European Journal of Gynaecological Oncology

Eur. J. Gynaecol. Oncol. **2022**; 43(2): 341–352
https://doi.org/10.31083/j.ejgo4302040

Review

Treatment Progress in Triple Negative Breast Cancer

Stefan Krämer[1], Christoph Rogmans[2], Dilek Saylan[1], Dominique Friedrich[1], Clayton Kraft[1], Gunther Rogmans[1], Marina Wirtz[1], Michael Friedrich[1,*]

[1]Department of Obstetrics and Gynecology, Helios Hospital, 47805 Krefeld, Germany
[2]Department of Obstetrics and Gynecology, University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany
*Correspondence: michael.friedrich@helios-gesundheit.de (Michael Friedrich)
Academic Editor: Enrique Hernandez
Submitted: 22 November 2021 Revised: 17 February 2022 Accepted: 18 February 2022 Published: 15 April 2022

Abstract

Triple-negative breast cancer (TNBC) lacks expression of the three biomarkers (the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) protein) and are typically higher grade. While the triple-negative clinical phenotype is heterogeneous, the basal-like molecular subtype comprises a large proportion, particularly for breast cancer susceptibility gene 1 (*BRCA1*)-associated breast cancer. New treatment options are checkpoint inhibitors like inhibition of PD-L1 pathway with pembrolizumab and atezolizumab, parp-inhibition with olaparib or talozoparib and treatment with the an antibody drug conjugate sacituzumab-govitecan.

Keywords: breast cancer; triple negative; chemotherapy; immunoncology; PD-L1; Parp; pembrolizumab; atezolizumab; olaparib; talozoparib; sacituzumab-govitecan

1. Introduction

Triple-negative breast cancer (TNBC) describes breast cancers that lack expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC behaves more aggressively than other types of breast cancer. Although immunotherapy (in combination with chemotherapy) is available for advanced TNBC that expresses programmed cell death ligand 1 (PD-L1), there are no approved targeted treatments in TNBC comparing with other breast cancer subtypes (i.e., ER-positive, HER2-positive subtypes). For purposes of this review, we consider "triple-negative" to mean cancers that have $\leq$1 percent expression of ER and PR (IHC) and are for HER2 either 0 to 1+ by IHC or IHC 2+ and fluorescence in situ hybridization (FISH) negative (not amplified), according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines [1–3]. Although the basic principles of diagnosis and management of TNBC are similar to those of breast cancer in general, many aspects, including risk factors, molecular and pathologic characteristics, natural history, and chemotherapy sensitivity, are unique to TNBC and will be reviewed here.

A more extensive discussion on surgical management, neoadjuvant chemotherapy, adjuvant chemotherapy of non-metastatic breast cancer, and the treatment of metastatic breast cancer is covered separately.

EPIDEMIOLOGY — TNBC accounts for approximately 15 percent of breast cancers diagnosed worldwide — almost 200,000 cases each year [4]. Compared with hormone receptor-positive breast cancer, TNBC is more commonly diagnosed in women younger than 40 years. In one study, there was a twofold higher attributable risk of TNBC in women under 40 years compared with women over 50 years (odds ratio (OR) 2.13, 95% confidence interval (CI) 1.34–3.39) [5]. In addition, TNBC appears to be relatively more common among black women compared with white women (OR 2.41, 95% CI 1.81–3.21) [5]. It is important to mention that different molecular subtypes of TNBC like basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem–like (MSL) and luminal androgen receptor (LAR) subtype are described with different prognostic impact and oncological behaviour [6].

Risk factors associated with the diagnosis of TNBC include:

• Positive *BRCA* mutation status — Up to 20 percent of patients with TNBC harbor a breast cancer susceptibility gene (*BRCA*) mutation, particularly in *BRCA1* [7]. By contrast, less than 6 percent of all breast cancers are associated with a *BRCA* mutation. Given this finding, any patient with triple-negative disease should be offered a referral to a genetic counselor to discuss *BRCA* germline testing [8]. Moreover, any patient age 60 years or younger with TNBC should undergo *BRCA* germline testing.

• Premenopausal status — Premenopausal status has been associated with increased incidence of TNBC diagnosis as compared with postmenopausal status [9–11]. As with African American women, premenopausal women can frequently have ER-positive and/or HER2-positive disease, and testing their tumors for these markers is essential.

• Other factors — Studies have suggested relationships between other factors such as obesity and a young age of first pregnancy with an increased risk of TNBC, while breastfeeding and parity may be associated with lower risks [5,9,12–14]. However, these factors are less well validated and rarely factor into clinical considerations [15–29].

2. Genetics Evaluation

BRCA testing—In light of the association of particular breast cancer susceptibility gene 1 (*BRCA1*) mutations with TNBC, we recommend that women diagnosed at 60 years or younger with a localized TNBC, or those of any age with metastatic TNBC, undergo *BRCA* mutation testing regardless of family history (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes").

For those with metastatic disease, results of *BRCA* testing have therapeutic implications (See 'Metastatic disease' below).

3. Non-Metastatic Disease

The neoadjuvant or adjuvant chemotherapy options for patients with TNBC are similar to the approaches used in other breast cancer phenotypes. The principles for the surgical management of and radiation therapy options for breast cancer are also applied in a similar way across breast cancer subtypes (See "Breast-conserving therapy" and "The role of local therapies in metastatic breast cancer" and "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer" and "Radiation therapy techniques for newly diagnosed, non-metastatic breast cancer").

