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REVIEW

Male breast cancer: a disease distinct from female breast cancer

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Abstract

Purpose Male breast cancer (BC) is rare, representing approximately 1% of cancers that occur in men and approximately 1% of all BCs worldwide. Because male BC is rare, not much is known about the disease, and treatment recommendations are typically extrapolated from data available from clinical trials enrolling female BC patients.

Methods We review the epidemiology, risk factors, prognosis, and the varied molecular and clinicopathologic features that characterize male BC. In addition, we summarize the available data for the use of systemic therapy in the treatment of male BC and explore the ongoing development of targeted therapeutic agents for the treatment of this subgroup of BCs.

Results There are important biological differences between male and female BC. Male BC is almost exclusively hormone receptor positive (+), including the androgen receptor (AR), and is associated with an increased prevalence of *BRCA2* germline mutations, especially in men with increased risk for developing high-risk BC. Additional research is warranted to better characterize male BC. To accomplish this, a multi-national consortium approach, such as the International Male Breast Cancer Program, is needed in response to the scarcity of patients. This approach allows the pooling of information from a large number of men with BC and the creation of registries for future therapeutic-focused clinical trials.

Conclusions Given the unique biology of BC in men, promising new therapeutic targets are currently under investigation, including the use of poly-ADP-ribose polymerase inhibitors or AR-targeted agents either as monotherapy or in combination with other agents.

Keywords Male breast cancer · Androgen receptor · Biomarkers · Anti-androgen · Endocrine therapy · Androgen and estrogen biosynthesis inhibition

Introduction

Male breast cancer (BC) is rare, representing approximately 1% of cancers that occur in men and approximately 1% of all BCs worldwide [1–6]. Less than 0.2% of cancer-related deaths in men can be attributed to male BC [7, 8]. Because male BC occurs at a very low incidence, BC literature, research, clinical trials, and development of new treatment options primarily focus on female BC. Although knowledge about female BC can inform male BC diagnosis and treatment, molecular and clinicopathologic features differ between male and female BC. Biologic factors, such as sex differences, hormonal regulation, and response to treatment (both tolerability and activity), must be considered when

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defining this disease in men and deciding upon treatment options [8]. Currently, no standard of care (SOC) exists for male BC, and there is an unmet need for research and therapeutic options for this disease. This review summarizes current knowledge of male BC to date with a discussion of future treatment options for the disease.

Demographics of male breast cancer

Almost 1% of all BCs occur in men. In 2018, about 2550 men will be diagnosed with BC in the US, and male BC will account for 480 deaths. In comparison, it is estimated that there will be approximately 266,120 new cases of female BC and approximately 40,920 deaths due to BC in women [9, 10]. According to Surveillance, Epidemiology, and End Results Program (SEER) data from 2015, the incidence of invasive BC in men is 1.1:100,000 men, whereas it is 126.5:100,000 in women [11]. However, the incidence and prevalence of male BC varies by race and ethnicity, and men in certain select populations such as African Americans have higher rates of male BC in comparison to their Caucasian, Hispanic, or Asian/Pacific Islander counterparts [12]. The median age at initial diagnosis of invasive BC is typically older in men than in women (68 vs. 62 years) [13]. In both men and women, the age-adjusted rate of BC sharply increases by the fifth decade of life. However, the rate plateaus in women by the sixth decade of life but continues to increase in men through the seventh decade.

Disease characteristics of male breast cancer

Initial diagnosis of male BC often occurs at a later stage than in female BC, and male BC often exhibits more advanced disease features, such as a larger tumor size, lymph node involvement, and distant metastases at the time of diagnosis [1, 2, 8, 14–18]. In developed countries, nearly two-thirds of invasive female BCs are localized at the time of diagnosis; in contrast, in men approximately half of the cases are localized and the other half are regional or distant disease [11].

Estimates of in situ carcinoma in men are approximately 10%; the remaining 90% can be attributed to infiltrating ductal carcinoma [1, 2, 4, 8, 19]. Infiltrating lobular carcinoma, medullary lesions, and tubular or neuroendocrine tumors are very rare in men, as is triple-negative BC (TNBC) [1, 2, 4, 19, 20]. Male BCs usually express the estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR); are hormonally responsive; and most commonly present as uni-lateral tumors [5, 17–19, 21–23]. Nipple retraction or the palpation of a retroareolar mass is a common physical examination finding and may be the first clinical manifestation of male BC [2].

