

Inadequate Treatment Evidence for BRCA-Positive Male Breast Cancer

Subjects: Oncology

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Male breast cancer (MBC) is an orphan disease that is on the rise but remains understudied. Mutations in genes sensitive to DNA damage response, *BRCA1* and *BRCA2*, are strongly implicated in MBC development. Evidence-based guidance for the treatment of MBC that have *BRCA* mutations is lacking with most published data arising from retrospective or case studies with small patient cohorts. There is a growing understanding that male and female BCs are distinct diseases with different clinicopathological and molecular characteristics. Despite extensive advancements in other *BRCA*-positive malignancies, there remains a striking unmet need for dedicated research for *BRCA*-related MBC to better understand and optimise clinical management for this subgroup of patients. Such studies are imperative to circumvent the scant information available currently to provide optimal screening and treatment strategies that are tailored for *BRCA*-positive MBC patients.

Keywords: male breast cancer ; *BRCA* ; clinical management ; PARP inhibitors

1. Introduction

Male breast cancer (MBC) is a rare disease that accounts for less than 1% of all breast cancers and male malignancies [1][2][3][4]. Due to difficulties in achieving sufficient patient numbers, few prospective MBC clinical trials have been conducted and most available data arises from female breast cancer (FBC) trials, small retrospective studies, and case reports/series. As a result, MBC patients generally follow previously established FBC clinical management strategies [5][6]. However, with the increasing knowledge of the differing clinical demographics [7], molecular landscapes [8][9][10][11], histological subtypes [12][13], and prognostic factors between male and FBC [11][14][15], maintaining this 'one size fits all' approach is no longer tenable.

Epidemiologically, the incidence of MBC increases with age and typically presents at an advanced stage due to a late presentation at diagnosis and poor MBC awareness within the general population [2][16]. The aetiological factors of MBC remain poorly understood, but a contribution of both hormonal and anthropometric factors that lead to abnormal oestrogen exposure, have been implicated [17]. These include obesity, liver disease, testicular abnormalities, exogenous oestrogen, and Klinefelter syndrome [17]. Like FBC, loss of function mutations in the DNA damage response (DDR) genes that are responsible for genomic stability, *BRCA1* and *BRCA2*, have been heavily implicated in the pathogenesis of MBC. Pathogenic *BRCA* alterations are detected in around 16% of all MBC cases, with 12.5% found in *BRCA2* [18]. Several other genes have been reported to confer a moderate risk of MBC at lower prevalence rates including *CHEK2* (4–8%), *PALB2* (1–2%), and *PTEN* [19][20][21][22][23][24][25][26]. Endeavours to better understand the genetic landscape of MBC have been attempted through genome-wide association and focused gene loci studies. Such studies have identified a number of common polymorphisms that confer MBC risk, including those shared by FBC [27][28][29][30]. Moreover, these susceptibility variants may produce a combinatorial effect on MBC risk in *BRCA*-mutation carriers through a polygenic inheritance model [31].

BRCA mutations account for 5–10% of all breast cancers and are responsible for 20–25% of all hereditary breast cancers [32][33]. In addition, driver alterations within *BRCA* provide a substantial risk of developing a number of malignancies other than breast, such as prostate, ovarian, melanoma, and pancreatic [34]. Major efforts have enabled the characterisation of *BRCA* pathogenic gene aberrations within a number of these cancers, including FBC. This has led to the subclassification of patients with preventative risk stratification implications, specific disease courses, and management pathways that include novel targeted therapeutics. However, MBC lags in *BRCA* biomarker-led improvements that influence clinical management, highlighting the lack and need for increased translational research within this area.

Targeted approaches of *BRCA*-mutated neoplasms utilise the homologous recombination repair (HRR) deficiency, and thus the impaired ability to repair double-stranded DNA breaks. This confers greater susceptibility to platinum-based chemotherapy and is the standard treatment for *BRCA*-positive patients in FBC [35][36]. Beyond *BRCA*, an additional important DDR pathway involves the poly(ADP-ribose) polymerase (PARP) enzyme-mediated repair of single-stranded DNA breaks [37][38][39]. Inhibition of PARP function in *BRCA*-related cancers further hinders DNA repair and therefore accelerates tumour cell death. PARP inhibitors (PARPi) have shown significant promise in FBC [40] and castrate-resistant prostate cancer [41], and give credence to their potential therapeutic efficacy in *BRCA*-related MBC.

Despite extensive advancements over the last two decades in the management of FBC patients and other *BRCA*-related cancers, evidence-based MBC-specific guidance is lacking, especially for those with targetable *BRCA* mutations. One bottleneck to this area of research has been the exclusion of male participants in breast cancer trials (although this is slowly changing), and a dearth of studies focused specifically on MBC.

2. The Genetic Landscape of MBC

Knowledge of MBC germline mutations has important clinical implications, including the discovery of novel therapeutic targets and specific biomarkers. An overview of high (*BRCA1* and *BRCA2*), moderate (*PALB2*, *EGFR*, *CCND1*, and *EMSY*) and low-penetrance (*ESR1*, *TOX3*, and *FGFR2*) germline alterations with clinical translation are summarised below.

2.1. *BRCA1* and *BRCA2*

BRCA1 and *BRCA2* are tumour suppressor genes that are strongly associated with the early development of breast cancers in both, men, and women, but with distinct differences. For example, the lifetime risk of breast cancer development in women carrying *BRCA1/2* is estimated to be 72 and 69%, respectively [42][43][44]. In addition, a *BRCA1*-mutation is associated with the more aggressive molecular phenotype of FBC (e.g., triple receptor-negative, oestrogen receptor (ER) negative, progesterone receptor (PR) negative, and HER2 negative), earlier disease onset, and family history of breast cancer [45]. As a result, women with *BRCA* mutations undergo annual mammographic screening and are recommended to undertake additional adjunct MRI review [46]. Moreover, *BRCA*-positive women are offered risk reduction strategies including prophylactic mastectomy for FBC, and salpingo-oophorectomy to reduce associated ovarian cancer [46].

In contrast to FBC, *BRCA2* mutations confer the greatest risk of MBC development compared to *BRCA1* patients and the general population (*BRCA2*, 8% versus *BRCA1*, 2% versus wild type (WT), 0.1%) [45][47]. Despite the overall absolute risk being lower than their female counterparts, the risk from baseline is substantially greater in males. *BRCA*-associated MBC are usually of a higher grade and commonly present with lymph node metastases [48][49][50][51][52]. Moreover, *BRCA*-associated MBC have been shown to have significantly lower survival rates than *BRCA*-WT patients [53]. In terms of hormone receptor status and HER2 expression, *BRCA1*-mutated MBC are typically ER⁺, PR⁺, and HER⁻, whilst *BRCA2*-positive MBC are ER⁻, PR⁻, and HER2⁺ [50][53][54].

2.2. Moderate to Low Penetrance Germline Mutations

Germline mutations in several genes other than *BRCA* have been associated with survival and prognostication in MBC. Reduced survival and aggressive prognostic features are linked to mutated *PIK3CA* and *GATA3* and copy number variations in *PALB2*, *EGFR*, *CCND1* and *EMSY* [8][10][21][55][56][57][58][59][60]. In general, mutations in DNA repair genes were associated with reduced survival, and enrichment of mutations in these genes were also higher in ER positive/HER2 negative MBCs compared to matched FBCs [8]. Single nucleotide polymorphisms such as rs3803662 in the *TOX3* gene and rs2981582 in the *FGFR2* gene have also been associated with an increased risk of MBC development, while the presence of the latter also predicted reduced overall survival [27][61][62].