Chemotherapy—Chemotherapy is recommended for women with TNBC >0.5 cm or with node-positive TNBC (regardless of tumor size). These patients have a higher risk of relapse compared with other breast cancer phenotypes and are not candidates for other forms of targeted therapy (i.e., HER2-directed treatment or endocrine therapy).

Neoadjuvant versus adjuvant administration — Neoadjuvant chemotherapy (NACT) is the preferable approach in patients with locally advanced breast cancer or for those who are not candidates for or unlikely to have a good cosmetic outcome with breast conservation. For patients receiving NACT, pathologic complete response is associated with improvement in disease-free survival (DFS) [30–32]. Additionally, patients with smaller (e.g., T1c) TNBCs may be offered neoadjuvant therapy, particularly if they might be candidates for additional treatments in the adjuvant setting if residual disease is identified. The approach to neoadjuvant therapy for patients with breast cancer, including further discussion of appropriate candidates, with special considerations for those with TNBC, is found elsewhere (See "General principles of neoadjuvant management of breast cancer" and "General principles of neoadjuvant management of breast cancer", section on 'Patient selection' and "Choice of neoadjuvant chemotherapy for HER2-negative breast cancer", section on 'Special considerations for triple-negative disease').

The role for additional chemotherapy in the adjuvant setting for women with residual cancer after neoadjuvant chemotherapy is discussed elsewhere.

Benefits—In general, there is a larger absolute benefit to adjuvant chemotherapy among patients with TNBC compared with those with hormone-positive disease [33].

An analysis of three randomized trials with a total of 6644 women with node-positive breast cancer comparing patients those with ER-positive breast cancer with those with ER-negative breast cancer showed the following significant outcomes at five years following adjuvant chemotherapy [33]:

• A larger reduction in the risk of recurrence (55% versus 26%) with a higher absolute improvement in DFS (23% versus 7%).

• A larger reduction in the risk of death (55% versus 23%) with a higher absolute improvement in overall survival (OS; 17% versus 4%).

These data emphasize the importance of neo/adjuvant chemotherapy for women with TNBC, who (unlike those with ER-positive or HER2-positive breast cancer) are not eligible for targeted therapies.

Choice of Regimen

• Preferred regimen — Anthracycline-, alkylator-, and taxane-based chemotherapy regimens remain the standard regimens for TNBC, for example, dose-dense doxorubicin and cyclophosphamide followed by paclitaxel (AC-T). Taxanes have significant activity in the treatment of TNBC, and there are no meaningful data regarding regimens lacking alkylator-based therapy [34–36]. As an example of the benefits of a taxane, the GEICAM 9906 trial (adjuvant fluorouracil, epirubicin, and cyclophosphamide (FEC) versus FEC followed by paclitaxel) showed, that the addition of paclitaxel was associated with an improvement in DFS at seven years (74% versus 56%) [36]. The ABC trials tested anthracycline/taxane-based regimens versus docetaxel and cyclophosphamide (TC) given for the same duration, finding a benefit overall for incorporation of the anthracycline, particularly in TNBC in subset analysis. However, the absolute benefit in node-negative TNBC appears modest [37]. Further discussion of these data is elsewhere (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'Rationale for anthracycline- and taxane-containing regimen').

• Non-anthracycline-based regimens are an appropriate alternative for patients with lower-risk TNBC (e.g., node-negative, <1 cm, or those with cardiac risk factors) and those who prefer to avoid the risks associated with anthracyclines. TC is an alternative in low-risk disease, and is discussed in more detail elsewhere (in patients with HER2-negative disease, irrespective of hormone receptor status).

For example, in a randomized trial of nearly 650 patients with operable TNBC, those assigned to six cycles of adjuvant paclitaxel and carboplatin (administered on days 1, 8, and 15 every 28 days) had a longer DFS relative to those assigned to an anthracycline and taxane based regimen (five-year DFS 87 versus 80%), with similar OS [38].

• Is there a role for an antimetabolite agent?—For patients with stage II or III TNBC, neoadjuvant regimens such as AC-T or TC are standard, followed by capecitabine for those with residual disease, given results of a randomized trial showing an OS benefit with the adjuvant addition of capecitabine when residual disease is present [39]. These results are discussed elsewhere (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'Regimen selection and administration').

However, for patients with stage I disease, adjuvant rather than neoadjuvant treatment is appropriate, using standard regimens such as AC-T or TC. In general, for patients who have not received neoadjuvant chemotherapy, adding antimetabolite agents such as capecitabine or gemcitabine to adjuvant chemotherapy has not improved OS outcomes in TNBC [40,41], and it is not our approach. A Chinese trial demonstrated improvement in DFS, but not OS, with capecitabine following standard adjuvant regimens [42]. Among 434 women with early-stage TNBC who received standard adjuvant treatment (94% of whom had not received neoadjuvant therapy), low-dose capecitabine maintenance therapy for one year improved five-year DFS compared with observation only (83 versus 73%; hazard ratio (HR) 0.64, 95% Confidence interval (CI) 0.42–0.95). The five-year OS was similar between the groups (86 versus 81%, with and without capecitabine, respectively; HR 0.75, 95% CI 0.47–1.19). The trial had important limitations; notably, there was an imbalance in randomization, with a higher proportion of older women assigned to placebo, which could have favored the capecitabine group.