Genetic/epigenetic alterations in male breast cancer

A study by Johansson and colleagues revealed that there are two main subtypes of male BC: the male complex subtype, which is similar to female luminal BC, and the male simplex subtype, which does not exist in female BC [24, 25]. These findings have been confirmed by results from the International Male Breast Cancer Program (IMBCP) [20]. The IMBCP results also revealed additional important alterations using RNA sequencing.

In addition, the research laboratory of one of the authors (J. Parker) has been investigating the gene expression patterns of BC using RNA sequencing and other methods [26]. In the current analysis, gene expression, somatic mutation, and copy number data for 1098 BC samples were acquired from The Cancer Genome Atlas (TCGA) Firehose (The Broad Institute Genome Data Analysis Center, http://www.gdac.broadinstitute.org/). Sex information was abstracted from the clinical data for 451 samples, including 5 samples from men. Samples without sex information in the available clinical data were assigned as 'likely' male ($N=7$) or female based on the expression of *UTY*. Gene expression intrinsic subtypes were assigned based on the PAM50 algorithm [27].

At the global level, BC gene expression analyzed with principal component analysis provides evidence that male BC is generally similar to female BC, as top components of variation do not segregate by sex. Instead, the predominant variation segregates by intrinsic subtype, with male BC overlapping with female luminal cases. Supporting this, the male BC samples were significantly enriched with luminal cells (Fisher's Exact $P=0.009$). This evidence that a majority of male BC samples tested were luminal-type is a distinctly different feature compared to female BC, which shows a greater diversity of subtypes. No difference in mutation rate was observed between female and male samples. Similar to female luminal tumors, individual mutations of *GATA3* and *PIK3CA* are frequent, although there are no TP53 mutations in the male BC samples. In a recently published study, the most frequently mutated genes in male BC were *PIK3CA* (20%) and *GATA3* (15%) [28], which agrees with the findings from the Parker laboratory.

From the perspective of copy number, differences in males and females are not observed after accounting for PAM50 intrinsic subtyping. While the number of males in the Parker dataset is small ($N=12$), these data provide strong support that many if not most male BC will be characterized as luminal breast cancer. The characterization of male BC as luminal-type is in agreement with recent studies in which 29 and 71% of male BCs were classified

as luminal A—like and B—like, respectively, by immunohistochemistry and in which genetic tests of male BC samples showed a pattern of aberrations similar to female BC samples of a luminal subgroup [25, 28].

Although male BC seems globally similar to female BC, the evidence from studies summarized above indicates that there are common genetic features of female BC that are not shared with male BC. Underlying genetic and epigenetic differences between male and female BC exist and are summarized in Table 1. For male BC—as with many cancers—family history plays a large role in an individual's risk of acquiring the disease. A family history of BC increases the risk of male BC [29] (a relative risk of 2.5 [4]), and 20% of men with BC have a first-degree relative with BC [6, 29]; the BC risk increases to more than five-fold when the number of relatives with BC, especially early onset, increases [30]. Inherited germline mutations are a likely etiology for 4–40% of male BCs (vs. 30–86% of female BCs) [6, 31, 32]. In particular, mutations in *BRCA1* and especially *BRCA2* are associated with increased BC risk [30]. Estimates of the life-time risk of developing male BC range from 1 to 5% for *BRCA1* mutation carriers and 5–10% for *BRCA2* mutation carriers, compared to 0.1% in the general population [33].

Mutations in other DNA-repair genes such as CHEK2 [34] and PALB2 [35] are also associated with male BC. In a recently reported study of male BC patients undergoing testing with a multigene panel of 8 or more common cancer-related mutations, it was shown that more than 13.3% of the men tested positive for one or more of the mutations, and the most common mutations in that subset of patients were in *BRCA2* (47%), followed by *CHEK2* (31%), *PALB2* (7%), *BRCA1* (9%), and *ATM* (4%) [36]. In addition, genetic variation in *CYP17*, the gene that encodes an enzyme responsible for sex-steroid production, has been proposed as a risk factor for breast and prostate cancer. Two case-control studies have investigated single nucleotide polymorphisms (SNPs) in *CYP17* [37, 38]. One study found a polymorphism (a T to C substitution in the promoter region) associated with increased risk of male BC but not female BC [37], while the other study found a statistically non-significant increased risk of the same polymorphism in men with the *BRCA2* 999del5 mutation [38]. Another study of *CYP17* in a large study of 8138 prostate cancer cases and 5333 BC cases from the Breast and Prostate Cancer Cohort Consortium found no association between common genetic variants in *CYP17*and prostate cancer or BC [39]. However, the majority of BC patients were female, and the results did not address male BC specifically.