3. Clinical Management of *BRCA*-Related MBC

In general, all MBC patients, dependent on their staging, undergo the same standard of care as per their female counterpart. This includes a modified radical mastectomy and endocrine therapy. Adjuvant chemotherapy and radiotherapy regimens that are offered resemble the treatment strategies of FBC patients. Hormonal therapies available include tamoxifen, which despite a lack of MBC efficacy data, is the adjuvant treatment of choice and is recommended for hormone-receptor-positive tumours for a minimum of 5 years [6][63][64]. However, side effects such as weight gain, depression, and impotence have led to high rates of non-compliance and discontinuation in MBC patients [64][65]. In a

metastatic setting, aromatase inhibitors are used in tamoxifen-resistant cases or in patients who are unsuitable for tamoxifen therapy, however, combination with a gonadotrophin-releasing agent, or orchidectomy is required [6][12][66].

In terms of *BRCA*-targeting therapies, encouragingly, MBC patients were included in the OlympiAD (NCT02000622) [38] and EMBRACA (NCT01945775) [40] phase III trials, which tested the efficacy of Olaparib and Talozoparib, respectively in *BRCA*-related breast cancer. These trials demonstrated 3-month Progression Free Survival (PFS) improvement with PARPi compared to physician's choice single agent chemotherapy in metastatic *BRCA*-related breast cancer and were subsequently approved as standard therapy in advanced diseased MBC patients. In addition, MBC patients were included in the recent landmark phase III OlympiAA (NCT02032823) [67] trial which demonstrated, for the first-time, improved survival of early breast cancer patients with Olaparib in an adjuvant setting [67]. As a result, the FDA has approved Olaparib while the National Institute for Health and Care Excellence (NICE) is currently evaluating the clinical and cost effectiveness within this clinical context [68].

4. *BRCA*-Related MBC Studies

While specific guidelines concerning the management of MBC patients have recently been published [6], men have traditionally been excluded from breast cancer clinical trials. Although this is slowly changing (e.g., the German MBC trial (NCT01638247) that investigated aromatase inhibitors or tamoxifen with gonadotropin-releasing hormone agonist [69]), significant clinical management gaps still remain.

Regarding *BRCA*-positive MBC, there are currently no registered ongoing or recruiting clinical trials. This is not surprising as in addition to frequent exclusion from FBC studies, many attempted clinical trials of MBC have closed due to low participant recruitment (e.g., SWOG-S0511 (NCT00217659)). This phase II trial [70], which evaluated the effects of goserelin and anastrozole in men with recurrent or metastatic breast cancer, was withdrawn due to poor recruitment [70]. In addition, despite the European Organisation for Research and Treatment of Cancer (EORTC) being successful in performing a comprehensive retrospective clinicopathological study of over 1400 MBCs [12], achieving their overarching objective of facilitating MBC clinical trials [5] appears to have been more challenging. Moreover, previous trials that included *BRCA*-positive MBC patients have focussed predominantly on female patients [71]. Despite inclusion, the number of male patients within these studies has been extremely low ($n \leq 7$) making it impossible to perform subgroup analyses [38][40][67]. As a result, most available data for *BRCA*-positive MBC patients are derived from retrospective studies and case reports [18][48][49][50][52][53][72][73][74][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90][91][92][93][94].

5. *BRCA* Mutations in Transgender Patients

Transgender persons harbouring *BRCA* mutations and receiving hormonal therapy represent a unique group of patients who also require careful clinical management. Despite an increased incidence of breast cancer in this group [95], there remains no established evidence-based guidance. This has been highlighted in a number of cases, for instance, a recent study describes a *BRCA1*-positive trans female youth receiving hormone therapy to suppress puberty [96]. An additional case involving a transgender woman with a *BRCA1*-alteration went on to develop breast cancer whilst receiving androgen blocking therapy [97]. The patient was subsequently treated with neoadjuvant chemotherapy, mastectomy and adjuvant radiotherapy [97]. With several accounts of breast cancer now noted in transgender women who received feminising hormonal therapy [98], a better understanding of the potential risks of treatment is vital.

6. Clinical Trial Led Advancements in Other *BRCA*-Related Cancers

6.1. Female Breast Cancer (FBC)

In FBC, clinical trials investigating PARPi have led to the licencing of both Olaparib and Talozoparib by the US Food and Drug Administration (FDA) and the European Medicine's Agency (EMA), respectively, for germline *BRCA* (*gBRCA*)-positive advanced breast cancer [38][40][99].

As a result of the randomised, open-label, phase III trial, OlympiAD (NCT02000622) [38], Olaparib was the first PARPi to be approved for *gBRCA*-related advanced FBC [38]. This evaluated patients who had received two or fewer previous lines of therapy ($n = 302$) using Olaparib monotherapy versus standard chemotherapy. The results demonstrated superior efficacy and tolerability of Olaparib than standard chemotherapy [38]. PFS was also significantly higher in the Olaparib trial arm in comparison to standard chemotherapy (7.0 vs. 4.2 months; hazard ratio (HR), 0.58 (95% confidence interval (CI), 0.43–0.80); $p < 0.001$). In addition, patient objective response rates (ORR) were greater in the PARPi-treated cohort: 59.9 versus 28.8% in those who received chemotherapy [38]. Although further follow up analysis demonstrated no difference in

overall survival (OS) between the two treatment groups, it did show that chemotherapy-naïve patients who received Olaparib had a longer median OS of 7.9 months, providing a rationale for Olaparib as a future first-line option for *gBRCA* mutated advanced FBC patients in the future [99]. Irrespective of the very small sample size of male participants, Olaparib was subsequently approved for both advanced male and FBC by the FDA and EMA.

Most recently, results of the landmark OlympiA (NCT02032823) [67] trial demonstrated, for the first-time, improved survival of FBC patients with a PARPi in an adjuvant setting [67]. This included *gBRCA*-positive early breast cancer patients ($n = 1836$) who had completed local treatment and neoadjuvant or adjuvant chemotherapy. The Olaparib arm of the study was shown to have superior 3-year distant disease-free survival or death than the placebo (HR 0.57 (95% CI 0.39–0.83); $p < 0.001$) [67]. In addition, interim analysis also demonstrated improved 3-year invasive disease-free survival in the therapeutic arm versus the placebo group (HR 0.58 (95% CI 0.41–0.82); $p < 0.001$) [67]. Furthermore, no significant adverse events were noted and all safety data were concordant with known side effects of Olaparib [67]. Pivotaly, the results have led to FDA approval of Olaparib as an adjuvant treatment for patients with *gBRCA*-mutated HER2-negative high-risk early breast cancer who have already been treated with chemotherapy either before or after surgery. However, this has not been adopted by the EMA or NICE yet. In keeping with the OlympiAD (NCT02000622) study, MBC inclusion within OlympiA (NCT02032823) was limited to just two patients in the Olaparib arm [67] and makes drawing any meaningful conclusions challenging.

The phase III EMBRACA (NCT01945775) [40] trial resulted in the approval of the PARPi, Talazoparib, for the use in *gBRCA*-related, advanced FBC [40]. By comparing the efficacy of Talazoparib ($n = 287$) with a standard single agent of a clinician's choice (capecitabine, eribulin, vinorelbine, and gemcitabine) ($n = 144$), the PARPi demonstrated a greater median PFS (8.6 versus 5.6 months; HR 0.54 (95% CI 0.41–0.71); $p < 0.001$) and superior ORR (62.2% versus 27.2% (95% CI 2.9–8.8); $p < 0.001$) [40]. Consequently, Talazoparib was also approved for MBC despite the study's involving only four MBC patients.