Another phase III trial of 876 women with early-stage TNBC demonstrated that the subsequent treatment with capecitabine after standard adjuvant chemotherapy versus placebo resulted in numerically, but not statistically, improved five-year DFS and OS (DFS, 80% versus 77%, HR 0.79, 95% CI 0.61–1.03; OS, 86.2 versus 85.9%, HR 0.92, 95% CI 0.66–1.28) [40]. Similarly, trials looking at adjuvant gemcitabine have proven negative.

Given the sum of data, we opt for standard anthracycline- and/or taxane-based chemotherapy regimens as adjuvant therapy in patients with TNBC who have not received neoadjuvant treatment. As discussed, in practice, only lower-risk patients (i.e., stage I TNBC) are treated with adjuvant rather than neoadjuvant chemotherapy, as most patients with higher-risk disease receive neoadjuvant therapy.

• Is there a role for platinums?—There is controversy as to whether adding platinum-based chemotherapy should be "standard" in stage II or III TNBC. Trials have shown that adding platinum-based chemotherapy to neoadjuvant regimens can improve the rate of complete pathologic response [43,44]. However, to date, this has not improved OS in women also receiving anthracycline-, alkylator-, and taxane-based treatment. This is discussed further elsewhere (See "Choice of neoadjuvant chemotherapy for HER2-negative breast cancer", section on 'Special considerations for triple-negative disease').

• Is there a role for immunotherapy?—The incorporation of immunotherapy in neoadjuvant regimens is discussed elsewhere. However, at present, there is no established role for immunotherapy in neoadjuvant or adjuvant treatment of breast cancer, regardless of the biologic subtype (See "Choice of neoadjuvant chemotherapy for HER2-negative breast cancer", section on 'Investigational approaches').

Treatment of tumors ≤0.5 cm—The prognosis of node-negative, triple-negative tumors ≤0.5 cm is generally favorable, and therefore, the benefits of adjuvant chemotherapy are likely to be very small and must be weighed against the chances of serious side effects of chemotherapy. In general, patients with microinvasive or very small (1 to 5 mm) breast cancers do not need chemotherapy, although we discuss the issue carefully with such patients, given that a small benefit cannot be ruled out, and, some patients, particularly those with 4 or 5 mm tumors, may reasonably elect to proceed with treatment.

In a retrospective review of almost 4400 patients with small, node-negative TNBCs (6.5 percent with pT1a, 21 percent with pT1b, and 72 percent with pT1c tumors), 53% of patients received adjuvant chemotherapy [45]. These patients had more unfavorable baseline characteristics including younger age, larger tumors, and higher tumor grade. A multivariate analysis showed, that adjuvant chemotherapy improved breast cancer-specific survival in the overall group (adjusted HR 0.65, 95% CI 0.48–0.89), but not for the subset of patients with pT1a tumors (adjusted HR 4.28, 95% CI 1.12–16.44). Although limitations of this study include its retrospective nature and that the number of patients with pT1a tumors was small (n = 18), the results suggest that the risks of chemotherapy may outweigh benefits in patients with these small tumors.

The natural history of small triple-negative tumors was demonstrated in a study of 143 patients with triple-negative tumors up to 1 cm in size and not treated with adjuvant chemotherapy [46]. Patients with triple-negative tumors had a 75 to 89 percent relapse-free survival and over 95 percent distant relapse-free survival at five years. Another study including 363 T1a-bN0 triple-negative tumors from the National Comprehensive Cancer Network (NCCN) database suggested a 90 to 93 percent distant relapse-free survival without chemotherapy [47]. Given the lack of prospective data on women who present with small tumors, the decision to administer adjuvant chemotherapy

must be individualized based on patient and provider preferences.

Prognosis—The peak of the risk of distant recurrence and death is approximately three years after diagnosis declining rapidly thereafter [31]. TNBC is characterized by higher relapse rates during this period of time compared with ER-positive breast cancers, although the latter tend to continue to recur for decades later while TNBCs tend not to do so. Therefore, overall in the long run the absolute risk of recurrence for the two subtypes approach one another. Furthermore, however, TNBC may be more likely to recur in locoregional areas as well as in visceral organs, such as liver, lung, and brain involvement at first recurrence [48–51]. By contrast, TNBC is less likely than ER-positive breast cancer to recur initially in bone [51]. In one study involving 116 patients with triple-negative metastatic breast cancer, brain metastases were the initial site of metastatic disease or occurred during their metastatic course in 14 and 46 percent, respectively [49]. The median survival following a diagnosis of central nervous system metastases is less than six months [52,53].

Patients with TNBC have a poorer short-term (first five to seven years) prognosis compared with patients with other breast cancer subtypes [15,26,51,54]. In a 2012 study of 12,902 women who presented to NCCN centers, compared with women with hormone receptor-positive, HER2-negative breast cancer, women with TNBC experienced, at a median follow-up of three years [51]:

- Worse breast cancer-specific survival (HR 2.99, 95% CI 2.59–3.45).
- Worse OS (HR 2.72, 95% CI 2.39–3.10).
- A dramatic increase in death within two years of diagnosis (HR 6.10, 95% CI 4.81–7.74). However, the magnitude of this risk declined substantially over time (HR of death two to six years from diagnosis 2.30, 95% CI 1.39–3.82; HR of death >6 years from diagnosis 0.86, 95% CI 0.30–2.46). Thus, the risk of recurrence and breast cancer mortality for hormone receptor-positive, HER2-negative disease becomes approximately equal to that of triple-negative cancers within the second decade.

