Review

Analysis of the Clinical Advancements for BRCA-Related Malignancies Highlights the Lack of Treatment Evidence for BRCA-Positive Male Breast Cancer

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Simple Summary: 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. Here, we review the lack of treatment evidence for BRCA-related MBC. We also highlight the impact of poly(ADP-ribose) polymerase (PARP) inhibitors which are used in the clinical management of BRCA-related female breast cancer and prostate cancer. In turn, we demonstrate the requirement for national and global collaborative efforts to address the striking unmet need for dedicated BRCA-related MBC research, including studies to better understand disease trajectory and improve clinical outcomes.

Abstract: Male breast cancer (MBC) is a rare disease that accounts for less than 1% of all breast cancers and male malignancies. Despite recognised clinico-pathological and molecular differences to female breast cancer (FBC), the clinical management of MBC follows established FBC treatment strategies. Loss of function mutations in the DNA damage response genes BRCA1 and BRCA2, have been strongly implicated in the pathogenesis of MBC. While there have been extensive clinical advancements in other BRCA-related malignancies, including FBC, improvements in MBC remain stagnant. Here we present a review that highlights the lack of treatment evidence for BRCA-related MBC and the required national and global collaborative effort to address this unmet need. In doing so, we summarise the transformative clinical advancements with poly(ADP-ribose) polymerase (PARP) inhibitors in other BRCA-related cancers namely, FBC and prostate cancer.

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 [1–4]. 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 our increasing knowledge of the differing clinical demographics [7], molecular landscapes [8–11], 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, \textit{BRCA1} and \textit{BRCA2}, have been heavily implicated in the pathogenesis of MBC. Pathogenic \textit{BRCA} alterations are detected in around 16% of all MBC cases, with 12.5% found in \textit{BRCA2} \[18\]. Several other genes have been reported to confer a moderate risk of MBC at lower prevalence rates including \textit{CHEK2} (4–8%), \textit{PALB2} (1–2%), and \textit{PTEN} \[19–26\]. 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 \[27–30\]. Moreover, these susceptibility variants may produce a combinatorial effect on MBC risk in \textit{BRCA}-mutation carriers through a polygenic inheritance model \[31\].

\textit{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 \textit{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 \textit{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 \textit{BRCA} biomarker-led improvements that influence clinical management, highlighting the lack and need of increased translational research within this area.

Targeted approaches of \textit{BRCA}-mutated neoplasms utilise the homologous recombination repair (HRR) deficiency, and thus the impaired ability to repair double stranded DNA breaks. This confers a greater susceptibility to platinum-based chemotherapy and is the standard treatment for \textit{BRCA}-positive patients in FBC \[35,36\]. Beyond \textit{BRCA}, an additional important DDR pathway involves the poly(ADP-ribose) polymerase (PARP) enzyme-mediated repair of single-stranded DNA breaks \[37–39\]. Inhibition of PARP function in \textit{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 gives credence to their potential therapeutic efficacy in \textit{BRCA}-related MBC.

Despite extensive advancements over the last two decades in the management of FBC patients, and other \textit{BRCA}-related cancers, evidence-based MBC specific guidance is lacking, especially for those with targetable \textit{BRCA} mutations. One bottle neck 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.

Here we present a review of the lack of evidence available for the treatment of \textit{BRCA}-mutated MBC patients and highlight the substantial gaps in knowledge that are required to better evaluate and understand this unique patient cohort to help inform and improve the current standard of care.

2. The Genetic Landscape of MBC

Knowledge of MBC germline mutations have important clinical implications, including the discovery of novel therapeutic targets and specific biomarkers. An overview of high (\textit{BRCA1} and \textit{BRCA2}), moderate (\textit{PALB2, EGFR, CCND1}, and \textit{EMSY}) and low-penetrance (\textit{ESR1, TOX3}, and \textit{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 [42–44]. 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 [48–52]. 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 [8,10,21,55–60]. 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 OlympiaAD (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 narrative 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 ≤ 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 (Table 1) and case reports (Table 2) [18,48–50,52,53,72–94].