PARPi have also been studied for their efficacy in combination with standard chemotherapy agents. For example, in the phase III randomised BROCADE (NCT02163694) [100] clinical study, carboplatin/paclitaxel with or without Celiparib was evaluated as a second line treatment in *gBRCA* advanced FBC patients [100]. Results showed a greater PFS (14.5 vs. 12.6 months; HR 0.71 (95% CI 0.57–0.88); $p = 0.002$) in patients treated with Veliparib; however, there was no significant difference in OS between the two trial arms (33.5 versus 28.2 months) [100]. Moreover, the addition of Veliparib to carboplatin and paclitaxel was well tolerated, with low discontinuation rates (<10%) [100].

6.2. Prostate Cancer

BRCA research-led advances have improved therapeutic options for metastatic and castrate resistant prostate cancer (mCRPC). For example, within the past year, Olaparib was granted FDA approval for mCRPC patients with germline or somatic deleterious HRR gene mutations, including *BRCA1* and *BRCA2*, who progressed following anti-androgen hormonal therapy. The pivotal phase III randomised trial, PROfound (NCT02987543) [41], involved 387 mCRPC patients who were allocated into two cohorts based on DDR defects (cohort A included *BRCA1* and *BRCA2* and *ATM*, while cohort B contained other DDR alterations) [41]. Treatment with Olaparib resulted in a greater median PFS than the anti-androgen control arm (7.4 versus 3.6 months; HR 0.34 (95% CI 0.25–0.47); $p < 0.0001$) [41]. Moreover, the ORR was 33 and 2.3% for experimental and control groups, respectively. In addition, *BRCA2*-related patients were found to have a greater PFS benefit after receiving Olaparib when compared to other DDR pathogenic variants (e.g., *ATM*) [41]. Moreover, the PROfound (NCT02987543) [41] study was the first to demonstrate an increase in OS in mCRPC with a PARPi versus physicians choice of second generation-hormonal therapy (19.1 months in cohort A versus 14.7 months in the control arm) (HR 0.69, $p = 0.02$) [101].

Based on the TRITON2 (NCT02952534) [102] trial, the PARPi, Rucaparib, gained accelerated FDA approval for *gBRCA* mCRPC patients progressing after prior androgen hormonal therapy and a taxane chemotherapy [102]. Furthermore, ORRs determined per independent radiology review and investigator assessment, were found to be greatest in those harbouring *BRCA* alterations (43.5% (95% CI 31.0–56.7) and 50.8% (95% CI 38.1–63.4), respectfully) [102]. Full FDA approval will be dependent on the TRITON3 (NCT02975934) [103] phase III randomised control trial which is comparing Rucaparib against physicians' choice of chemotherapy or second generation hormonal agent in patients who have previously received a hormonal agent but not a taxane drug for mCRPC [103].

Niraparib and Talazoparib PARPi are also being investigated in *BRCA*-related mCRPC. Interim results of the active phase II GALAHAD (NCT02854436) [104] study demonstrated good ORR (41% (95% CI 23.5–61.1)) and PFS (8.2 months (95% CI 5.2–11.1)) with Niraparib in *BRCA*-positive mCRPC patients who have progressed on a second-generation hormonal agent and a taxane chemotherapeutic [104]. In regard to Talazoparib, the phase II TALAPRO-1 (NCT03148795) [105] study

showed that patients with *BRCA*-positive mCRPC had superior ORR to the PARPi than other DDR mutations [105]. Both Niraparib and Talazoparib are currently being evaluated in phase III trials for mCRPC.

With promising preclinical support [106][107][108][109], the efficacy of PARPi in prostate cancer is currently being investigated in combination with other agents such as anti-androgens [110][111][112], immunotherapeutics [113], chemotherapy [114], radiotherapy [115], and ATR (ataxia-telangiectasia and Rad3-related) protein inhibitors [116]. A total of three trials are currently underway for the evaluation of anti-androgen compounds and PARPi. The phase III PROpel (NCT03732820) [110] trial is exploring Olaparib in combination with abiraterone as first-line therapy in patients with mCRPC [110]. A further phase III study, MAGNITUDE (NCT03748641) [111] is being conducted in both mCRPC patients with and without HRR alterations and the efficacy of niraparib and abiraterone [111]. The benefit of combining Talazoparib and enzalutamide in mCRPC is also being studied in the phase III TALAPRO-2 (NCT03395197) trial [112]. In terms of immunotherapy, one phase I/II study has shown early promise in safety and response profiles when using Durvalumab plus Olaparib in mCRPC (NCT02484404) [113]. Further exploiting the vulnerability of DDR-altered mCRPC to DNA damage, a phase II trial is investigating the impact of the ATRi, Ceralasertib, and Olaparib (NCT03787680) [116]. Other DNA-inhibition strategies that are also being studied include high-dose testosterone (NCT03516812) [117]. Ultimately, the amalgamation of PARPi with other anti-cancer compounds could increase the number of DDR-gene mutation-positive prostate cancer patients benefiting from PARPi therapy.

7. Future Directions in *BRCA*-Related MBC

PARPi are driving transformative improvements in the clinical management of *BRCA*-mutated malignancies. Future directions should aim to evaluate the impact of PARPi, and other targeted approaches, in *BRCA*-positive MBC. This will require the generation of national MBC registries, global collaboration, and pre-clinical studies.

7.1. National Registry and Combining Efforts

As an orphan disease, efforts to improve the clinical management of MBC, especially those identified as *BRCA*-positive, will require a global collaborative approach. Impressive efforts by Cardoso et al. [12] have already shown the importance of such collaborations in providing further characterisation of MBC (EORTC International Male Breast Cancer Program). However, *BRCA* MBC focused investigations remain scarce and therefore, consideration should be made on country-specific national registry studies for *BRCA*-mutated male patients (e.g., Scottish/Dutch/French/German national registry studies). This will enable synergistic efforts to carefully design and implement clinical trials with large enough cohorts to prevent early termination and generate enough statistical power to accurately characterise *BRCA*-related MBC, including therapeutic sensitivities. In the long run, this will help improve the clinical management of these patients.

7.2. Translational Research

To bridge the gap in the interim of clinical trial development, in vitro and in vivo approaches in *BRCA*-related MBC should also be explored. These could include the generation of patient-derived tumour organoid (PDTO) and patient-derived xenograft (PDX) mouse models to better understand *BRCA*-mutated MBC. Currently, PDTOs do not exist for MBC and are based on FBC organoid derivation, and there are recognised challenges generating organoids from ER-positive disease. In contrast, HER2-positive, and triple negative FBC, have had greater successes [118][119], with the latter phenotype being rarer in MBC [13]. Similar successes have also been achieved with *BRCA*-positive PDX models of FBC. For example, a *BRCA*-mutated (L1780P) PDX model demonstrated a partial response to Olaparib [120].

With coordinated efforts, PDTOs, and PDX models, may be derived from MBCs offering the potential to encompass the clinical diversity of each subtype, including those that are *BRCA*-positive. This will allow further characterisation and exploration of genetic alterations and the identification of corresponding therapeutic sensitivities in male breast cancer.