The risk of late recurrence is low for women with TNBC. In a single-center retrospective series of 783 women with stage I, II, or III TNBC who were alive and without recurrence at five years after treatment for the original diagnosis, the yearly recurrence-free interval at 10 and 15 years was 97 and 95 percent, respectively, and the relapse-free survival rates were 91 and 83 percent, respectively [55]. In a prospective cohort study in which patients with stage I to III breast cancer diagnosed between 1986 and 1992 were matched with patients diagnosed between 2004 and 2008, the hazard rate of relapse for those with triple-negative disease had dropped to essentially zero after year 6 among patients treated in the later cohort [56].

Post-treatment surveillance — There are no specific post-treatment surveillance guidelines for patients with TNBC. Patients with breast cancer should undergo a similar surveillance routine according to American Society of Clinical Oncology guidelines following breast cancer treatment, regardless of breast cancer subtype. This should include history and complete physical exam every three months for the first three years, then every 6 to 12 months for surveillance. A further discussion on post-treatment surveillance is covered separately (See “Approach to the patient following treatment for breast cancer”, section on ‘Guidelines for post-treatment follow-up’).

4. Metastatic Disease

Many of the general principles applicable to advanced breast cancer of other phenotypes apply to that of TNBC. The cornerstone of systemic treatment for TNBC has been chemotherapy because endocrine and HER2-directed therapies are ineffective. However, several trials have suggested a role for targeted therapies in TNBC including inhibitors of poly(ADP-ribose) polymerase (PARP) and immune checkpoints (See “Systemic treatment for metastatic breast cancer: General principles” and “Systemic treatment of metastatic breast cancer in women: Chemotherapy”).

Repeat biopsy—In patients with metastatic breast cancer, a confirmatory biopsy of a suspected lesion should be obtained when possible, with the following assessments:

- Reassessment of ER, PR, and HER2 — This is because there is a possible discordance of these markers between primary and metastatic disease [57–61]. As an example of discordance between primary and metastatic lesions, in a pooled analysis of two prospective studies, the rates of discordance in ER, PR, and HER2 between the primary and recurrent disease were 13, 28, and 5 percent, respectively [58].
- Programmed cell death ligand 1 (PD-L1) expression — The companion diagnostic immunohistochemical assay for PD-L1-positive immune cells, SP142, is approved for selecting TNBC patients for atezolizumab, and the 22C3 pharmDX assay is used to identify patients for pembrolizumab (See ‘PD-L1-positive tumors’ below).

Because the US Food and Drug Administration (FDA) has approved each test as a “companion diagnostic” with a specific immune checkpoint inhibitor rather than approval as a class, either of the companion diagnostics is acceptable.

- Tumor mutational burden (TMB), microsatellite instability (MSI), and mismatch repair deficiency (dMMR) — Additionally, TMB, MSI, and dMMR should be performed if there is sufficient tissue. Further details of testing are found elsewhere (See “Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors”, section on ‘Assessing mismatch repair’ and “Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors”, section on ‘Approach to testing dMMR as a predictive marker’).

However, if needed, these assessments can instead be performed in a subsequent biopsy after progression, given that they will not dictate choice of initial therapy and that these abnormalities are relatively rare in breast cancer.

In addition to these assays performed on tissue biopsy, all patients with TNBC should undergo genetics evaluation to determine if they are *BRCA* carriers, given the therapeutic implications in advanced disease (See 'No germline BRCA mutation' below and 'Germline BRCA mutation' below).

Initial treatment for rapidly progressive visceral disease—Combination chemotherapy may be appropriate for those with extensive or rapidly progressive visceral disease, in whom the higher chance of response is thought to outweigh the higher risks of toxicity, due to concerns about impending organ dysfunction. However, both clinicians and patients should know there are no prospective data that show combination chemotherapy improves overall survival (OS) compared with single-agent sequential cytotoxic chemotherapy. Further details are discussed elsewhere (See "Systemic treatment of metastatic breast cancer in women: Chemotherapy", section on 'Combination chemotherapy').

Initial treatment in the absence of rapidly progressive visceral disease — As discussed above, patients with metastatic TNBC should have germline testing for *BRCA*, as well as tumor assessment for PD-L1 (See 'Genetics evaluation' above and 'Repeat biopsy' above).

The initial treatment approach depends on the outcomes of these assessments.

4.1 No Germline BRCA Mutation

PD-L1-negative tumors—Our approach to most patients with advanced, sporadic, triple-negative metastatic breast cancer that does not express programmed cell death ligand 1 (PD-L1) is to use single-agent chemotherapy. However, combination chemotherapy strategies may be appropriate in some such patients with rapidly progressive visceral disease (See "Systemic treatment of metastatic breast cancer in women: Chemotherapy", section on 'Single-agent chemotherapy' and "Systemic treatment of metastatic breast cancer in women: Chemotherapy", section on 'Combination chemotherapy').