Epigenetic alterations have also been implicated in the development and progression of cancer. Similar to female BC, promoter hypermethylation is also common in male BC, and the methylated genes are common between men and women [40]. The difference is that many of the genes investigated have decreased methylation frequency compared to female BC, which provides additional differences between male and female BC development and progression.

Endocrine risk factors associated with male breast cancer

Klinefelter's syndrome, a rare genetic condition characterized by the presence of an extra X chromosome (XXY genotype) and associated with testicular dysgenesis, gynecomastia, an altered balance of androgens and estrogens, and increased gonadotrophins, increases the risk of developing male BC up to 50-fold compared to unaffected men [4, 41]. Similar to the increased estrogen levels associated with Klinefelter's syndrome, the use of exogenous estrogens, such as estrogen treatment of prostate cancer [42] and hormone therapy for male-to-female transsexuals [43], increases the risk of male BC. Endogenous causes of hyperestrogenization in men, including obesity, cirrhosis, mumps orchitis, undescended testes, or testicular injury also have been associated with increased risk of male BC [4, 29]. In a comprehensive overview of risk factors for male BC, alcohol consumption, occupation, and radiation exposure were implicated as additional risk factors [4]. Interestingly, invasive lobular BC is very rare in men due to a lack of terminal breast lobules, except for those who are exposed to increased estrogens from endogenous or exogenous sources [44].

Table 1 presents a summary of the major differences between male and female invasive breast cancer.

Treatment options for male breast cancer

While significant efforts have been made to increase female BC awareness, screening, diagnostics, and treatment options, research and outreach directed at male BC has been limited until recently. Management of male BC has mainly relied on adopting clinical practices developed to treat female BC patients [2, 51]. Several studies have indicated that the overall survival (OS) estimates for male BC are significantly lower than for female BC [15, 21, 52], which emphasizes the need for earlier screening and effective treatments in male BC. However, it is important to note that many men with BC tend to have additional comorbidities and/or other neoplasms (e.g., prostate cancer, colon cancer, lung cancer) and are more likely to die from other causes compared to women with BC [53]. Because of this, some researchers suggest that disease-specific survival (DSS) may be a more accurate benchmark for male BC prognosis and survival rates than OS [8, 15] and in particular adjusted breast cancer–specific survival (adjusted for age, comorbidities, and stage at diagnosis). Studies have found that men had slightly better

Table 1 Comparison of male and female invasive breast cancer

Characteristic	Male	Female	Comments
Patient demographics			
Incidence	2550	266,120	2018 US estimates [9, 10]
Annual deaths	480	40,920	2018 US estimates [9, 10]
Median age at diagnosis, years	68 [13]	62 [13]	
Age-adjusted incidence rates (per 100,000 individuals)			
All years	1.2	124.8	SEER 2011–2015 [11]
20–49 years	0.2	7.14	
50–64 years	1.8	270.1	
65–74 years	5.2	426.0	
75+ years	7.7	414.3	
Disease characteristics			
BC distribution at diagnosis			
Localized	63.1%	45.4%	SEER 2006–2015 [11]
Regional	29.1%	43.6%	
Distant	5.7%	8.1%	
Unstaged	2.1%	2.9%	
Histological type			
Ductal	89%	73%	Prospective analysis of 449 male BC patients samples [45]; Retrospective analysis of 190,458 female BC cases [46]
Lobular	1%	8%	
Other	9%	19%	
Receptor status			
ER+	99%	77%	Retrospective analysis of 1483 male BC patients samples [20]; Retrospective analysis 2171 female BC patient samples [47]
PR+	82%	64%	
AR+	97%	77%	
HER2+	9%	11%	
TNBC	0.3%	11%	
Genetic/epigenetic alterations			
CYP17 gene aberration	Common	Rare [37, 38]	
Klinefelter's syndrome (XXY)	BC rates increase 20- to 50-fold compared to XY males [4]	None [4]	
Hypermethylation of *BRCA1, BRCA2, CD44, ESR1, STK11, RARB*, and *ATM* promoter regions	Rare [40]	Common [40]	
BRCA1 germline mutation	Rare (~1%) [30]	Rare (~5–10%) [48]	
BRCA2 germline mutation	Common (~12%) (60–76% in male BC patients with multiple family members with BC) [30]; pathogenic variants increase risk 13.9-fold [49]	Rare (~5%) [48]	
CHEK2 mutations	Pathogenic variants increase risk 3.7-fold [49]		
CHEK2 1100delC deletion	Deletion increases risk 3.13-fold [50]	Deletion increases risk 2.88-fold [50]	
PALB2 mutations	Pathogenic variants increase risk 6.6-fold [49]		