References

1. SEER Cancer Statistics Review (CSR) 1975–2018. Available online: https://seer.cancer.gov/csr/1975_2018/ (accessed on 5 June 2021).
2. Anderson, W.F.; Jatoi, I.; Tse, J.; Rosenberg, P.S. Male breast cancer: A population-based comparison with female breast cancer. *J. Clin. Oncol.* 2010, 28, 232–239.
3. Giordano, S.H.; Cohen, D.S.; Buzdar, A.U.; Perkins, G.; Hortobagyi, G.N. Breast carcinoma in men: A population-based study. *Cancer* 2004, 101, 51–57.

4. White, J.; Kearins, O.; Dodwell, D.; Horgan, K.; Hanby, A.M.; Speirs, V. Male breast carcinoma: Increased awareness needed. *Breast Cancer Res.* 2011, 13, 219.
5. Korde, L.A.; Zujewski, J.A.; Kamin, L.; Giordano, S.; Domchek, S.; Anderson, W.F.; Bartlett, J.M.S.; Gelmon, K.; Nahleh, Z.; Bergh, J.; et al. Multidisciplinary meeting on male breast cancer: Summary and research recommendations. *J. Clin. Oncol.* 2010, 28, 2114–2122.
6. Hassett, M.J.; Somerfield, M.R.; Baker, E.R.; Cardoso, F.; Kansal, K.J.; Kwait, D.C.; Plichta, J.K.; Ricker, C.; Roshal, A.; Ruddy, K.J.; et al. Management of male breast cancer: ASCO guideline. *J. Clin. Oncol.* 2020, 38, 1849–1863.
7. Greif, J.M.; Pezzi, C.M.; Klimberg, S.V.; Bailey, L.; Zuraek, M. Gender differences in breast cancer: Analysis of 13,000 breast cancers in men from the national cancer data base. *Ann. Surg. Oncol.* 2012, 19, 3199–3204.
8. Piscuoglio, S.; Ng, C.K.Y.; Murray, M.P.; Guerini-Rocco, E.; Martelotto, L.G.; Geyer, F.C.; Bidard, F.C.; Berman, S.; Fusco, N.; Sakr, R.A.; et al. The genomic landscape of male breast cancers. *Clin. Cancer Res.* 2016, 22, 4045–4056.
9. Callari, M.; Cappelletti, V.; De Cecco, L.; Musella, V.; Miodini, P.; Veneroni, S.; Gariboldi, M.; Pierotti, M.A.; Daidone, M.G. Gene expression analysis reveals a different transcriptomic landscape in female and male breast cancer. *Breast Cancer Res. Treat.* 2011, 127, 601–610.
10. Moelans, C.B.; De Ligt, J.; Van Der Groep, P.; Prins, P.; Besselink, N.J.M.; Hoogstraat, M.; ter Hoeve, N.D.; Lacle, M.M.; Kornegoor, R.; Van Der Pol, C.C.; et al. The molecular genetic make-up of male breast cancer. *Endocr. Relat. Cancer* 2019, 26, 779–794.
11. Humphries, M.P.; Rajan, S.S.; Droop, A.; Suleman, C.A.B.; Carbone, C.; Nilsson, C.; Honarpisheh, H.; Cserni, G.; Dent, J.; Fulford, L.; et al. A case-matched gender comparison transcriptomic screen identifies eIF4E and eIF5 as potential prognostic markers in male breast cancer. *Clin. Cancer Res.* 2017, 23, 2575–2583.
12. Cardoso, F.; Bartlett, J.M.S.; Slaets, L.; van Deurzen, C.H.M.; van Leeuwen-Stok, E.; Porter, P.; Linderholm, B.; Hedenfalk, I.; Schröder, C.; Martens, J.; et al. Characterization of male breast cancer: Results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Ann. Oncol.* 2018, 29, 405–417.
13. Humphries, M.P.; Sundara Rajan, S.; Honarpisheh, H.; Cserni, G.; Dent, J.; Fulford, L.; Jordan, L.B.; Jones, J.L.; Kanthan, R.; Litwiniuk, M.; et al. Characterisation of male breast cancer: A descriptive biomarker study from a large patient series. *Sci. Rep.* 2017, 7, 45293.
14. Yadav, S.; Karam, D.; Bin Riaz, I.; Xie, H.; Durani, U.; Duma, N.; Giridhar, K.V.; Hieken, T.J.; Boughey, J.C.; Mutter, R.W.; et al. Male breast cancer in the United States: Treatment patterns and prognostic factors in the 21st century. *Cancer* 2020, 126, 26–36.
15. Shaaban, A.M.; Ball, G.R.; Brannan, R.A.; Cserni, G.; Di Benedetto, A.; Dent, J.; Fulford, L.; Honarpisheh, H.; Jordan, L.; Jones, J.L.; et al. A comparative biomarker study of 514 matched cases of male and female breast cancer reveals gender-specific biological differences. *Breast Cancer Res. Treat.* 2012, 133, 949–958.
16. Jylling, A.M.B.; Jensen, V.; Lelkaitis, G.; Christiansen, P.; Nielsen, S.S.; Lautrup, M.D. Male breast cancer: Clinicopathological characterization of a National Danish cohort 1980–2009. *Breast Cancer* 2020, 27, 683–695.
17. Brinton, L.A.; Cook, M.B.; McCormack, V.; Johnson, K.C.; Olsson, H.; Casagrande, J.T.; Cooke, R.; Falk, R.T.; Gapstur, S.M.; Gaudet, M.M.; et al. Anthropometric and hormonal risk factors for male breast cancer: Male breast cancer pooling project results. *J. Natl. Cancer Inst.* 2014, 106, djt465.
18. Ibrahim, M.; Yadav, S.; Ogunleye, F.; Zakalik, D. Male BRCA mutation carriers: Clinical characteristics and cancer spectrum. *BMC Cancer* 2018, 18, 179.
19. Liang, M.; Zhang, Y.; Sun, C.; Rizeq, F.K.; Min, M.; Shi, T.; Sun, Y. Association Between CHEK2*1100delC and Breast Cancer: A Systematic Review and Meta-Analysis. *Mol. Diagnosis. Ther.* 2018, 22, 397–407.
20. Meijers-Heijboer, H.; Van den Ouweland, A.; Klijn, J.; Wasielewski, M.; De Shoo, A.; Oldenburg, R.; Hollestelle, A.; Houben, M.; Crepin, E.; Van Veghel-Plandsoen, M.; et al. Low-penetrance susceptibility to breast cancer due to CHEK2*1100delC in noncarriers of BRCA1 or BRCA2 mutations: The CHEK2-breast cancer consortium. *Nat. Genet.* 2002, 31, 55–59.
21. Rizzolo, P.; Zelli, V.; Silvestri, V.; Valentini, V.; Zanna, I.; Bianchi, S.; Masala, G.; Spinelli, A.M.; Tibiletti, M.G.; Russo, A.; et al. Insight into genetic susceptibility to male breast cancer by multigene panel testing: Results from a multicenter study in Italy. *Int. J. Cancer* 2019, 145, 390–400.
22. Fackenthal, J.D.; Marsh, D.J.; Richardson, A.L.; Cummings, S.A.; Eng, C.; Robinson, B.G.; Olopade, O.I. Male breast cancer in Cowden syndrome patients with germline PTEN mutations. *J. Med. Genet.* 2001, 38, 159–164.
23. Rahman, N.; Seal, S.; Thompson, D.; Kelly, P.; Renwick, A.; Elliott, A.; Reid, S.; Spanova, K.; Barfoot, R.; Chagtai, T.; et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat. Genet.* 2007, 39, 165–167.

