients with metastatic breast cancer in oncologic crisis. *Breast Cancer Res Treat*. 2023;199(2):389-397.
12. Batalini F, Madison R, Pavlick DC, et al. Analysis of real-world (RW) data for metastatic breast cancer (mBC) patients (pts) with somatic BRCA1/2 (sBRCA) or other homologous

recombination (HR) pathway gene mutations (muts) treated with PARP inhibitors (PARPi). *J Clin Oncol*. 2021;39:15s (suppl; abstr 10512).

13. Tutt ANJ, Garber JE, Kaufman B, et al; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med*. 2021;384(25):2394-2405.

14. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379(8):753-763.

15. Gruber JJ, Afghahi A, Hatton A, et al. Talazoparib beyond BRCA: a phase II trial of talazoparib monotherapy in BRCA1 and BRCA2 wild type patients with advanced HER2-negative breast cancer or other solid tumors with a mutation in homologous recombination (HR) pathway genes. *J Clin Oncol*. 2019;37:15s (suppl; abstr 3006).

16. Gruber JJ, Gross W, McMillan A, Ford JM, Telli ML. A phase II clinical trial of talazoparib monotherapy for PALB2 mutation-associated advanced breast cancer. *J Clin Oncol*. 2021;39:15s (suppl; abstr TPS1109).

17. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med*. 2017;377(6):523-533.

18. MedpageTODAY, Olaparib Shows 'Unbelievable' Response Rate in MBC With PALB2 or BRCA Mutations, Expanded trial data confirm potentially practice-changing results, by Greg Laub, Director, Video, MedPage Today,July 8, 2024.

19. https://ww.astrazeneca.com.au media-releaseslynparza-breast-listed-pbs-july-2024.

20. https://www.pbs.gov.au/medicinestatus/document/1210.html.

21. Olaparib plus trastuzumab in HER2-positive advanced breast cancer patients with germline *BRCA1/2* mutations: The OPHELIA phase 2 study. Alés-Martínez, José Enrique et al. The Breast, Volume 77, 103780. https://doi.org/10.1016/j.breast.2024.103780

22. Judy Garber, MD, MPH, Dana Faber, General Session 1 presentation, OlympiA Study History, San Antonio Breast Cancer Symposium, December 10-14 2024.

23. https://www.aacr.org/about-the-aacr/newsroom/news-releases/parp-inhibition-shows-long-term-survival-benefits-for-patients-with-high-risk-brca-positive-breast-cancer-in-olympia-trial/

24. Sara M. Tolaney MD, MPH, Management of Metastatic Breast Cancer satellite Series presentation, Targeting DNA Repair, San Antonio Breast Cancer Symposium December 10-14, 2024.

Appendix 1

TBCRC 048, an investigator-initiated proof of principle phase II trial as reported at ASCO June 2024, demonstrated responses with monotherapy olaparib in MBC patients with g*PALB2* or s*BRCA* mutations. Results for additional patients with g*PALB2* (Cohort 1a) or s*BRCA* (Cohort 2a) mutations are outlined below. **Methods:** 24 MBC pts with g*PALB2*m and 30 pts with s*BRCA*m were enrolled in the expansion cohorts from Sept 2020 to Oct 2023.Eligibility included: MBC with measurable disease; documented g*PALB2*m or s*BRCA*m (with normal g*BRCA* testing); progression on < 2 metastatic chemotherapy regimens. Prior PARP inhibitor or progression on platinum was not allowed. Patients received olaparib 300 mg until progression or unacceptable toxicity. The null hypothesis for each expansion cohort [≤ 30% objective response rate (ORR)] would be rejected if > 13 responses were seen. Secondary endpoints include clinical benefit rate (CBR) at 18 weeks, progression-free survival (PFS), duration of response (DOR) and whether the mutant allele frequency (MAF) is significantly higher in responders than in non-responders. Enrolment to the g*PALB2* cohort was closed early due to slow enrolment. PFS and DOR were estimated using the Kaplan-Meier method. Association between MAF and response status was assessed using Wilcoxon rank sum test. In Cohort 1a (g*PALB2*, n=24), median age was 52.5 years (range: 26-86). 19 pts had ER+ HER2-negative, 2 HER2-positive, and 3 triple-negative breast cancer (TNBC).

Results: There were 18 confirmed responses for ORR of 75% (80% CI: 60.2%-86.3%); CBR at 18 weeks was 83.3% (90% CI: 65.8%-94.1%). Median PFS was 9.6 months (90% CI: 8.3-12.4). Median DOR was 7.1 months (90% CI: 5.6-11.0).

In Cohort 2a (s*BRCA1/2, n=30*) 15 pts had s*BRCA1*m and 15 s*BRCA2*m. 23 pts had ER+ HER2-negative, 3 HER2-positive, and 4 TNBC. There were 11 confirmed responses for ORR of 36.7% (80% CI: 24.8%-50%). CBR was 53.3% (90% CI: 37%-69.2%) and median PFS was 5.6 months (90% CI: 3.0-8.3). Median DOR was 12.4 months (90% CI: 4.3-not reached). One additional patient with a s*BRCA*m had a PR, which was not confirmed. Clinical and molecular factors associated with response to olaparib are being evaluated. MAF was available and evaluable for 33 of the 46 patients in Cohorts 2 plus 2a who had s*BRCA*m identification by tumour biopsy. The mean MAF was 43% in responders and 39 % in non-responders (p=0.7), which was not significantly different.

Conclusions: The notable ORR (75%) with olaparib in this second cohort of women with MBC and g*PALB2*m was again demonstrated. Olaparib activity in MBC pts with s*BRCA*m was also confirmed. Clinical trial information: NCT02032823.