| Author (Year)         | Study Population | No. of Patients | Study Objective                                                        |
|-----------------------|------------------|-----------------|-----------------------------------------------------------------------|
| Tirkkonen et al. (1999) [94] | MBC patients BRCA2-mutated | 25 | 5 | Somatic genetic alterations in BRCA2-associated and sporadic MBC |
| Basham et al. (2002) [75] | MBC patients BRCA1-mutated BRCA2-mutated | 94 | 0 | BRCA1/2-mutation status and risk of breast cancer in female relatives |
| Ottini et al. (2003) [48] | MBC patients BRCA1-mutated BRCA2-mutated | 25 | 1 | The Characterisation of BRCA1 and BRCA2 MBC |
| Kwiatkowska et al. (2003) [76] | MBC patients BRCA2-mutated | 43 | 12 | Investigation of the prognostic value of BRCA2 status in MBC |
| Palli et al. (2007) [93] | MBC patients | 99 | | The association between the BRCA2 N732H variant and MBC risk |
| Ottini et al. (2009) [49] | MBC patients BRCA1-mutated BRCA2-mutated | 108 | 2 | Characterisation the clinic-pathological features of BRCA1/2-positive MBC |
| Ding et al. (2011) [78] | MBC patients BRCA2-mutated | 115 | 18 | To determine the frequency of pathogenic mutations in BRCA2 and PALB2 in MBC cases and to investigate the correlations between mutation status and cancer phenotype |
| Ottini et al. (2012) [50] | MBC patients BRCA1-mutated BRCA2-mutated | 382 | 4 | Investigation of the clinical–pathologic features of MBC in association with BRCA mutations |
| de Juan et al. (2015) [92] | MBC patients BRCA1-mutated BRCA2-mutated | 312 | 20 | BRCA1/2 mutations in males with familial breast and ovarian cancer syndrome |
Table 1. Cont.

| Author (Year) | Study Population | No. of Patients | Study Objective |
|---------------|------------------|-----------------|----------------|
| Gargiulo et al. (2016) [53] | MBC patients <br> BRCA1-mutated <br> BRCA2-mutated | 47 <br> 1 <br> 5 | Characterisation of MBC, including BRCA1/2-mutated patients, and the impact on long-term survival |
| Silvestri et al. (2016) [74] | MBC patients <br> BRCA1-mutated <br> BRCA2-mutated | 366 * <br> 40 <br> 326 | To determine if BRCA1/2 mutation carriers display specific pathologic features and if these differ from FBCs |
| Deb et al. (2017) [90] | MBC patients <br> BRCA1-mutated <br> BRCA2-mutated | 60 <br> 3 <br> 25 | Investigation of a panel of commonly methylated breast cancer genes in familial MBCs |
| Rizzolo et al. (2018) [77] | MBC patients <br> BRCA1-mutated <br> BRCA2-mutated | 69 <br> 2 <br> 8 | Gene-specific methylation profiles in BRCA-mutation positive and negative MBC |
| Ibrahim et al. (2018) [18] | MBC patients <br> BRCA1-mutated <br> BRCA2-mutated | 102 <br> 0 <br> 9 | Evaluation of clinical characteristics, pathology findings, treatment selection and survival in BRCA-positive males |
| André et al. (2019) [52] | MBC patients <br> BRCA1-mutated <br> BRCA2-mutated | 196 <br> 0 <br> 13 | Specific biological characteristics and survival in MBC |
| Vietri et al. (2020) [72] | MBC patients <br> BRCA1-mutated <br> BRCA2-mutated | 28 <br> 2 <br> 8 | Characterisation of BRCA1/BRCA2 and PALB2 mutations in MBC patients |

* Original cohort of 419 was restricted to invasive male breast cancer (n = 366). MBC = male breast cancer.

Table 2. Summary of case studies involving BRCA-positive MBC patients.

| Author (Year) | Study Population | No. of Patients | Study Objective |
|---------------|------------------|-----------------|----------------|
| Savelyeva et al. (1998) [84] | BRCA2-mutated MBC | 3 | Case report describing three brothers with BRCA2 mutation, two of which developed infiltrating ductal breast cancer |
| Scheidbach et al. (2000) [87] | BRCA2-mutated MBC | 1 | Describe a case of BRCA2-mutation positive MBC |
| Kwiatkowska et al. (2002) [89] | BRCA2-mutated MBC | 2 | Novel BRCA2 mutation (frameshift mutation 6621del4 in exon 11) in two male breast cancer cases (father and son) in a Polish family. |
| Brenner et al. (2004) [86] | BRCA2-mutated MBC | 1 | Highlight a case of BRCA2-mutation positive MBC and the implications for screening |
| Karamanakos et al. (2004) [83] | BRCA1-mutated MBC | 1 | A case of male breast adenocarcinoma in a prostate cancer patient following prolonged anti-androgen monotherapy |
| Azzouzi et al. (2007) [88] | BRCA2-mutated MBC | 3 | To highlight three BRCA2-positive MBC patients who were identified following positive prostate cancer screening |
| Panchal et al. (2009) [85] | BRCA2-mutated MBC | 1 | A case of BRCA2-mutation positive MBC case with a history of prostate cancer |
| Guoaua et al. (2014) [82] | BRCA2-mutated MBC | 1 | An account of a novel BRCA2c.6428C>A p.Ser2143Ter nonsense mutation in a man with familial breast cancer |
| Benjamin & Riker (2015) [73] | BRCA1/HER2-positive MBC | 1 | To describe a case of a BRCA1/HER2 positive MBC |
Table 2. Cont.