24. Erkkö, H.; Xia, B.; Nikkilä, J.; Schleutker, J.; Syrjäkoski, K.; Mannermaa, A.; Kallioniemi, A.; Pylkäs, K.; Karppinen, S.M.; Rapakko, K.; et al. A recurrent mutation in PALB2 in Finnish cancer families. *Nature* 2007, 446, 316–319.
25. Casadei, S.; Norquist, B.M.; Walsh, T.; Stray, S.; Mandell, J.B.; Lee, M.K.; Stamatoyannopoulos, J.A.; King, M.C. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. *Cancer Res.* 2011, 71, 2222–2229.
26. Pritzlaff, M.; Summerour, P.; McFarland, R.; Li, S.; Reineke, P.; Dolinsky, J.S.; Goldgar, D.E.; Shimelis, H.; Couch, F.J.; Chao, E.C.; et al. Male breast cancer in a multi-gene panel testing cohort: Insights and unexpected results. *Breast Cancer Res. Treat.* 2017, 161, 575–586.
27. Orr, N.; Cooke, R.; Jones, M.; Fletcher, O.; Dudbridge, F.; Chilcott-Burns, S.; Tomczyk, K.; Broderick, P.; Houlston, R.; Ashworth, A.; et al. Genetic variants at chromosomes 2q35, 5p12, 6q25.1, 10q26.13, and 16q12.1 influence the risk of breast cancer in men. *PLoS Genet.* 2011, 7, 1002290.
28. Orr, N.; Lemnrau, A.; Cooke, R.; Fletcher, O.; Tomczyk, K.; Jones, M.; Johnson, N.; Lord, C.J.; Mitsopoulos, C.; Zvelebil, M.; et al. Genome-wide association study identifies a common variant in RAD51B associated with male breast cancer risk. *Nat. Genet.* 2012, 44, 1182–1184.
29. Silvestri, V.; Rizzolo, P.; Scarnò, M.; Chillemi, G.; Navazio, A.S.; Valentini, V.; Zelli, V.; Zanna, I.; Saieva, C.; Masala, G.; et al. Novel and known genetic variants for male breast cancer risk at 8q24.21, 9p21.3, 11q13.3 and 14q24.1: Results from a multicenter study in Italy. *Eur. J. Cancer* 2015, 51, 2289–2295.
30. Maguire, S.; Perraki, E.; Tomczyk, K.; Jones, M.E.; Fletcher, O.; Pugh, M.; Winter, T.; Thompson, K.; Cooke, R.; Trainer, A.; et al. Common Susceptibility Loci for Male Breast Cancer. *J. Natl. Cancer Inst.* 2021, 113, 453–461.
31. Lecarpentier, J.; Kuchenbaecker, K.B.; Barrowdale, D.; Dennis, J.; McGuffog, L.; Leslie, G.; Lee, A.; Al Olama, A.A.; Tyrer, J.P.; Frost, D.; et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. *J. Clin. Oncol.* 2017, 35, 2240–2250.
32. Campeau, P.M.; Foulkes, W.D.; Tischkowitz, M.D. Hereditary breast cancer: New genetic developments, new therapeutic avenues. *Hum. Genet.* 2008, 124, 31–42.
33. Easton, D.F. How many more breast cancer predisposition genes are there? *Breast Cancer Res.* 1999, 1, 14–17.
34. Mersch, J.; Jackson, M.A.; Park, M.; Nebgen, D.; Peterson, S.K.; Singletary, C.; Arun, B.K.; Litton, J.K. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. *Cancer* 2015, 121, 269–275.
35. Byrski, T.; Gronwald, J.; Huzarski, T.; Grzybowska, E.; Budryk, M.; Stawicka, M.; Mierzwa, T.; Szwiec, M.; Wiśniowski, R.; Siolek, M.; et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. *J. Clin. Oncol.* 2010, 28, 375–379.
36. Von Minckwitz, G.; Schneeweiss, A.; Loibl, S.; Salat, C.; Denkert, C.; Rezai, M.; Blohmer, J.U.; Jackisch, C.; Paepke, S.; Gerber, B.; et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): A randomised phase 2 trial. *Lancet Oncol.* 2014, 15, 747–756.
37. Roy, R.; Chun, J.; Powell, S.N. BRCA1 and BRCA2: Different roles in a common pathway of genome protection. *Nat. Rev. Cancer* 2012, 12, 68–78.
38. Robson, M.; Im, S.-A.; Senkus, E.; Xu, B.; Domchek, S.M.; Masuda, N.; Delaloge, S.; Li, W.; Tung, N.; Armstrong, A.; et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N. Engl. J. Med.* 2017, 377, 523–533.
39. Farmer, H.; McCabe, H.; Lord, C.J.; Tutt, A.H.J.; Johnson, D.A.; Richardson, T.B.; Santarosa, M.; Dillon, K.J.; Hickson, I.; Knights, C.; et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005, 434, 917–921.
40. Litton, J.K.; Rugo, H.S.; Ettl, J.; Hurvitz, S.A.; Gonçalves, A.; Lee, K.-H.; Fehrenbacher, L.; Yerushalmi, R.; Mina, L.A.; Martin, M.; et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N. Engl. J. Med.* 2018, 379, 753–763.
41. de Bono, J.; Mateo, J.; Fizazi, K.; Saad, F.; Shore, N.; Sandhu, S.; Chi, K.N.; Sartor, O.; Agarwal, N.; Olmos, D.; et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *N. Engl. J. Med.* 2020, 382, 2091–2102.
42. Kuchenbaecker, K.B.; Hopper, J.L.; Barnes, D.R.; Phillips, K.A.; Mooij, T.M.; Roos-Blom, M.J.; Jervis, S.; Van Leeuwen, F.E.; Milne, R.L.; Andrieu, N.; et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017, 317, 2402–2416.
43. Chen, S.; Parmigiani, G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J. Clin. Oncol.* 2007, 25, 1329–1333.
44. Ford, D.; Easton, D.F.; Bishop, D.T.; Narod, S.A.; Goldgar, D.E. Risks of cancer in BRCA1-mutation carriers. *Lancet* 1994, 343, 692–695.