AR androgen receptor, *ATM* ataxia telangiectasia mutated, *BC* breast cancer, *BRCA* breast cancer gene, *CD44* CD44 molecule (Indian blood group), *CHEK2* checkpoint kinase 2, *ER* estrogen receptor, *ESR1* estrogen receptor 1, *HER2* human epidermal growth factor receptor 2, *PALB2* partner and localizer of *BRCA2*, PR progesterone receptor, *RARB* retinoic acid receptor beta, *SEER* Surveillance, Epidemiology, and End Results Program, *STK11* serine/threonine kinase 11, *TNBC* triple-negative breast cancer, *US* United States

or equivalent DSS compared to women [53, 54], although note that these studies were not controlled for BC subtype. Importantly, both the retrospective joint analyses and the prospective registry parts of the IMBCP have shown that overall quality of care for male patients with breast cancer is worrisomely inferior than that for female patients with BC [19, 20].

Treatment options for early-stage male breast cancer

Treatment for early-stage male BC includes 4 main treatment modalities: surgery, radiation therapy, chemotherapy, and endocrine therapy [1, 8, 55]. Typically, men with BC are treated with modified radical mastectomy, with axillary lymph node dissection or sentinel node biopsy [56]. Breast conservation or nipple-sparing or skin-sparing mastectomies may also be performed in selected cases; oncoplastic techniques should be used in view of the significant psychological and emotional impact of the physical consequences of locoregional therapies in male patients. Men are more likely than women to undergo mastectomy and to receive adjuvant radiotherapy as they are often diagnosed at a later stage and have nipple or skin involvement at diagnosis [29]. While there are limited data on chemotherapy use for male BC, clinicians choosing to use chemotherapy typically assess similar clinicopathologic risk factors (including tumor size, nodal involvement, hormone receptor status, HER2 status, and the underlying biology of the cancer) in male BC patients as they do in female BC patients with early-stage disease.

As a majority of male BCs express the ER, the use of endocrine therapy such as tamoxifen is routine for the management of male BC. Tamoxifen is the SOC for adjuvant endocrine therapy, and aromatase inhibitors should not be used alone in this setting. Aromatase inhibitors are not commonly used for the initial treatment of male BC. In gonad-intact men, aromatase inhibitors may cause a partial decrease in estrogens but also cause an increase in androgens, presumably from a lack of estradiol negative feedback on gonadotropin release [57, 58]. This increase in androgens could be problematic given the nearuniversal AR positivity of male BC. In addition, estrogen production in men is 80% by peripheral aromatization but 20% by direct testicular production, the latter not being inhibited by an aromatase inhibitor alone (insert REF post QC). For these reasons, if an aromatase inhibitor is used, it is recommended that it be co-administered with chemical or surgical castration [1]. However, this combination has substantial side effects, which usually are associated with low compliance and should be reserved for very select cases. Tamoxifen, a selective estrogen receptor modulator therapy, is the current endocrine therapy of choice for male BC, given that nearly all male BC tumors are ER+ and that tamoxifen has been shown to improve survival rates in ER+ female BC [4, 8]. Although tamoxifen has been shown to be effective for male BC, it has drawbacks: frequency of recurrence and side effects that include hot flashes, changes in vision, cognitive changes, and a lower sex drive [51, 59–62]. Such quality of life issues may discourage male patients from continuing treatment, as 20–25% of men with BC discontinue tamoxifen due to side effects [4, 62]. Retrospective observational analysis has shown that survival of men with ER+, lymph node−negative tumors improved with tamoxifen but not with aromatase inhibitors [63]. In male subjects with hormone receptor–positive (HR+) disease receiving adjuvant hormonal therapy, a significantly ($P = 0.007$) higher proportion of subjects who received aromatase inhibitors died (32%) compared to those who received tamoxifen (18%) [64], providing further support of tamoxifen in the adjuvant setting. A prospective, randomized, Phase 2 trial of tamoxifen ± gonadotropin-releasing hormone (GnRH) analog versus exemestane + GnRH analog investigating endocrine changes in men with HR + BC found that tamoxifen or exemestane given in combination with GnRH analog resulted in reductions in sex steroids (testosterone and estradiol) and gonadotropins (follicle stimulating hormone and luteinizing hormone) while tamoxifen alone resulted in increases in sex-steroid and gonadotropin concentrations that were significantly different than either combination [65]. Tumor assessments were not reported.