Either platinum- or non-platinum-based regimens are appropriate, with a choice driven by toxicity profiles. A meta-analysis with 10 randomized trials comparing platinum-containing chemotherapy with regimens not containing platinum in 958 cases of metastatic TNBC demonstrated, that the death rate in the platinum group was 46% versus 51% in the non-platinum group (hazard ratio (HR) 0.85, 95% CI 0.73–1.00) at one year [62]. However, the platinum recipients complained more grade 3 and 4 toxicities, including nausea/vomiting (relative risk (RR) 4.8) and anemia (RR 3.8).

Outcomes of platinum and non-platinum regimens in breast cancer susceptibility gene (*BRCA*)-associated TNBCs are discussed below (See 'Chemotherapy-naive patients, or those with progression on PARP inhibitors' below).

PD-L1-Positive Tumors

For those with tumor expression of programmed cell death ligand 1 (PD-L1), we recommend the addition of an immune checkpoint inhibitor to chemotherapy, rather than chemotherapy alone.

The checkpoint inhibitor atezolizumab is European Medicines Agency (EMA) approved for use with nabpaclitaxel for those with advanced TNBC with PD-L1-stained, tumor-infiltrating immune cells of any intensity covering $\geq$1 percent of the tumor area, based on observed benefits in OS. Additionally, pembrolizumab is approved in combination with chemotherapy for patients with metastatic TNBC whose tumors express PD-L1 with a Combined Positive Score (CPS) $\geq$10 (the percentage of total cells (tumor cells, lymphocytes, macrophages) that stain for PD-L1) [63]. This is a reasonable alternative to atezolizumab and nabpaclitaxel, particularly for those in whom a taxane may not be preferable, e.g., those with poor tolerance of previous taxane therapy or with a short interval of progression from prior taxane (i.e., <12 months). However, OS data have not yet been reported for this approach.

Although these therapies are approved irrespective of treatment line, the supporting data were based on patient experiences receiving first-line treatment for metastatic disease. The benefits as later-line treatment for metastatic disease are not known. Recognizing this limitation, patients with prior taxane treatment (either in the (neo)adjuvant or metastatic setting) are still candidates for the atezolizumab/nabpaclitaxel combination.

- Atezolizumab — In a randomized trial (IMpassion 130), 902 patients who had not received treatment for metastatic TNBC were randomly assigned to nabpaclitaxel with either atezolizumab or placebo [64]. To be enrolled, patients had to be at least 12 months out from (neo)adjuvant chemotherapy, and approximately half had received prior taxanes for early-stage disease. *BRCA* status was not a part of the eligibility criteria.

Overall, at a median follow-up of 13 months, there was only a modest but statistically significant difference in progression-free survival (PFS) in favor of incorporating atezolizumab. PFS for those receiving atezolizumab versus those who did not was 7.2 versus 5.5 months (HR for progression or death 0.80, 95% CI 0.69–0.92), with a non-significant trend towards improved OS (21.3 versus 17.6 months; HR for death 0.84, 95% CI 0.69–1.02).

However, a prospectively planned subset analysis of outcomes according to PD-L1-expression showed, that atezolizumab improved both PFS (7.5 versus 5 months; HR 0.62, 95% CI 0.49–0.78), and OS (25 versus 15.5 months; HR 0.62, 95% CI 0.45–0.86). Final OS analysis at 20 months' follow-up demonstrated continued improved survival in the PD-L1-positive subset with the addition of ate-

zolizumab to nabpaclitaxel (median OS (95% CI): 17.9 months (13.6–20.3) versus 25.4 months (19.6–30.7); stratified HR (95% CI): 0.67 (0.53, 0.86)) and similar adverse events, with 23 percent experiencing thyroid disease and approximately 10 percent with other immune-related adverse events. But it has to be mentioned OS analysis was not formally tested for statistical significance [65].

• Grade ≥3 adverse events occurred in 49 percent receiving atezolizumab and 42 percent receiving placebo, with grade 3 or 4 neuropathy occurring more frequently among those receiving atezolizumab (5.5 versus 2.8%). Three treatment-related deaths occurred among the 451 patients being treated with atezolizumab (0.7%), which is consistent with other studies of checkpoint inhibitors. Due to adverse events treatment discontinuation was found in 16% in the atezolizumab arm versus 8% in the control arm.

Another trial, IMpassion 131, examined atezolizumab combined with paclitaxel in first-line metastatic TNBC, with a focus on PD-L1-positive tumors defined similarly to IMpassion 130. However, unlike IMpassion 130, no significant improvement in PFS in the PD-L1-positive subset was observed, at just under nine months' follow-up (5.7 versus 6 months) [66]. The explanation for the discordance in results is unclear; however, given that the main difference between IMpassion 130 and 131 was the chemotherapy backbone, the preferred combination with atezolizumab remains nabpaclitaxel.