45. Tun, N.M.; Villani, G.; Ong, K.; Yoe, L.; Bo, Z.M. Risk of having BRCA1 mutation in high-risk women with triple-negative breast cancer: A meta-analysis. *Clin. Genet.* 2014, 85, 43–48.
46. NICE. Familial Breast Cancer: Classification, Care and Managing Breast Cancer and Related Risks in People with a Family History of Breast Cancer; NICE: London, UK, 2019.
47. Evans, D.G.R.; Susnerwala, I.; Dawson, J.; Woodward, E.; Maher, E.R.; Laloo, F. Risk of breast cancer in male BRCA2 carriers. *J. Med. Genet.* 2010, 47, 710–711.
48. Ottini, L.; Masala, G.; D'Amico, C.; Mancini, B.; Saieva, C.; Aceto, G.; Gestri, D.; Vezzosi, V.; Falchetti, M.; De Marco, M.; et al. BRCA1 and BRCA2 mutation status and tumor characteristics in male breast cancer: A population-based study in Italy. *Cancer Res.* 2003, 63, 342–347.
49. Ottini, L.; Rizzolo, P.; Zanna, I.; Falchetti, M.; Masala, G.; Ceccarelli, K.; Vezzosi, V.; Gulino, A.; Giannini, G.; Bianchi, S.; et al. BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: A population-based study in central Italy. *Breast Cancer Res. Treat.* 2009, 116, 577–586.
50. Ottini, L.; Silvestri, V.; Rizzolo, P.; Falchetti, M.; Zanna, I.; Saieva, C.; Masala, G.; Bianchi, S.; Manoukian, S.; Barile, M.; et al. Clinical and pathologic characteristics of BRCA-positive and BRCA-negative male breast cancer patients: Results from a collaborative multicenter study in Italy. *Breast Cancer Res. Treat.* 2012, 134, 411–418.
51. Sun, X.; Gong, Y.; Rao, M.S.; Badve, S. Loss of BRCA1 expression in sporadic male breast carcinoma. *Breast Cancer Res. Treat.* 2002, 71, 1–7.
52. André, S.; Pereira, T.; Silva, F.; Machado, P.; Vaz, F.; Aparício, M.; Silva, G.L.; Pinto, A.E. Male breast cancer: Specific biological characteristics and survival in a Portuguese cohort. *Mol. Clin. Oncol.* 2019, 10, 644–654.
53. Gargiulo, P.; Pensabene, M.; Milano, M.; Arpino, G.; Giuliano, M.; Forestieri, V.; Condello, C.; Lauria, R.; De Placido, S. Long-term survival and BRCA status in male breast cancer: A retrospective single-center analysis. *BMC Cancer* 2016, 16, 1–11.
54. Deb, S.; Jene, N.; Investigators, K.C.F.; Fox, S.B. Genotypic and phenotypic analysis of familial male breast cancer shows under representation of the HER2 and basal subtypes in BRCA-associated carcinomas. *BMC Cancer* 2012, 12, 510.
55. Kornegoor, R.; Moelans, C.B.; Verschuur-Maes, A.H.J.; Hogenes, M.C.H.; De Bruin, P.C.; Oudejans, J.J.; Marchionni, L.; Van Diest, P.J. Oncogene amplification in male breast cancer: Analysis by multiplex ligation-dependent probe amplification. *Breast Cancer Res. Treat.* 2012, 135, 49–58.
56. Szwiec, M.; Tomiczek-Szwiec, J.; Kluźniak, W.; Wokolorczyk, D.; Osowiecka, K.; Sibilski, R.; Wachowiak, M.; Gronwald, J.; Gronwald, H.; Lubiński, J.; et al. Genetic predisposition to male breast cancer in Poland. *BMC Cancer* 2021, 21, 1–8.
57. Bärlund, M.; Kuukasjärvi, T.; Syrjäkoski, K.; Auvinen, A.; Kallioniemi, A. Frequent amplification and overexpression of CCND1 in male breast cancer. *Int J. Cancer* 2004, 111, 968–971.
58. Rizzolo, P.; Navazio, A.S.; Silvestri, V.; Valentini, V.; Zelli, V.; Zanna, I.; Masala, G.; Bianchi, S.; Scarnò, M.; Tommasi, S.; et al. Somatic alterations of targetable oncogenes are frequently observed in BRCA1/2 mutation negative male breast cancers. *Oncotarget* 2016, 7, 74097.
59. Vermeulen, M.A.; Doebar, S.C.; Van Deurzen, C.H.M.; Martens, J.W.M.; Van Diest, P.J.; Moelans, C.B. Copy number profiling of oncogenes in ductal carcinoma in situ of the male breast. *Endocr. Relat. Cancer* 2018, 25, 173–184.
60. Lacle, M.M.; Kornegoor, R.; Moelans, C.B.; Maes-Verschuur, A.H.; Van Der Pol, C.; Witkamp, A.J.; Van Der Wall, E.; Rueschoff, J.; Buerger, H.; Van Diest, P.J. Analysis of copy number changes on chromosome 16q in male breast cancer by multiplex ligation-dependent probe amplification. *Mod. Pathol.* 2013, 26, 1461–1467.
61. Zanna, I.; Silvestri, V.; Palli, D.; Magrini, A.; Rizzolo, P.; Saieva, C.; Zelli, V.; Bendinelli, B.; Vezzosi, V.; Valentini, V.; et al. Smoking and FGFR2 rs2981582 variant independently modulate male breast cancer survival: A population-based study in Tuscany, Italy. *Breast* 2018, 40, 85–91.
62. Ottini, L.; Silvestri, V.; Saieva, C.; Rizzolo, P.; Zanna, I.; Falchetti, M.; Masala, G.; Navazio, A.S.; Graziano, V.; Bianchi, S.; et al. Association of low-penetrance alleles with male breast cancer risk and clinicopathological characteristics: Results from a multicenter study in Italy. *Breast Cancer Res. Treat.* 2013, 138, 861–868.
63. Giordano, S.H.; Perkins, G.H.; Broglio, K.; Garcia, S.G.; Middleton, L.P.; Buzdar, A.U.; Hortobagyi, G.N. Adjuvant Systemic therapy for male breast carcinoma. *Cancer* 2005, 104, 2359–2364.
64. Bradley, K.L.; Tyldesley, S.; Speers, C.H.; Woods, R.; Villa, D. Contemporary systemic therapy for male breast cancer. *Clin. Breast Cancer* 2014, 14, 31–39.
65. Khan, M.H.; Allerton, R.; Pettit, L. Hormone therapy for breast cancer in men. *Clin. Breast Cancer* 2015, 15, 245–250.