Treatment options for metastatic male breast cancer

Since male BC is almost always ER+, the preferred treatment option for first-line therapy of metastatic disease is endocrine therapy [66]. Tamoxifen is again the treatment of choice, unless relapse occurs while on treatment with this agent. In this circumstance, other therapeutic options should be considered such as an aromatase inhibitor (preferably associated with a luteinizing hormone-releasing hormone agonist) or fulvestrant. Chemotherapy should be reserved for highly symptomatic or visceral crisis situations [66].

The evidence of activity of aromatase inhibitors or fulvestrant in metastatic or locally advanced male BC is primarily derived from case reports. In a series of 15 cases of patients with metastatic or locally advanced male BC who received aromatase inhibitors, 2 patients (13%) had a complete response, 4 patients (27%) had a partial response, 2 patients (13%) had stable disease, and 7 patients (47%) had progressive disease; the median progression-free survival (PFS) was 4.4 months [67]. A limited number of case studies of the selective estrogen receptor degrader fulvestrant in men with metastatic BC have shown extended partial responses or stable disease [68–70]. Combinations of endocrine and targeted agents, such as mTOR and CDK

inhibitors, can be used in metastatic male BC patients, as the same indications are used for their female counterparts. When chemotherapy is indicated, the same agents and regimens recommended for female metastatic BC should be used for male metastatic BC.

Clinical trials in male breast cancer

Due to the rarity of male BC, therapeutic clinical trials targeting solely male BC patients or larger BC trials with distinct male cohorts are limited. To date, most male BC patients treated in clinical trials have been enrolled in trials that predominantly enroll female patients but also allow enrollment of men when eligible. A report in 2010 indicated that there was only one therapeutic BC clinical trial that focused solely on men, which closed without patient enrollment due to logistical problems and pushback from trial sites [1]. Since then, there have been two additional interventional clinical trials opened with a focus on male BC. An overview of current or recent clinical trials in male BC is provided in Table 2. Clinical trials are organized by intervention, with a focus on male BC (i.e., solely male BC subjects or separate male BC cohort if enrolling female BC subjects), observational male BC, or interventional that specifically mention combined enrollment of male and female subjects.

http://www.ClinicalTrials.gov was searched for interventional or non-interventional BC clinical trials that are recruiting, enrolling by invitation, active, or completed. Of the more than 600 BC clinical trials listed, approximately one-third were not exclusionary to male participation. Overall, approximately 2% ($N=12$) of the trials listed specifically mention the enrollment of men. A blog post in May 2016 indicated that the male BC clinical trial landscape is mostly the same as in 2013: male participants are eligible for only one-third of BC trials and about 18% of Phase 3 trials [71]. Of the 12 trials listed in http://www.ClinicalTrials.gov that specifically mention the enrollment of men, only 3 are interventional clinical trials (Table 2). Due to the lack of interventional clinical trial data, data from observational or retrospective trials, case studies, or meta-analyses are leveraged to inform male BC. However, these approaches have drawbacks compared to interventional trials, emphasizing the need for randomized, controlled, interventional male BC trials. Such an approach requires focused and coordinated efforts to increase the feasibility of successful recruitment and completion. However, rare disease trials are difficult to operate. For this reason, male BC patients should not be excluded from any BC trial unless there is a strong biological reason to do so. This will allow for the generation of data on efficacy of new agents in this rare patient population.

Multi-national consortium approach

Given the paucity of male BC subjects for prospective observational or interventional clinical trials, multinational consortium studies are warranted. A major advancement on this front is the ongoing International Male Breast Cancer Program, coordinated by the European Organisation for Research and Treatment of Cancer (EORTC) and the Translational Breast Cancer Research Consortium (TBCRC), under the umbrella of the Breast International Group (BIG) and the North American Breast Cancer Group (NABCG), funded by the Breast Cancer Research Foundation (BCRF). This program has 3 parts. Part 1 is a retrospective joint central analysis of 1822 men, and Part 2 is a 30-month prospective registry that has enrolled 557 subjects. Part 3, which involves prospective clinical trials, is yet to be initiated.

Part 1 showed low levels of breast-conserving surgery in M0 patients even though a majority (56%) of men had T1 tumors [20]. Despite > 90% of the tumors being ER+, only 77% of patients used adjuvant endocrine therapy. While half of the node-positive patients received adjuvant radiotherapy, 36% of N1 and 15% of N2 patients did not. Almost one-third of patients received adjuvant therapy. Centralized pathology review of these cases showed that the luminal A—like subtype was the most common [72], and that unlike female BC, histological grade was not associated with overall survival. An analysis of male BC precursor lesions found that ductal carcinoma in situ was the most commonly observed precursor lesion in male BC, and its presence seems to be associated with a better outcome, particularly in luminal B HER2 + cases [73].