• Pembrolizumab — Results of a separate trial of pembrolizumab and chemotherapy are qualitatively similar to those of Impassion 130, although OS results are immature. We therefore prefer the atezolizumab-based strategy discussed above for those with PD-L1-expressing tumors. In KEYNOTE 355, 847 patients with locally recurrent, inoperable, or metastatic TNBC with a disease-free interval of ≥6 months, were randomly assigned to chemotherapy (nabpaclitaxel, paclitaxel, or gemcitabine/carboplatin), with or without pembrolizumab [67,68]. Overall, there was an improvement in median PFS with the addition of pembrolizumab (7.5 versus 5.6 months; HR 0.82, 95% CI 0.69–0.97). Results were also stratified according to CPS that stain for PD-L1. These results suggest that benefit is limited to those with CPS ≥10, in whom the addition of pembrolizumab to chemotherapy improved median OAS by approximately 6.9 months (23.0 versus 16.1 months; HR 0.73, 95% CI 0.55–0.95, $p = 0.0093$) and PFS by approximately two months (9.7 versus 5.6 months; HR 0.66, 95% CI 0.50–0.88). Although there were also improvements in PFS among those with CPS ≥1 (7.6 versus 5.6 months, respectively), this improvement may have been driven by those with CPS scores ≥10 (CPS scores between 1 and 10 percent were not provided). Grade 3 to 4 adverse events were comparable between the two groups (approximately 70 percent), although one patient in the pembrolizumab arm died from treatment-related toxicity. Immune mediated adverse events of all grades for example hypo- and hyperthyroidism and pneumonitis occurred with 26.5% versus 6.4% more often in the pembolizumab treatment arm.

In addition to the chemotherapy combination trials noted above, early clinical experience with immunotherapy (pembrolizumab (anti PD-1 anibody); avelumab and atezolozumab (anti PD-L1-antibody)) in the setting of TNBC shows response rates <20 percent in PD-L1-positive tumors [69–71]. Future studies are exploring combination treatments of immunotherapy and other systemic treatments or radiotherapy. Furthermore, current investigations are looking for optimizing the prediction of response to immunotherapy by different biomarkers.

4.2 Germline BRCA Mutation

Patients with previous exposure to chemotherapy — Inhibitors of PARP may be particularly useful in breast cancer susceptibility gene (*BRCA*)-mutated breast cancers, of which the majority are triple negative. For most patients with TNBC with germline *BRCA* mutations who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic disease setting, we suggest an oral inhibitor of PARP rather than chemotherapy, since the data suggest improved efficacy and fewer side effects. However, chemotherapy is appropriate if and when a patient suffers progressive disease on a PARP inhibitor; or for those who are chemotherapy naive, having never received chemotherapy either in the early-stage or metastatic setting; or, as discussed above, for those with rapidly progressive visceral disease (See 'Initial treatment for rapidly progressive visceral disease' above).

Additionally, the combination of immunotherapy and chemotherapy is an acceptable alternative to a PARP inhibitor for those with PD-L1-positive disease (See 'Chemotherapy-naive patients, or those with progression on PARP inhibitors' below and 'PD-L1-positive tumors' above).

In the OlympiAD trial (subset of 121 *BRCA* mutation carriers with metastatic triple-negative disease having been treated with an anthracycline and a taxane in either the adjuvant or metastatic setting) patients receiving olaparib experienced an improved PFS (HR 0.43, 95% CI 0.29–0.63) [72]. Compared with hormone receptor-positive, HER2-negative patients the triple negative patients had a greater beneifit from olaparib treatment. In the TNBC gBRCA mutated subgroup of the EMBRACA trial, talazoparib also improved PFS (HR 0.60, 95% CI 0.41–0.87). Further details of these studies are discussed elsewhere. It should be noted that the comparator single-agent chemotherapy options did not include either taxanes or platinums in these studies, so the trial realistically only compared PARP inhibitors against second-line therapies. It is unknown how PARP inhibitors would compare with first-line drugs (See "Systemic treatment for metastatic breast cancer: General principles", section on 'PARP inhibition for BRCA carriers').

There are several other PARP inhibitors in clinical development [73–79]. For example, veliparib (ABT-888) was evaluated (single arm phase II trial) in combination with the alkylating agent temozolomide in a group of 41 women with advanced TNBC (of whom 8 had a *BRCA* germline mutation) [79]. While the overall response and clinical benefit rates were 7 and 17% across the entire study population, a clear improvement was noticed in patients with *BRCA* mutations with an overall response and clinical benefit rates of 37.5 and 62.5%, respectively. The results of the ISPY trial that evaluated the combination of veliparib plus carboplatin when combined with standard chemotherapy as part of a neoadjuvant treatment program in women with TNBC are discussed elsewhere (See "Choice of neoadjuvant chemotherapy for HER2-negative breast cancer", section on 'Special considerations for triple-negative disease').

There is mechanistic rationale for use of PARP inhibition as anticancer therapy. PARP is involved in the molecular events leading to cell recovery from DNA damage. The inhibition of PARP1 leads to an accumulation of double-strand DNA breaks. Normally, these breaks are repaired by the *BRCA* pathway-dependent homologous recombination mechanism [80]. There is the hypothesis that the combination treatment of PARP inhibition with DNA-damaging chemotherapeutics would affect tumors lacking *BRCA* function [73,81–83].

Chemotherapy-naive patients, or those with progression on PARP inhibitors;

Although we typically start with a poly (ADP-ribose) polymerase (PARP) inhibitor for metastatic disease in those with germline *BRCA* mutations who have had chemotherapy in the (neo)adjuvant setting, chemotherapy is the preferred option for those who have never been exposed to chemotherapy (in the early or metastatic settings); or for those who have experienced progression on a PARP inhibitor; or for those with rapidly progressive visceral disease, as discussed above.