66. Cardoso, F.; Costa, A.; Senkus, E.; Aapro, M.; André, F.; Barrios, C.H.; Bergh, J.; Bhattacharyya, G.; Biganzoli, L.; Cardoso, M.J.; et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann. Oncol.* 2017, 28, 16–33.
67. Tutt, A.N.J.; Garber, J.E.; Kaufman, B.; Viale, G.; Fumagalli, D.; Rastogi, P.; Gelber, R.D.; de Azambuja, E.; Fielding, A.; Balmaña, J.; et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2- Mutated Breast Cancer. *N. Engl. J. Med.* 2021, 384, 2394–2405.
68. NICE. Olaparib for Adjuvant Treatment of High-Risk HER2-Negative, BRCA-Positive Early Breast Cancer after Chemotherapy . 2022. Available online: <https://www.nice.org.uk/guidance/indevelopment/gid-ta10903> (accessed on 18 May 2022).
69. Reinisch, M.; Seiler, S.; Hauzenberger, T.; Kamischke, A.; Schmatloch, S.; Strittmatter, H.J.; Zahm, D.M.; Thode, C.; Furlanetto, J.; Strik, D.; et al. Efficacy of Endocrine Therapy for the Treatment of Breast Cancer in Men: Results from the MALE Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2021, 7, 565–572.
70. ClinicalTrials.gov. S0511, Goserelin and Anastrozole in Treating Men with Recurrent or Metastatic Breast Cancer. Available online: <https://clinicaltrials.gov/ct2/show/NCT00217659> (accessed on 7 July 2021).
71. Han, H.S.; Diéras, V.; Robson, M.; Palácová, M.; Marcom, P.K.; Jager, A.; Bondarenko, I.; Citrin, D.; Campone, M.; Telli, M.L.; et al. Veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with BRCA1/2 locally recurrent/metastatic breast cancer: Randomized phase II study. *Ann. Oncol.* 2018, 29, 154–161.
72. Vietri, M.T.; Caliendo, G.; D'Elia, G.; Resse, M.; Casamassimi, A.; Minucci, P.B.; Cioffi, M.; Molinari, A.M. BRCA and PALB2 mutations in a cohort of male breast cancer with one bilateral case. *Eur. J. Med. Genet.* 2020, 63, 103883.
73. Benjamin, M.A.; Riker, A.I. A case of male breast cancer with a BRCA gene mutation. *Ochsner. J.* 2015, 15, 448–451.
74. Silvestri, V.; Barrowdale, D.; Mulligan, A.M.; Neuhausen, S.L.; Fox, S.; Karlan, B.Y.; Mitchell, G.; James, P.; Thull, D.L.; Zorn, K.K.; et al. Male breast cancer in BRCA1 and BRCA2 mutation carriers: Pathology data from the Consortium of Investigators of Modifiers of BRCA1/2. *Breast Cancer Res.* 2016, 18, 15.
75. Basham, V.M.; Lipscombe, J.M.; Ward, J.M.; Gayther, S.A.; Ponder, B.A.; Easton, D.F.; Pharoah, P.D. BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. *Breast Cancer Res.* 2002, 4, R2.
76. Kwiatkowska, E.; Teresiak, M.; Filas, V.; Karczewska, A.; Breborowicz, D.; Mackiewicz, A. Mutations and Androgen Receptor Expression as Independent Predictors of Outcome of Male Breast Cancer Patients. *Clin. Cancer Res.* 2003, 9, 4452–4459.
77. Rizzolo, P.; Silvestri, V.; Valentini, V.; Zelli, V.; Zanna, I.; Masala, G.; Bianchi, S.; Palli, D.; Ottini, L. Gene-specific methylation profiles in BRCA-mutation positive and BRCA-mutation negative male breast cancers. *Oncotarget* 2018, 9, 19783.
78. Ding, Y.C.; Steele, L.; Kuan, C.J.; Greilac, S.; Neuhausen, S.L. Mutations in BRCA2 and PALB2 in male breast cancer cases from the United States. *Breast Cancer Res. Treat.* 2011, 126, 771–778.
79. Cheng, Y.; Li, N.; Eapen, A.; Parajuli, R.; Mehta, R. Somatic BRCA2 Mutation-Positive Concurrent Accessory Male Breast Cancer (BC) and Non-Small Cell Lung Cancer (NSCLC): Excellent Efficacy of Palbociclib, Fulvestrant and Leuprolide in Platinum-Exposed and Endocrine-Refractory BC Associated with Cyclin D1 an. *Case Rep. Oncol.* 2019, 12, 494–499.
80. Singer, C.F.; Rappaport-Fuerhauser, C.; Sopik, V.; Narod, S.A. Prostate cancer in a man with a BRCA2 mutation and a personal history of bilateral breast cancer. *Clin. Genet.* 2015, 88, 187–189.
81. Saha, D.; Tannenbaum, S.; Zhu, Q. Treatment of Male Breast Cancer by Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade and Response Prediction Using Novel Optical Tomography Imaging: A Case Report. *Cureus* 2017, 9, e1481.
82. Guaoua, S.; Ratbi, I.; Lyahyai, J.; El Alaoui, S.C.; Laarabi, F.-Z.; Sefiani, A. Novel nonsense mutation of BRCA2 gene in a Moroccan man with familial breast cancer. *Afr. Health Sci.* 2014, 14, 468.
83. Karamanakis, P.; Mitsiades, C.S.; Lembessis, P.; Kontos, M.; Trafalis, D.; Koutsilieris, M. Male Breast Adenocarcinoma in a Prostate Cancer Patient Following Prolonged Anti-androgen Monotherapy. *Anticancer Res.* 2004, 24, 1077–1081.
84. Savelyeva, L.; Claas, A.; Gier, S.; Schlag, P.; Finke, L.; Mangion, J.; Stratton, M.R.; Schwab, M. An interstitial tandem duplication of 9p23-24 coexists with a mutation in the BRCA2 gene in the germ line of three brothers with breast cancer. *Cancer Res.* 1998, 58, 863–866.
85. Panchal, S.; Shachar, O.; O'Malley, F.; Crystal, P.; Escallon, J.; Crook, J.; Bane, A.; Bordeleau, L. Breast cancer in a BRCA2 mutation carrier with a history of prostate cancer. *Nat. Rev. Clin. Oncol.* 2009, 6, 604–607.

86. Brenner, R.J.; Weitzel, J.N.; Hansen, N.; Boasberg, P. Screening-detected Breast Cancer in a Man with BRCA2 Mutation: Case Report. *Radiology* 2004, 230, 553–555.
87. Scheidbach, H.; Dworak, O.; Schmucker, B.; Hohenberger, W. Lobular carcinoma of the breast in an 85-year-old man. *Eur. J. Surg. Oncol.* 2000, 26, 319–321.
88. Azzouzi, A.R.; Stoppa-Lyonnet, D.; Roupret, M.; Larre, S.; Mangin, P.; Cussenot, O. BRCA2 mutation screening is clinically relevant in breast and early prostate cancer families. *Int. J. Urol.* 2007, 14, 445–446.
89. Kwiatkowska, E.; Brozek, I.; Izycka-Swieszewska, E.; Limon, J.; Mackiewicz, A. Novel BRCA2 mutation in a Polish family with hamartoma and two male breast cancers. *J. Med. Genet.* 2002, 39, E35.
90. Deb, S.; Goringe, K.L.; Pang, J.-M.B.; Byrne, D.J.; Takano, E.A.; Investigators, K.; Dobrovic, A.; Fox, S.B. BRCA2 carriers with male breast cancer show elevated tumour methylation. *BMC Cancer* 2017, 17, 1–11.
91. Huszno, J.; Fiszer-Kierzkowska, A.; Pigłowski, W.; Mazur, M. BRCA2 gene mutation, c.2808_2811delACAA (p.Ala938Profs), in male breast cancer—Clinicopathological analysis based on a case report. *Prz Menopauzalny* 2019, 8, 227–229.
92. de Juan, I.; Palanca, S.; Domenech, A.; Feliubadaló, L.; Segura, Á.; Osorio, A.; Chirivella, I.; de la Hoya, M.; Sánchez, A.B.; Infante, M.; et al. BRCA1 and BRCA2 mutations in males with familial breast and ovarian cancer syndrome. Results of a Spanish multicenter study. *Fam Cancer* 2015, 14, 505–513.
93. Palli, D.; Falchetti, M.; Masala, G.; Lupi, R.; Sera, F.; Saieva, C.; D'Amico, C.; Ceroti, M.; Rizzolo, P.; Caligo, M.A.; et al. Association between the BRCA2 N372H variant and male breast cancer risk: A population-based case-control study in Tuscany, Central Italy. *BMC Cancer* 2007, 7, 1–7.
94. Tirkkonen, M.; Kainu, T.; Loman, N.; Jóhannsson, Ó.T.; Olsson, H.; Barkardóttir, R.B.; Kallioniemi, O.P.; Borg, Å. Somatic genetic alterations in BRCA2-associated and sporadic male breast cancer. *Genes Chromosom Cancer* 1999, 24, 56–61.
95. De Blok, C.J.M.; Wiepjes, C.M.; Nota, N.M.; Van Engelen, K.; Adank, M.A.; Dreijerink, K.M.A.; Barbé, E.; Konings, I.R.H.M.; Den Heijer, M. Breast cancer risk in transgender people receiving hormone treatment: Nationwide cohort study in the Netherlands. *BMJ* 2019, 365, l1652.
96. Wolf-Gould, C.S.; Riley, M.R.; Carswell, J.M. Complex medical decision-making for a trans-feminine youth with a BRCA1 mutation. *LGBT Health* 2018, 5, 221–225.
97. Colebunders, B.; T'Sjoen, G.; Weyers, S.; Monstrey, S. Hormonal and surgical treatment in trans-women with BRCA1 mutations: A controversial topic. *J. Sex. Med.* 2014, 11, 2496–2499.
98. Eismann, J.; Heng, Y.J.; Fleischmann-Rose, K.; Tobias, A.M.; Phillips, J.; Wulf, G.M.; Kansal, K.J. Interdisciplinary Management of Transgender Individuals at Risk for Breast Cancer: Case Reports and Review of the Literature. *Clin. Breast Cancer* 2019, 19, e12–e19.
99. Robson, M.E.; Tung, N.; Conte, P.; Im, S.A.; Senkus, E.; Xu, B.; Masuda, N.; Delaloge, S.; Li, W.; Armstrong, A.; et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann. Oncol.* 2019, 30, 558–566.
100. Diéras, V.; Han, H.S.; Kaufman, B.; Wildiers, H.; Friedlander, M.; Ayoub, J.P.; Puhalla, S.L.; Bondarenko, I.; Campone, M.; Jakobsen, E.H.; et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2020, 21, 1269–1282.
101. Hussain, M.; Mateo, J.; Fizazi, K.; Saad, F.; Shore, N.; Sandhu, S.; Chi, K.N.; Sartor, O.; Agarwal, N.; Olmos, D.; et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. *N. Engl. J. Med.* 2020, 383, 2345–2357.
102. Abida, W.; Patnaik, A.; Campbell, D.; Shapiro, J.; Bryce, A.H.; McDermott, R.; Sautois, B.; Vogelzang, N.J.; Bambury, R.M.; Voog, E.; et al. Rucaparib in Men with Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. *J. Clin. Oncol.* 2020, 38, 3763–3772.
103. ClinicalTrials.gov. A Study of Rucaparib versus Physician's Choice of Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer and Homologous Recombination Gene Deficiency. Available online: <https://clinicaltrials.gov/ct2/show/NCT02975934> (accessed on 6 June 2021).
104. Smith, M.R.; Sandhu, S.K.; Kelly, W.K.; Scher, H.I.; Efsthathiou, E.; Lara, P.; Yu, E.Y.; George, D.J.; Chi, K.N.; Summa, J.; et al. Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): Preliminary results of GALAHAD. *J. Clin. Oncol.* 2019, 37, 202.
105. De Bono, J.S.; Mehra, N.; Higano, C.S.; Saad, F.; Buttiglieri, C.; van Oort, I.M.; Mata, M.; Chen, H.-C.; Healy, C.G.; Czibere, A.; et al. TALAPRO-1: Phase II study of talazoparib (TALA) in patients (pts) with DNA damage repair alterations (DDRM) and metastatic castration-resistant prostate cancer (mCRPC). *J. Clin. Oncol.* 2021, 39, 93.