| Author (Year)          | Study Population | No. of Patients | Study Objective                                                                                                                                 |
|------------------------|------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Singer et al. (2015)   | BRCA2-mutated MBC| 1               | Highlight the risk of BRCA2 on multiple cancer risk through a case of prostate and MBC.                                                        |
| Saha et al. (2017)     | BRCA1-mutated MBC| 1               | Describe the treatment of MBC by dual HER2 blockade and response prediction using novel optical tomography imaging.                             |
| Cheng et al. (2019)    | BRCA2-mutated MBC| 1               | To describe an account of metachronous MBC that progressed following radio and chemotherapy which responded to palbociclib, fulvestrant and leuprolide. |
| Huszno et al. (2019)   | BRCA2-mutated MBC| 1               | Clinicopathological analysis of BRCA2 gene variant, c. 2808_2811delACAA (p. Ala938Profs) in MBC.                                             |

The majority of BRCA-focused retrospective studies available have provided clinicopathological characterisation of the differing phenotypic features of BRCA- positive MBC compared to FBC, and on the whole have described their aggressive nature, differing hormone positivity (ER/PR), familial risk, and associated poorer prognosis [18,48–50,52,53,72–94]. This is especially true for BRCA2-positive MBC which has been shown to pose a greater risk of earlier aggressive disease onset (age < 60), with associated hypermethylation patterns (e.g., RASSF1) that may serve as prognostic epigenetic markers [49,76,78,90,93]. To date, the largest of these retrospective studies utilised data on 419 MBCs with BRCA mutations from an international consortium (Consortium of Investigators of Modifiers) and demonstrated that the majority of MBC cases (89.5%) were BRCA2 mutation carriers and of high grade [74]. In addition, a study assessing BRCA-related cancers in males showed promising results using platinum-based therapy in BRCA-related MBC with more than two thirds of patients (n = 7) still alive with no disease recurrence after a median follow up of 5.6 years [18]. Nonetheless, these studies are limited by their retrospective nature and, on the most part, low cohort sizes.

In regard to case reports, a number of BRCA-positive MBC cases have been reported in the literature (n = 13) [73,79–89,91] (Table 2). The majority of these studies (10 of 13) describe accounts of BRCA2-mutated MBC cases and highlight the significant familial risk and increased lifetime likelihood of developing MBC or prostate cancer in patients with BRCA2 alterations [79,80,82,84–87,89,91]. For example, a male with prior prostate cancer, who possessed a germline BRCA2 mutation and a significant family history for breast cancer, was subsequently diagnosed with MBC and underwent curative mastectomy [85]. A further case also reported an account of a BRCA2-mutated MBC that received a therapeutic regimen of cyclophosphamide, methotrexate, and 5-fluorouracil, and additional tamoxifen treatment [86]. The patient then went on to develop a new primary cancer of a different hormonal profile which was treated with modified mastectomy [86]. Other studies of particular note include a BRCA2-positive patient with metachronous breast and primary lung cancer [79]. Despite a good response from the lung malignancy, the breast cancer was refractive to radiation and platinum-based chemotherapy, and anastrozole [79]. Interestingly, this case was successfully treated with the cyclin dependant kinase inhibitor, Palbociclib, and anti-androgen therapy with a response duration of nearly two years [79]. Palbociclib, and inhibitors of the same class, have shown significant improved outcomes in FBC [95,96]; however, these are yet to be explored in MBC.

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 [97], 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 [98]. An additional case involving a transgender woman with a BRCA1-alteration went on to develop breast cancer whilst receiving androgen blocking therapy [99]. The patient was subsequently treated with neoadjuvant chemotherapy, mastectomy and adjuvant radiotherapy [99]. With several accounts of breast cancer now noted in transgender women who received feminising hormonal therapy [100], a better understanding of the potential risks of treatment is vital.