When administering chemotherapy, our approach is as follows:

• For the subset of patients with *BRCA*-associated breast cancers that also express PD-L1, we recommend nabpaclitaxel/atezolizumab as the initial chemotherapy regimen, over other chemotherapy options (See 'PD-L1-positive tumors' above).

• However, for those with *BRCA*-associated, PD-L1-negative tumors, both platinums and taxanes are considered appropriate options for chemotherapy, with a choice driven by scheduling and toxicity considerations. Guidelines from the American Society of Clinical Oncology have, however, suggested platinum agents over taxanes for *BRCA1/2* carriers with advanced breast cancers [84], based on a randomized trial of carboplatin versus docetaxel in first-line therapy of TNBC described below.

The TNT randomized trial directly compared carboplatin and docetaxel in the first-line treatment setting for women with metastatic TNBC. Overall response rates were similar in the overall group, but among the 43 women with a known *BRCA1/2* mutation, carboplatin resulted in a higher response rate (68 versus 33%; absolute difference 35 percent, 95% CI 6.3–63.1%) and PFS (6.8 versus 4.4 months; absolute difference 2.6 months, 95% CI 0.11–5.12 months) [85]. However, the trial had a crossover design, and no statistically significant OS difference was seen (12.8 months, 95% CI 10.6–15.3; and 12 months, 95% CI 10.2–13) for those allocated carboplatin or docetaxel, respectively, suggesting that either agent may be administered first, without compromising outcomes.

Grade $\geq$3 toxicities among those receiving carboplatin versus docetaxel included febrile neutropenia in 2 and 20 percent, diarrhea in 3 and 7 percent, and thrombocytopenia in 7 and 0 percent, respectively. Any-grade toxicities for carboplatin versus docetaxel included alopecia in 35 and 89 percent, arthralgias in 4 and 21 percent, diarrhea in 34 and 64 percent, and peripheral neuropathy in 33 and 71 percent, respectively. Fatigue occurred in 95 percent in both arms.

4.3 Sacituzumab Govitecan

Trop-2 is expressed in the majority of TNBCs. Sacituzumab govitecan is an antibody-drug conjugate that targets Trop-2 for the selective delivery of SN-38, the active metabolite of irinotecan. It is approved by the Food and Drug Administration (FDA) for the treatment of adult patients with metastatic TNBC who have received at least two prior therapies for metastatic disease [86]. Severe neutropenia and diarrhea may occur with this agent, including cases of neutropenic colitis. Management of enterotoxicity of this agent is discussed elsewhere.

In a single-arm trial of 108 patients with previously treated metastatic TNBC (median of three previous treatments), the objective response rate to sacituzumab govitecan was 34 percent, with a median PFS of 5.5 months, duration of response of 9.1 months, and OS of 13 months [87]. Grade $\geq$3 adverse events included neutropenia (42 percent), leukopenia (11 percent), anemia (11 percent), and diarrhea (8 percent).

Pembrolizumab for tumors with high TMB or MSI-H/dMMR tumors—The immune checkpoint inhibitor pembrolizumab is approved by the FDA for the treatment of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors, as well as tumors with high tumor mutational burden (TMB; $\geq$10 mutations/megabase), that have progressed following prior treatment and that have no satisfactory alternative treatment options. We offer pembrolizumab for immunotherapy-naïve patients with these molecular markers, but only when chemotherapy (and PARP inhibitors, for *BRCA* carriers) is no longer effective or tolerated.

We acknowledge, in discussion with patients, that the trials supporting the approval of pembrolizumab for these indications did not include breast cancer patients, but efficacy was demonstrated in other cancer types, including cervical, endometrial, and ovarian cancer.

5. Investigational Options

Several promising treatment options are under active clinical investigation but should not be used at this time outside of a clinical trial. These are discussed below.

• Epidermal growth factor receptor inhibitors: To date, cetuximab as an anti-EGFR monoclonal antibody is evaluated in three phase II clinical trials, in combination with chemotherapy in advanced TNBC and have shown it has only modest activity [88–90]. Similarly, trials of EGFR inhibitors have not shown clinical impact in TNBC. These are not recommended for treatment of TNBC.

• Androgen receptor inhibitor — The androgen receptor (AR) is expressed in both normal and malignant breast tissue [91] with an expression rate luminal hormone-receptor positive breast cancer of up to 91% and of about 30% in TNBC [92]. So far, prognosis of AR-positive TNBC seems to be more favourable than the one of AR-negative TNBC [6]. Antitumor activity of AR inhibition in advanced TNBC is described in several studies with for example a six-month clinical benefit rate (CBR) of 19 percent for AR antagonist bicalutamide in metastastic AR positive TNBC [93]. Another trial was looking for efficacy of the AR inhibitor enzalutamide [94]. Two complete responses and five partial responses were observed. CBR at 16 weeks was 35 percent (95% CI 24–46), and was 39 percent (95% CI 27–53) in AR-positive tumors.