106. Asim, M.; Tarish, F.; Zecchini, H.I.; Sanjiv, K.; Gelali, E.; Massie, C.E.; Baridi, A.; Warren, A.Y.; Zhao, W.; Ogris, C.; et al. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. *Nat. Commun.* 2017, 8, 374.
107. Li, L.; Karanika, S.; Yang, G.; Wang, J.; Park, S.; Broom, B.M.; Manyam, G.C.; Wu, W.; Luo, Y.; Basourakos, S.; et al. Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. *Sci. Signal.* 2017, 10, eaam7479.
108. Shen, J.; Zhao, W.; Ju, Z.; Wang, L.; Peng, Y.; Labrie, M.; Yap, T.A.; Mills, G.B.; Peng, G. PARPI triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCANess. *Cancer Res.* 2019, 79, 311–319.
109. Lloyd, R.L.; Wijnhoven, P.W.G.; Ramos-Montoya, A.; Wilson, Z.; Illuzzi, G.; Falenta, K.; Jones, G.N.; James, N.; Chabbert, C.D.; Stott, J.; et al. Combined PARP and ATR inhibition potentiates genome instability and cell death in ATM-deficient cancer cells. *Oncogene* 2020, 39, 4869–4883.
110. ClinicalTrials.gov. Study on Olaparib plus Abiraterone as First-Line Therapy in Men with Metastatic Castration-Resistant Prostate Cancer. Available online: <https://clinicaltrials.gov/ct2/show/NCT03732820> (accessed on 27 June 2021).
111. ClinicalTrials.gov. A Study of Niraparib in Combination with Abiraterone Acetate and Prednisone versus Abiraterone Acetate and Prednisone for Treatment of Participants with Metastatic Prostate Cancer. Available online: <https://clinicaltrials.gov/ct2/show/NCT03748641> (accessed on 27 June 2021).
112. ClinicalTrials.gov. Talazoparib + Enzalutamide vs. Enzalutamide Monotherapy in mCRPC. Available online: <https://clinicaltrials.gov/ct2/show/NCT03395197> (accessed on 27 June 2021).
113. Zimmer, A.S.; Nichols, E.; Cimino-Mathews, A.; Peer, C.; Cao, L.; Lee, M.J.; Kohn, E.C.; Annunziata, C.M.; Lipkowitz, S.; Trepel, J.B.; et al. A phase I study of the PD-L1 inhibitor, durvalumab, in combination with a PARP inhibitor, olaparib, and a VEGFR1-3 inhibitor, cediranib, in recurrent women's cancers with biomarker analyses. *J. Immunother Cancer* 2019, 7, 197.
114. ClinicalTrials.gov. Study of Olaparib Maintenance Following Cabazitaxel-Carbo in Men with AVPC. Available online: <https://clinicaltrials.gov/ct2/show/NCT03263650> (accessed on 27 June 2021).
115. ClinicalTrials.gov. Olaparib and Radium Ra 223 Dichloride in Treating Men with Metastatic Castration-Resistant Prostate Cancer that Has Spread to the Bone. Available online: <https://clinicaltrials.gov/ct2/show/NCT03317392> (accessed on 27 June 2021).
116. ClinicalTrials.gov. Targeting Resistant Prostate Cancer with ATR and PARP Inhibition (TRAP Trial). Available online: <https://clinicaltrials.gov/ct2/show/NCT03787680> (accessed on 27 June 2021).
117. ClinicalTrials.gov. Testosterone and Olaparib in Treating Patients with Castration-Resistant Prostate Cancer. Available online: <https://clinicaltrials.gov/ct2/show/NCT03516812> (accessed on 27 June 2021).
118. Mazzucchelli, S.; Piccotti, F.; Allevi, R.; Truffi, M.; Sorrentino, L.; Russo, L.; Agozzino, M.; Signati, L.; Bonizzi, A.; Villani, L.; et al. Establishment and Morphological Characterization of Patient-Derived Organoids from Breast Cancer. *Biol. Proced Online* 2019, 21, 12.
119. Sachs, N.; de Ligt, J.; Kopper, O.; Gogola, E.; Bounova, G.; Weeber, F.; Balgobind, A.V.; Wind, K.; Gracanin, A.; Begthel, H.; et al. A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity. *Cell* 2018, 172, 373–386.e10.
120. Park, H.S.; Lee, J.D.; Kim, J.Y.; Park, S.; Kim, J.H.; Han, H.J.; Choi, Y.A.; Choi, A.R.; Sohn, J.H.; Kim, S. II Establishment of chemosensitivity tests in triple-negative and BRCA-mutated breast cancer patient-derived xenograft models. *PLoS ONE* 2019, 14, e00225082.