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

As described above, large randomised clinical trials have led to several advancements in other BRCA-related malignancies such as FBC and prostate cancer which are summarised below. These have resulted in the introduction of PARPi into clinical practice and offer a less toxic option than conventional chemotherapeutic agents with significant reductions in quality-of-life deterioration [101].

6.1. Female Breast Cancer (FBC)

In FBC, clinical trials investigating PARPi have led to the licencing of both Olaparib and Talazoparib by the US Food and Drug Administration (FDA) and the European Medicine’s Agency (EMA), respectively, for germline BRCA (gBRCA)-positive advanced breast cancer (Table 3) [38,40,102]

Table 3. Summary of clinical trials involving PARPi and BRCA-positive FBC and MBC patients.

| Phase III Trial (Year) | Trial Arms | Study Population | No. of Patients | Study Result |
|-----------------------|------------|------------------|-----------------|-------------|
|                       |            |                  | PARPi (F/M)     | PFS HR (95%CI) | mPFS (Months) | ORR (%)       |
| **Advanced breast cancer** |            |                  |                 |              |              |               |
| OlympiAD (2017) [38]  | Olaparib vs. standard chemotherapy | Patients with <2 lines of previous chemotherapy | 205 (200/5) | 0.58 (0.43–0.80); p < 0.001 | 7.0 vs. 4.2 | 59.9 vs. 28.8 |
| EMBRACA (2018) [40]   | Talazoparib vs. standard single agent of a clinician’s choice * | gBRCA-mutated | 287 (283/4) | 0.54 (0.41–0.71); p < 0.001 | 8.6 vs. 5.6 | 62.2 vs. 27.2 |
| BROCADE (2020) [103]  | Veliparib with carboplatin/paclitaxel vs. carboplatin/paclitaxel alone | gBRCA-mutated | 337 (333/4) | 0.71 (0.57–0.88); p = 0.0016 | 14.5 vs. 12.6 |
| **Early breast cancer** |            |                  |                 |              |              |               |
| OlympiA (2021) [67]   | Olaparib vs. placebo | gBRCA-mutated with local treatment and neoadjuvant or adjuvant chemotherapy | 921 (919/2) | 0.57 (0.39–0.83); p < 0.001 | 0.58 (0.41–0.82); p < 0.001 |

* Capecitabine, eribulin, vinorelbine, or gemcitabine. Trial results that led to approval are in Bold. CI, Confidence Interval; DD, Distant disease; HR, Hazard Ratio; ID, Invasive disease; mPFS, median Progression Free Survival; PARPi, Poly(ADP-Ribose) Polymerase inhibitor; PFS, Progression Free Survival.

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 study 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); \( p < 0.001 \) (Table 3). 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 [102]. Irrespective of the very small sample size of male participants within this study (Table 3), Olaparib was subsequently approved for both advanced male and FBC by the FDA and EMA, as discussed in Section 3.

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 study included \( gBRCA \)-positive early breast cancer patients (\( n = 1836 \)) who had completed local treatment and neoadjuvant or adjuvant chemotherapy (Table 3). 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] (Table 3). 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] (Table 3). Furthermore, no significant adverse events were noted and all safety data were concordant with known side effects of Olaparib [67]. Pivotal, the results of this study 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, Talazoparid, 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); \( p < 0.001 \)) (Table 3) and superior ORR (62.2% versus 27.2% (95% CI 2.9–8.8); \( p < 0.001 \)) [40]. Consequently, Talazoparid was also approved for MBC despite the study’s involving only four MBC patients (Table 3).

PARPi have also been studied for their efficacy in combination with standard chemotherapy agents. For example, in the phase III randomised BROCADE (NCT02163694) [103] clinical study, carboplatin/paclitaxel with or without Celiparib was evaluated as a second line treatment in \( gBRCA \) advanced FBC patients [103]. Results showed a greater PFS (14.5 vs. 12.6 months; HR 0.71 (95% CI 0.57–0.88); \( p = 0.002 \)) (Table 3) in patients treated with Veliparib; however, there was no significant difference in OS between the two trial arms (33.5 versus 28.2 months) [103]. Moreover, the addition of Veliparib to carboplatin and paclitaxel was well tolerated, with low discontinuation rates (<10%) [103].

### 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] (Table 4).
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) (Table 4) [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, \(p = 0.02\)) (Table 4) [104].