Initial baseline data from 557 patients enrolled between 2013 and 2017 in the prospective registry (Part 2) were recently reported [45]. There continues to be discordance with normal treatment patterns with female BC: while 46% of M0 patients enrolled were node-positive, only 29% received radiotherapy, and while 98% of men had ER+ disease, only 65% received endocrine therapy. Longer follow-up, disease characterization, and comparison to a similar female BC population are ongoing.

To date, this program has helped to better understand male BC treatment patterns, tumor characteristics, and quality of life, while establishing the foundation for larger multinational therapeutic clinical trials, which is the goal for Part 3.

Table 2 Clinical trials for male breast cancer or clinical trials in breast cancer enrolling men

NCT number/study type	Status	Population	Total N (Male BC N)	Arms	Primary endpoint	Sponsor
Interventional trial—male BC focus						
NCT01638247/open-label Phase 3	Ongoing, not recruiting	Men only, hormone receptor +	56 (56)	Tamoxifen, tamoxifen + GnRH analogue, exemestane + GnRH analogue	Estradiol blood concentration	German Breast Group
NCT00217659/open-label Phase 2	Withdrawn due to low accrual and site logistics [1]	Men only, recurrent or metastatic or recurrent BC, ER+ or PR+	0	Anastrozole + goserelin acetate	PFS, OS, ORR	Southwest Oncology Group
NCT02580448/open-label Phase 1/2	Actively recruiting	Men and postmenopausal women; Phase 1: women only, TNBC or ER+/ Phase 2: TNBC, AR + or ER+	175 (21)	Seviteronel	CBR16 (female TNBC and male BC), CBR24 (female ER+)	Innocrin Pharmaceuticals
Non-interventional—male BC focus						
NCT01703520/Register-based, case-control	Completed Nov 2017	Men only with or without male BC, > 35 yrs old, finasteride users or non-users	575,216 (575,216)	N/A	Association between finasteride exposure and the development of breast cancer in men	Merck Sharp & Dohme Corp
NCT01101425/observational	Ongoing, not recruiting	Men only, invasive breast carcinoma Part 1: retrospective observational diagnosed since 19,902,010 Part 2: prospective observational recently (≤ 3 months) diagnosed	Not available	N/A	Survival, PFS, time to locoregional or distant relapse, time to second primary, treatment patterns, patient and disease characteristics, and biological characterization	European Organisation for Research and Treatment of Cancer – EORTC; Translational Breast Cancer Research Consortium – TBCRC
Interventional trial—combined male and female BC cohort						
NCT02437318/placebo-controlled Phase 3	Ongoing, not recruiting	Men and postmenopausal women, ER+, HER2−, identified PIK3CA status	572	Alpelisib + fulvestrant, placebo + fulvestrant	PFS for patients with PIK3CA mutant status	Novartis Pharmaceuticals
NCT02941926/open-label Phase 3	Actively recruiting	Men and women, recurrent or metastatic BC, ER+, PR+, HER2−	3775	Ribociclib + letrozole	Safety and tolerability (AEs/SAEs)	Novartis Pharmaceuticals
NCT00754325/open-label Phase 2	Completed Jan 2014	Men (1) and postmenopausal women (99), ER+ and/or PR+	100	Dasatinib + fulvestrant, fulvestrant	PD or death, PFS	Bristol-Myers Squibb
NCT00875979/open-label Phase 1b/2	Completed Aug 2011	Men (1) and women (66), HER2+, locally advanced or metastatic BC	67	Trastuzumab emtansine 3 mg/kg + pertuzumab 420 mg, trastuzumab emtansine 3.6 mg/kg + pertuzumab 420 mg	Objective response	Hoffmann-La Roche

Table 2 (continued)

NCT number/study type	Status	Population	Total N (Male BC N)	Arms	Primary endpoint	Sponsor
NCT02753595/open-label Phase 1/2	Ongoing, not recruiting	Men and women, metastatic BC, HER2−	114	PEGPH20 + eribulin (several doses)/eribulin	RP2D and ORR	Eisai Inc
NCT02980341/open-label Phase 1/2	Actively recruiting	Men and women, advanced or metastatic BC, HER3+	80	Drug U31402	Safety and tolerability (AEs/SAEs) and tumor response	Daiichi Sankyo Co., Ltd
NCT02060253/open-label Phase 1	Completed June 2018	Men and women, advanced or metastatic BC, HER2+	9	Ganetespib, paclitaxel, and trastuzumab with pertuzumab	MTD and RP2D	Memorial Sloan Kettering Cancer Center