• Angiogenesis inhibitor — Angiogenesis is considered to be an important target for cancer therapy. However, to date, prospective studies have not shown that incorporation of angiogenesis inhibitors has an impact on overall survival (OS) for women with TNBC. Therefore, we do not administer an angiogenesis inhibitor in the adjuvant or metastatic setting for these patients. We do encourage the participation in well-designed clinical trials. Of agents in this class, bevacizumab has been the most widely studied. Unfortunately, data consistently show that while incorporation of bevacizumab can improve PFS, there is virtually no impact on OS [95–99]. This appears to be true even for patients with TNBC when bevacizumab was administered in the adjuvant [98] and first-line metastatic settings [97].

• Immunotherapy and chemotherapy combinations in early-stage disease — Evidence that this approach may be useful in early breast cancer comes from a small neoadjuvant trial that found improved pathologic complete response with the anti-programmed cell death protein-1 (PD-1) antibody pembrolizumab added to anthracycline/taxane-based chemotherapy [100]. However, autoimmune complications were seen, and a more definitive trial must be completed before incorporating immune checkpoint inhibition into non-metastatic breast cancer.

6. Conclusions

Triple-negative breast cancer (TNBC) lacks expression of the three most commonly evaluated biomarkers (the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) protein) and are both typically higher grade and are more likely to be diagnosed clinically rather than mammographically than ER-positive cancers. While the triple-negative clinical phenotype is heterogeneous, the basal-like molecular subtype comprises a large proportion, particularly for breast cancer susceptibility gene 1 (*BRCA1*)-associated breast cancer.

In the non-metastatic disease the principles that apply to the surgical treatment and use of radiation therapy in breast cancer, and the systemic treatment approach in both the neoadjuvant and adjuvant settings, are similar in TNBC and other HER2-negative subtypes. For patients with TNBC and either a tumor size >0.5 cm or pathologically involved lymph nodes (regardless of tumor size), chemotherapy is recommended (Grade 1B), to be administered in either the adjuvant or neoadjuvant setting. Risk of recurrence increases on a continuum, such that larger tumors are more likely to derive benefit from chemotherapy than smaller ones. In general, patients with tumors of 1 to 5 mm do not need chemotherapy, although this issue has to be discussed carefully with such patients, given that a small benefit cannot be ruled out. For most patients receiving chemotherapy for non-metastatic TNBC an anthracycline- and taxane-based combination is the treatment of choice, such as dose-dense doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) rather than a non-anthracycline-based treatment (Grade 2B). Although no regimen has provided to be superior to AC-T, the non-anthracycline-based regimen docetaxel and cyclophosphamide (TC) is an appropriate alternative for patients who have indications for chemotherapy but have lower-risk disease. For patients who have completed a full course of neoadjuvant treatment, additional chemotherapy in the adjuvant setting for those with residual disease is discussed. Despite a higher risk of relapse compared with other breast cancer subtypes, there are no specific post-treatment surveillance guidelines for patients with TNBC.

In the metastatic setting, combination chemotherapy may be appropriate for those with extensive or rapidly progressive visceral disease, in whom the higher chance of response is thought to outweigh the higher risks of toxicity. However, there are no prospective data that show combination chemotherapy improves overall survival (OS) compared with single-agent sequential cytotoxic chemotherapy. In the metastatic TNBC setting, for those who are not in visceral crisis, therapy depends on prior treatment history, programmed cell death ligand 1 (PD-L1) expression, and germline *BRCA* mutation status. For PD-L1-positive TNBC in *BRCA*-wildtype patients, as well as in chemotherapy-naive *BRCA* carriers, the combination of an immune checkpoint inhibitor and chemotherapy as initial

treatment for metastatic disease is recommended rather than single-agent chemotherapy (Grade 1B). The checkpoint inhibitor atezolizumab is EMA approved for use with nabpaclitaxel in advanced TNBC with PD-L1 $\geq$1 percent, based on observed benefits in OS. Additionally, pembrolizumab is US Food and Drug Administration approved in combination with chemotherapy for patients with metastatic TNBC whose tumors express PD-L1 with a Combined Positive Score $\geq$10. For PD-L1-negative TNBC in *BRCA*-wildtype patients, as well in chemotherapy-naive *BRCA* carriers, single-agent chemotherapy remains the preferred initial treatment option and is discussed elsewhere. Pembrolizumab is an appropriate later-line option for those whose tumors have either high tumor mutational burden or are microsatellite instability high or mismatch repair deficient. For *BRCA* carriers with previous exposure to chemotherapy in the neoadjuvant/adjuvant setting, we suggest an inhibitor of poly(ADP-ribose) polymerase (PARP) as initial treatment for metastatic disease (Grade 2B), although chemotherapy is also acceptable, particularly in those with PD-L1-positive disease, in whom chemotherapy plus an immune checkpoint inhibitor is an appropriate alternative. Sacituzumab govitecan is an antibody-drug conjugate that targets Trop-2 for the selective delivery of SN-38, the active metabolite of irinotecan, and is an option for patients with metastatic TNBC who have received at least two prior therapies for metastatic disease.

Author Contributions

MF, SK, MW and DS designed the manuscript idea. MF, SK, MW and DS analyzed the literature data. DF, CR, GR and CK reviewed the manuscript. DF, CR, GR and CK edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of Interest

MF is serving as one of the Editorial Board members of this journal and the guest editor for the special issue titled "Breast Cancer". We declare that MF had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Enrique Hernandez. The other authors declare no conflict of interest.

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