**Table 4.** Summary of clinical trials involving PARPi and BRCA-positive mCRPC patients.

| Trial (Year) | Phase | Trial Arms | Study Population | No. of Patients | Study Result |
|-------------|-------|------------|------------------|-----------------|-------------|
| PROfound (2020) [41] | III | Olaparib versus standard anti-androgen therapy | Cohort A (BRCA1, BRCA2, or ATM mutation) | 162 | rPFS 7.4 m vs. 3.6 m; HR 0.34 (95% CI 0.25–0.47); \(p < 0.001\) |
| | | | Cohort A+ B (Other DDR alterations *) | 256 | rPFS 5.8 m vs. 3.5 m; HR 0.49 (0.38–0.63); \(p < 0.001\) |
| TRITON2 (2020) [105] | II | Rucaparib | gBRCA-mutated mCRPC patients progressing after previous androgen hormonal therapy and a taxane chemotherapy | 177 | rORR \(^a\) BRCA-mutated 43.5% (95% CI 31.0–56.7) and independent investigator ORR 50.8% (95% CI 38.1–63.4) rORR \(^a\) for other HRD-mutation 28.6%; CHEK2-mutation 11.1%; ATM-mutation 10.5%; CDK2-mutation 0% |
| GALAHAD (2019) [106] | II | Niraparib | mCRPC and biallelic DRD mutated mCRPC patients with disease progression on taxane and androgen receptor-targeted therapy. | 81 | rORR \(^a\) BRCA1/2-WT HRD-mutation 9% (95% CI 1.1–29.2); rPFS 5.3 (95% CI 1.9–5.7) |
| TALAPRO-1 (2020) [107] | II | Talazoparib | BRCA- mutated mCRPC patients with disease progression on taxane and androgen receptor-targeted therapy | 46 | ORR 43.9%; rPFS 9.3 (95% CI 8.1–13.7) |
| | | | BRCA-WT mCRPC patients | 40 | ORR PALB2-mutated 33%; rPFS 7.4 (95% CI 2.7–14.3); ATM-mutated 11.8%; rPFS 5.5 95% CI (1.7–8.2) |

* Genes included BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L. * Determined by Response Evaluation Criteria in Solid Tumors. Trial results that led to approval are in **Bold. CI, Confidence Interval; DDR, DNA Damage Response; HR, Hazard Ratio; HRD, Homologous Repair Deficiency; ORR, Objective Response Rate; PARPi, Poly(ADP-Ribose) Polymerase inhibitor; rPFS, radiological Progression Free Survival; rORR, radiological Objective Response Rate.

Based on the TRITON2 (NCT02952534) [105] trial, the PARPi, Rucaparib, gained accelerated FDA approval for gBRCA mCRPC patients progressing after prior androgen hormonal therapy and a taxane chemotherapy [105]. 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) (Table 4) [105]. Full FDA approval will be dependent on the TRITON3 (NCT02975934) [108] 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 [108].
Niraparib and Talazoparib PARPi are also being investigated in BRCA-related mCRPC. Interim results of the active phase II GALAHAD (NCT02854436) [106] 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 (Table 4) [106]. In regard to Talazoparib, the phase II TALAPRO-1 (NCT03148795) [107] study showed that patients with BRCA-positive mCRPC had superior ORR to the PARPi than other DDR mutations (Table 4) [107]. Both Niraparib and Talazoparib are currently being evaluated in phase III trials for mCRPC.

With promising preclinical support [109–112], the efficacy of PARPi in prostate cancer is currently being investigated in combination with other agents such as anti-androgens [113–115], immunotherapeutics [116], chemotherapy [117], radiotherapy [118], and ATR (ataxia-telangiectasia and Rad3-related) protein inhibitors [119]. Studies involving DDR alterations within their inclusion or primary/secondary outcome measures are outlined in Table 5 and will be described briefly. A total of three trials are currently underway for the evaluation of anti-androgen compounds and PARPi. The phase III PROpel (NCT03732820) [113] trial is exploring Olaparib in combination with abiraterone as first-line therapy in patients with mCRPC [113]. A further phase III study, MAGNITUDE (NCT03748641) [114] is being conducted in both mCRPC patients with and without HRR alterations and the efficacy of niraparib and abiraterone [114]. The benefit of combining Talazoparib and enzalutamide in mCRPC is also being studied in the phase III TALAPRO-2 (NCT03395197) trial [115]. 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) [116]. 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) [119]. Other DNA-inhibition strategies that are also being studied include high dose testosterone (NCT03516812) [120]. 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.