AE adverse event, *AR* androgen receptor, *Aug* August, *BC* breast cancer, *CBR16* clinical benefit rate at 16 weeks, *CBR24* clinical benefit rate at 24 weeks, *DLT* dose-limiting toxicity, *ER* estrogen receptor, *GnRH* gonadotropin-releasing hormone, *HER2* human epidermal growth factor receptor 2, *HER3* human epidermal growth factor 3, *Jan* January, *MTD* maximum tolerated dose, *N/A* not applicable, *ORR* objective response rate, *OS* overall survival, *PD* progressive disease, *PEGPH20* PEGylated recombinant human hyaluronidase, *PFS* progression-free survival, *PR* progesterone receptor, *RP2D* recommended Phase 2 dose, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *TNBC* triple-negative breast cancer

Note: Bolded NCT numbers indicate clinical trials with only male participants

Future perspectives on male breast cancer and treatment options

The research and available literature on male BC has expanded in the past few decades, and the progress of the IMBCP is an important step; however, knowledge is limited as clinical/translational research on male BC is still in its infancy. Although common female BC treatment practices are applied to the management of male BC, the medical community recognizes male BC as a distinct disease characterized by varied molecular and clinicopathologic features. Modified radical mastectomy as well as radiotherapy and adjuvant tamoxifen are still used in the treatment of male BC; however, the role of adjuvant systemic therapies in male BC is less understood [8]. Several endocrine, cytotoxic, and targeted therapies studied in in the metastatic male BC setting have shown variable responses [1, 4, 8, 14, 22, 74]. As indicated in Table 2, some ongoing BC trials evaluating a variety of new therapies include male patient recruitment and will provide important information. However, research specifically dedicated to male BC, especially research related to the best endocrine-based approaches, is warranted.

As discussed above, DNA damage repair (DDR) genes, specifically *BRCA2*, are frequently mutated or overexpressed in male BC. Given this, therapies targeting the poly-ADP-ribose polymerase (PARP) family of proteins could provide therapeutic benefit to male BC patients and warrant investigation. Specifically, PARP1 has been the focus of the most oncology research, as it is involved in 80–90% of DNA-repair via the base excision repair (BER) pathway [75, 76]. Inhibition of PARP causes accumulation of single-strand DNA breaks, which are converted to double-strand breaks during DNA replication [77, 78]. Since mutation of *BRCA2* results in the inability to resolve double-strand breaks (DSBs) via the high-fidelity homologous recombination pathway, DSBs are resolved by the more error-prone nonhomologous end joining pathway, which accelerates genomic instability to facilitate tumor cell death via the principle of synthetic lethality [78]. Knowledge about the efficacy of PARP1 in male BC is very limited. However, PARP inhibitors have shown activity in other *BRCA*-mutated male tumors, including prostate cancer. Indeed, results from the TOPARP-A trial (Trial of PARP Inhibition in Prostate Cancer) showed 88% of the patients who had a DDR pathway mutation responded to the PARP inhibitor, olaparib [79]. Thus, investigation of PARP inhibitors in DDR-deficient male BC should be considered.

The role of AR in BC is an area of active research [80], and AR has become a promising potential target for the treatment of male BC [51]. Recently, AR has been found

to have prognostic significance in ER+ male BC [81]. A review by Imamura and Sadar provide a list of current therapies targeting AR that are used to treat castration-resistant prostate cancer (CRPC) [82], and some of these therapies are also potential candidates for treating male BC. To date, data exists from female BC trials of 3 compounds that have activity in CRPC: bicalutamide (a competitive inhibitor of AR binding), enzalutamide (a competitive inhibitor of AR binding and signaling), and seviteronel (a CYP17 lyase and AR inhibitor). A trial of the third compound, sevitoronel, includes separate male BC activity data.

In a Phase 2 trial of bicalutamide in women with metastatic AR + TNBC, 5 of 26 patients had stable disease for at least 6 months. The resulting 24-week clinical benefit rate (CBR, the proportion of patients who showed a complete response, partial response, or stable disease) was 19% [83], and the median PFS was 12 weeks (95% confidence interval [CI], 11–22 weeks). Bicalutamide was well tolerated in this patient population and could provide a potential new therapeutic option for male BC, but it has not been evaluated to date.