Table 5. Summary of clinical trials involving a PARPi in combination with an anti-cancer agent in BRCA-positive mCRPC patients.

| Trial                  | Phase | PARPi       | Combined Agent          |
|------------------------|-------|-------------|-------------------------|
| Anti-androgen therapy  | III   | Olaparib    | Abiraterone             |
| PROpel [113]           | III   | Niraparib   | Abiraterone             |
| MAGNITUDE [114]        | III   | Talazoparib | Enzalutamide            |
| TALAPRO-2 [115]        | III   | Olaparib    |                         |
| Immunotherapy          | I/II  | Olaparib    | Durvalumab              |
| NCT02484404 [116]      |       |             |                         |
| ATRi                   | II    | Olaparib    | Ceralasertib            |
| High dose testosterone | II    | Olaparib    | Testosterone enanthate or cyionate |
| NCT03516812 [120]      |       |             |                         |

PARPi, Poly(ADP-Ribose) Polymerase inhibitor.

7. Future Directions in BRCA-Related MBC

As highlighted in this review, 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. Impressiv
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 [121,122], 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 [123].

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.

8. Conclusions

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.

Due to the rarity of this cancer, dedicated research can only be successful if carried out on a national basis leading into a worldwide collaborative network with established BRCA-positive registries in combination with tissue collection for translational research. More imminently, exploration of in vitro and in vivo approaches, such as PDTOs and PDX models, may be invaluable in aiding BRCA-positive MBC disease characterisation.

Author Contributions: Study Concepts and Design: D.P.M., V.S. and B.E.; Supervision, V.S. and B.E.; Writing (original draft), D.P.M.; Manuscript Editing, D.P.M., V.S., B.E., G.U., T.M., S.C. and Z.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by The University of Aberdeen Development Trust, Breast Cancer UK and NHS Grampian Breast Cancer Endowment Fund. S.C. is in receipt of an Elphinstone Scholarship.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the writing or interpretation of this work.
24. Erkko, 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. [CrossRef] [PubMed]

25. Casadei, S.; Norquist, B.M.; Walsh, T.; Stray, S.; Mandelli, J.B.; Lee, M.K.; Stamatoypanopoulos, 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. [CrossRef]

26. Pritzflaff, 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-genome panel testing cohort: Insights and unexpected results. *Breast Cancer Res. Treat.* 2017, 161, 579–586. [CrossRef]

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. [CrossRef]

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. [CrossRef]

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, 9p13.3, 11q13.3, and 14q24.1: Results from a multicenter study in Italy. *Eur. J. Cancer* 2015, 51, 2289–2295. [CrossRef]

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. Inhl. 2021*, 113, 453–461. [CrossRef]

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. [CrossRef]

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. [CrossRef]

33. Easton, D.F. How many more breast cancer predisposition genes are there? *Breast Cancer Res. Rev.* 1999, 1, 14–17. [CrossRef]

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. [CrossRef]

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. [CrossRef]

36. Von Minckwitz, G.; Schneweiss, A.; Loibl, S.; Salat, C.; Denkert, C.; Rezai, M.; Blohmer, J.U.; Jackisch, C.; Paecke, 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. [CrossRef]

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. [CrossRef] [PubMed]

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. [CrossRef] [PubMed]

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 BRCA1-positive breast cancer. *Nature* 2005, 434, 917–921. [CrossRef] [PubMed]

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 BRCA2 Mutation. *N. Engl. J. Med.* 2018, 379, 753–763. [CrossRef] [PubMed]

41. de Bono, J.; Mateo, J.; Fizzi, 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. [CrossRef] [PubMed]

42. Kuchenbaecker, K.B.; Hopper, J.L.; Barnes, D.R.; Phillips, K.A.; Mook, 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 using polygenic risk scores. *J. Clin. Oncol.* 2017, 35, 2240–2250. [CrossRef] [PubMed]

43. Chen, S.; Parmigiani, G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J. Clin. Oncol.* 2007, 25, 1329–1333. [CrossRef] [PubMed]

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. [CrossRef]

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. [CrossRef] [PubMed]

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. [CrossRef] [PubMed]
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. [CrossRef]

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. [CrossRef]

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. [CrossRef]

52. André, S.; Perea, T.; Silva, F.; Machado, P.; Vaz, F.; Aparicio, 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. [CrossRef]

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. [CrossRef] [PubMed]

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. [CrossRef] [PubMed]

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. [CrossRef] [PubMed]

56. Szwiec, M.; Tomiczek-Sziewc, J.; Kluzniak, W.; Wokolorzcyk, D.; Osoviecka, K.; Sibilski, R.; Wachowiak, M.; Gronwald, J.; Gronwald, H.; Lubirsiki, J.; et al. Genetic predisposition to male breast cancer in Poland. *BMC Cancer* 2021, 21, 1–8. [CrossRef] [PubMed]

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. [CrossRef]

58. Rizzolo, P.; Navazio, A.S.; Silvestri, V.; Valentini, V.; Zelli, V.; Zanna, I.; Masala, G.; Bianchi, S.; Scarnelli, F.; et al. Somatic alterations of targetable oncogenes are frequently observed in BRCA1/2 mutation negative male breast cancers. *Oncotarget* 2016, 7, 74097. [CrossRef]

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. [CrossRef]

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.; Buenger, 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. [CrossRef]

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 Cancer Res.* 2018, 40, 85–91. [CrossRef]

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. [CrossRef]

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. [CrossRef] [PubMed]

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. [CrossRef] [PubMed]

65. Khan, M.H.; Allerton, R.; Pettit, L. Hormone therapy for breast cancer in men. *Clin. Breast Cancer* 2015, 15, 245–250. [CrossRef] [PubMed]

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. [CrossRef] [PubMed]

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. [CrossRef]

68. NICE. Olaparib for Adjuvant Treatment of High-Risk HER2-Negative, BRCA-Positive Early Breast Cancer after Chemotherapy [ID3893]. 2022. Available online: https://www.nice.org.uk/guidance/indevelopment/gid-ta10903 (accessed on 18 May 2022).

69. Reiniisch, 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. [CrossRef]

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.; Palaciová, 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. [CrossRef]

72. Vietri, M.T.; Caliendo, G.; D’Elia, G.; Resse, M.; Casamassimi, A.; Minucci, P.B.; Cioffi, M.; Molarini, A.M. BRCA and PALB2 mutations in a cohort of male breast cancer with one bilateral case. *Eur. J. Med. Genet.* 2020, 63, 105883. [CrossRef]

73. Benjamin, M.A.; Riker, A.I. A case of male breast cancer with a BRCA gene mutation. *Ochsner. J.* 2015, 15, 448–451. [CrossRef]

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. [CrossRef]

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. [CrossRef] [PubMed]

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. [PubMed]

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. [CrossRef] [PubMed]

78. Ding, Y.C.; Steele, L.; Kuan, C.J.; Greilac, S.; Neuhausen, S.L. Mutations in *BRCA* profiles in *BRCA* mutation-negative male breast cancers. *Ann. Oncol.* 2018, 29, 1107–1113. [CrossRef] [PubMed]

79. Cheng, Y.; Li, N.; Eapen, A.; Parajuli, R.; Mehta, R. Somatic alterations in *BRCA* between the *BRCA* and *BRCA* carriers. *Int. J. Urol.* 2017, 24, 1077–1081. [CrossRef]

80. 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 a Moroccan man with familial breast cancer. *Afr. Health Sci.* 2014, 14, 468. [CrossRef]

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 Topography Imaging: A Case Report. *Carcinomas* 2017, 9, e1481. [CrossRef]

82. Guassa, S.; 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.* 2019, 88, 187–189. [CrossRef]

83. Karamanakos, P.; Mitsiades, C.; 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. [PubMed]

84. 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. [CrossRef] [PubMed]

85. 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. [CrossRef]

86. Azzouzi, A.R.; Stoppa-Lyonnet, D.; Roupret, M.; Larre, S.; Mangin, P.; Cussenot, O. *BRCA* and *BRCA* carriers with a history of prostate cancer. *Nat. Rev. Clin. Oncol.* 2009, 6, 604–607. [CrossRef] [PubMed]

87. Chung, Y.; Li, N.; Aepen, A.; Parajuli, R.; Mehta, R. Somatic *BRCA* 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. [CrossRef] [PubMed]

88. 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. [CrossRef] [PubMed]

89. Kwiatkowska, E.; Brozek, I.; Izycka-Swieszewska, E.; Limon, J.; Mackiewicz, A. Novel nonsense mutation of BRCA2 gene in a Moroccan man with familial breast cancer. *Afr. Health Sci.* 2014, 14, 468. [CrossRef]

90. 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.