Similarly, the activity of enzalutamide has been suggested in AR + TNBC and AR+/ER+ BC [84, 85]. For patients with AR + metastatic TNBC, a Phase 2 study of single-agent enzalutamide 160 mg met its primary endpoint with a CBR at 16 weeks of 35% and a median PFS of 14 weeks. Eight percent of patients had either a partial or complete response confirmed by RECIST criteria [86]. A randomized, placebo-controlled, Phase 2 study was conducted to evaluate exemestane with or without enzalutamide in 247 patients with HR+/HER2− male BC. The study met its primary endpoint, improving median PFS with the addition of enzalutamide to exemestane in the prespecified subset of patients who tested positive for the predictive biomarker developed in parallel [87]. Comparable improvement in PFS was not observed in women who had 1 prior endocrine therapy for advanced BC. Enzalutamide was well tolerated in both of these studies [87, 88]. Despite initial activity in female BC patients, development of enzalutamide in BC and the planned Phase 3 trial in TNBC were suspended [89].

Seviteronel, a nonsteroidal CYP17A1 and AR inhibitor, is in Phase 2 development for advanced prostate and breast cancers (Table 2), and unlike bicalutamide or enzalutamide, it has specifically been investigated in male BC [82]. Seviteronel blocks the synthesis of sex steroids (androgens and downstream estrogens) via CYP17 lyase inhibition and competitively inhibits the AR [90]. Fast-track designation was granted for seviteronel for CRPC in 2016 [91] and for male and female BC in 2017 [92]. Full results for the initial Phase 2 trials of seviteronel in BC and CRPC are not yet available; however, preliminary data from the Phase 2 trial in BC (NCT02580448) indicate that clinical benefit in Stage 1 of the trial was encouraging and sufficient to support accrual to Stage 2 for both women with ER+ BC and women with TNBC [93] as well as men with BC. Early Phase 2 results for the male BC cohort recently reported that 2 of the first 7 subjects enrolled met the initial activity endpoint of CBR at 16 weeks, with 1 of 2 patients remaining on seviteronel at 24 weeks. The most common adverse event was fatigue [94]. Phase 2 enrollment is ongoing. While these results are preliminary, this is the largest prospective therapeutic male BC clinical trial to date and the results highlight the potential for AR-targeted agents for the treatment of male BC.

Conclusions

While male BC is a rare and often neglected disease, there is a growing understanding of the biological differences between male and female BC. Such differences indicate that male BC should be seen as a separate disease, distinct from female BC. The effective treatment of patients with male BC remains a clinically challenging scenario with many unanswered questions. Research in this area is focused on evaluating the underlying biology of this subtype of tumors with the goal of developing improved therapeutic strategies for the management of this underrepresented population. An understanding of germline mutations with increased prevalence in male BC, such as *BRCA2*, may help with the identification of novel treatment options such as PARP inhibitors. Also, given the near universal expression of the AR in male BC tumors and relatively benign safety profile, AR-targeted agents may prove beneficial as a treatment option, either as monotherapy or in combination with other agents. Early activity of seviteronel in male BC highlights the targeting of the sex-steroid biosynthesis pathway and AR activation as a promising therapeutic approach for male BC. Future research in this area will require coordinated multicenter international collaboration to conduct larger, successful therapeutic clinical trials in male BC that lead to the development and approval of novel targeted agents for the management of this rare disease.

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Compliance with ethical standards

Conflict of interest Ayca Gucalp receives salary support to conduct clinical trials from Innocrin Pharmaceuticals, Pfizer, Novartis, and Merck. She also received an honorarium for participating on an advisory board for Pfizer. Tiffany A. Traina is a compensated Seviteronel Breast Cancer Steering Committee member (Innocrin Pharmaceuticals) and receives research support from Innocrin Pharmaceuticals

for trials of seviteronel. Joel R. Eisner and Edwina S. Baskin-Bey declare that they are employed by and have stock ownership in Innocrin Pharmaceuticals. Joel S. Parker is a compensated advisor to Innocrin Pharmaceuticals and author of the PAM50 patent and related patents for Nanostring Technologies, Inc. Ben H. Park has ownership interest and is a paid member of the scientific advisory board of Loxo Oncology and is a paid consultant for Foundation Medicine, Inc.; Jackson Laboratories; Casdin Capital; and Roche. Under separate licensing agreements between Horizon Discovery, Ltd and The Johns Hopkins University, Ben H. Park is entitled to a share of royalties received by the university on sales of products. The terms of this arrangement are managed by The Johns Hopkins University in accordance with its conflict of interest policies. Fatima Cardoso serves on advisory boards for Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Seattle-Genetics, and Teva. All other authors declare that they have no potential conflict of interest.

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