91. Panchal, S.; Shachar, O.; O’Malley, F.; Crystal, P.; Escallon, J.; Crook, J.; Bane, A.; Bordeleau, L. Breast cancer in a *BRCA2* mutation carrier—Clinicopathological analysis based on a case report. *J. Med. Genet.* 2007, 44, 445–446. [CrossRef]

92. Karamanakos, P.; Mitsiades, C.S.; Lembessis, P.; Kontos, M.; Trafalis, D.; Koutsilieris, M. Male Breast Adenocarcinoma in a Breast Cancer Patient Following Prolonged Anti-androgen Monotherapy. *Anticancer Res.* 2004, 24, 1077–1081. [PubMed]

93. Karamanakos, P.; Mitsiades, C.S.; Lembessis, P.; Kontos, M.; Trafalis, D.; Koutsilieris, M. Male Breast Adenocarcinoma in a Breast Cancer Patient Following Prolonged Anti-androgen Monotherapy. *Anticancer Res.* 2004, 24, 1077–1081. [PubMed]

94. Palibessis, P.; Kontos, M.; Trafalis, D.; Koutsilieris, M. Male Breast Adenocarcinoma in a Breast Cancer Patient Following Prolonged Anti-androgen Monotherapy. *Anticancer Res.* 2004, 24, 1077–1081. [PubMed]

95. Palibessis, P.; Kontos, M.; Trafalis, D.; Koutsilieris, M. Male Breast Adenocarcinoma in a Breast Cancer Patient Following Prolonged Anti-androgen Monotherapy. *Anticancer Res.* 2004, 24, 1077–1081. [PubMed]
97. 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, i1652. [CrossRef] [PubMed]

98. 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. [CrossRef] [PubMed]

99. Colebunders, B.; T’Sjoen, G.; Weyers, S.; Monstrely, S. Hormonal and surgical treatment in trans-women with BRCA1 mutations: A controversial topic. *J. Sex. Med.* 2014, 11, 2496–2499. [CrossRef] [PubMed]

100. 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. [CrossRef] [PubMed]

101. Poggio, F.; Bruzzone, M.; Ceppi, M.; Conte, B.; Martel, S.; Maurer, C.; Tagliamento, M.; Viglietti, G.; Del Mastro, L.; De Azambuja, E.; et al. Single-agent PARP inhibitors for the treatment of patients with BRCA1-mutated HER2-negative metastatic breast cancer: A systematic review and meta-analysis. *ESMO Open* 2018, 3, e000361. [CrossRef]

102. 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 BRCA2 mutation and HER2-negative metastatic breast cancer. *Ann. Oncol.* 2019, 30, 558–566. [CrossRef]

103. 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 BRCA1-mutated advanced breast cancer (BROCADE3): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2020, 21, 1269–1282. [CrossRef]

104. 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. [CrossRef]

105. 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. [CrossRef] [PubMed]

106. Smith, M.R.; Sandhu, S.K.; Kelly, W.K.; Scher, H.I.; Efstratiou, 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. [CrossRef]

107. 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 defects (DRD): Preliminary results of GALAHAD. *J. Clin. Oncol.* 2021, 39, 93. [CrossRef]

108. 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).

109. Asim, M.; Tarish, F.; Zecchini, H.I.; Sanjiv, K.; Gelati, 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. [CrossRef]

110. Li, L.; Karanika, S.; Yang, G.; Wang, J.; Park, S.; Broom, B.M.; Manyam, G.C.; Wu, W.; Luo, Y.; Basourakos, S.; Czibere, A.; et al. Androgen receptor inhibitor-induced “BRCAness” and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. *Sci. Signal.* 2017, 10, eaam7479. [CrossRef]

111. Shen, J.; Zhao, W.; Ju, Z.; Wang, L.; Eng, R.; Labrie, M.; Yap, T.A.; Mills, G.B.; Peng, G. PARP1 triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of NEss. *Cancer Res.* 2019, 79, 311–319. [CrossRef] [PubMed]

112. Lloyd, R.L.; Wijnhoven, P.W.G.; Ramos-Montoya, A.; Wilson, Z.; Iluzzi, 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. [CrossRef]

113. ClinicalTrials.gov. Study of 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).

114. 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).

115. ClinicalTrials.gov. Talazoparib + Enzalutamide vs. Enzalutamide Monotherapy in mCRPC. Available online: https://clinicaltrials.gov/ct2/show/NCT03395197 (accessed on 27 June 2019).

116. 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 VEGFRI-3 inhibitor, cediranib, in recurrent women’s cancers with biomarker analyses. *J. Immunother Cancer* 2019, 7, 197. [CrossRef]

117. 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).

118. 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).
119. 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).

120. 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).

121. Mazzucchelli, S.; Piccotti, F.; Allevi, R.; Truffì, 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. [CrossRef] [PubMed]

122. 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. [CrossRef]

123. 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. [CrossRef] [PubMed]