Review Article

A narrative review of chemotherapy in advanced triple negative breast cancer

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Abstract: Triple-negative breast cancers (TNBCs) are a heterogeneous group of aggressive tumors with high relapse rates and propensity to develop visceral or brain metastasis, representing 15% of the breast carcinomas. Their overall survival (OS) has remained static over the past 20 years. Cytotoxic chemotherapy (CT) was the only treatment option for all stages of TNBC until the first targeted therapy Olaparib was approved in patients with germline BRCA-mutation. This unsystematic narrative review is aimed at presenting an overview of the use of CT in advanced/metastatic triple-negative breast cancer (mTNBC) in these times when the personalized medicine era is slowly reaching TNBC with new therapeutic options. The information used to write it was collected from the published literature, treatment guidelines and hand searches of retrieved literature references. Standard anthracycline-based CT is the treatment of choice as first-line for metastatic breast cancer patients not previously treated with anthracyclines. First-line single-agent taxane is offered to patients who have received prior adjuvant anthracyclines or presented anthracycline failure, or as the second line in patients who have received prior anthracyclines in the metastatic setting. TNBC tumors that carry the germline BRCA1/2 mutations can benefit from the targeted use of platinum. Other drugs as eribulin, capecitabine, platinum, and gemcitabine, that have proven efficacy as single-agents or in combination as further lines, but the sequencing is not established. Combination chemotherapy can be considered when the patient presents a severe organ dysfunction aiming to achieve disease stabilization. CT remains the cornerstone treatment for mTNBC which not express targetable receptors or defective molecular pathways, and as a counterpart for targeted or immune therapies; given the limited access to these last in most countries, CT will continue in the landscape for much longer.

Keywords: Advanced; metastatic; triple-negative; breast-cancer; chemotherapy

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Introduction

Triple-negative breast cancer (TNBC) represents 15% of breast carcinomas (1). It is defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PR) on immunohistochemistry, and a lack of human epidermal growth factor receptor 2 (HER-2) overexpression/amplification (2). TNBC is more prevalent in women of African ancestry and in younger patients (3).

TNBCs are a heterogeneous group of tumors characterized by an aggressive nature, high relapse rates, and a peak of recurrence within the first three years after diagnosis. TNBC patients with residual disease after neoadjuvant chemotherapy are six times more likely to have a recurrence and have twelve times higher risk of dying of metastatic disease (4,5).

The lack of efficacious therapy within the metastatic TNBC (mTNBC) cohort, combined with the propensity to develop visceral or brain metastasis has translated into an overall survival (OS) that has remained static over the past 20 years (6). In this setting, the median OS is less than one year, usually, after 1 or 2 lines of chemotherapy, meaningful responses are rare, and all patients eventually die from their disease (7).

In a recent retrospective observational, population-based study of 3,271 Ontarian women diagnosed with TNBC from 2012 to 2016, 5.8% had stage IV, showing a poor 5-year OS rate of 7.4% compared to 93.3%, 78.9%, 47.2% for stage I, II, and III, respectively. The most common first-line systemic therapy was single-agent taxane, while the most common second-line regimens were capecitabine and combination gemcitabine-platinum (8).

Cytotoxic chemotherapy (CT) was the only treatment option for all stages of TNBC until the FDA approved the first targeted therapy Olaparib a poly (ADP-ribose) polymerase (PARP) inhibitor for the treatment of locally advanced or metastatic HER2-negative breast cancer in patients with germline BRCA-mutated (*gBRCAm*) in January 2018 (9,10). In March 2019, the FDA approved Atezolizumab, the first immune checkpoint inhibitor indicated for unresectable locally advanced or mTNBC expressing PD-L1 ≥1%, in combination with nab-paclitaxel (11).

However, with most TNBCs lacking targetable receptors, chemotherapy is still the predominant treatment option for patients with mTNBC (8). Given the scarce new agents that have been approved for this subset of patients, single-agent chemotherapy continues to serve as the backbone of mTNBC treatment, aiming to prolong the disease-free and OS and increase the quality of life reducing or stabilizing the burden of disease and other cancer-related symptoms (6).

Although the personalized medicine era is slowly reaching TNBC with new therapeutic options, CT largely remains the cornerstone treatment for TNBC, particularly given the limited access to targeted therapies and immunotherapies in most countries. This narrative review is aimed at presenting an overview of the use of chemotherapy in advanced/metastatic triple-negative breast cancer (mTNBC). Other reviews within this series are dedicated to the discussion of the use of targeted therapies and immunotherapy in TNBC. We present the following article in accordance with the narrative review checklist (available at: http://dx.doi.org/10.21037/pcm-20-69).

Methods

This is an unsystematic narrative review; the information used to write it was collected from the published literature, treatment guidelines and hand searches of retrieved literature references.

Discussion

TNBC molecular subtypes

In 2000 Perou *et al.* developed a classifying system for breast cancer based on their gene expression patterns (12). They identified five molecular subtypes: Luminal A, Luminal B, Her-2 enriched, Normal-like and Basal-like. The gene expression cluster characteristic of basal epithelial cells included keratin 5, keratin 17, integrinb4, and laminin. Approximately 70% of TNBC are basal-like, leading to a misconception that these two terms were synonymous, but they are not because considerable discordance exists, approximately 25 percent (12-14).

In 2011 Lehmann *et al.* (5) analyzed TNBC gene expression profiles identifying six molecular subtypes, which latter in 2016 were refined into four (TNBCtype-4): Basal-like 1 (BL1), Basal-like 2 (BL2), Mesenchymal (M), and Luminal Androgen Receptor (LAR); displaying different clinical characteristics. BL1 tumors showed higher grade, lower stage, better prognosis, and displayed the greatest likelihood of achieving a pathological complete response (PCR) after NAT (41%). BL2 tumors had the highest average percentage of lymphocytes (23%) and the least likelihood of achieving a PCR after NAT (18%). LAR tumors noticed increase regional spread and preferential bone metastasis. Lobular carcinomas were exclusive LAR subtype. M tumors have the least average percentage of lymphocytes (9%) and preferentially metastasize to the lung. Metaplastic carcinomas were either M or BL2 (5).

The immunomodulatory component (IM) of the tumor describes the part that is highly enriched for immune cell markers and signaling and has high levels of the immune checkpoint regulatory genes, given substantial infiltrating lymphocytes; now is considered as a descriptor of the immune state of the tumor rather than an independent subtype (5).

This knowledge has led to promising therapeutic

strategies, including modified chemotherapy approaches targeting the DNA damage response, angiogenesis inhibitors, immune checkpoint inhibitors, or anti-androgens (1).

Germline mutations associated

An important number of TNBCs arise as a result of inherited mutations in BRCA1 and BRCA2. The triple-negative phenotype is displayed in approximately 60% to 80% of breast cancers diagnosed on BRCA1 mutation carriers. In patients with Ashkenazi Jewish background diagnosed with TNBC the BRCA1 mutation is presented in 29%. In patients diagnosed with TNBC at a young age, this mutation is found in 20%, disregarding their BC family history. The germline BRCA2 mutation is presented in patients diagnosed with TNBC in 9% of those with Ashkenazi Jewish ancestry and 3.9% patients with a median age at diagnosis of 51 years (15).

In a large series, 1,824 TNBC tumors of patients unselected for cancer family history were analyzed for germline mutations noticing that 11.2% carried germline BRCA1 and BRCA2 mutations (15).

The term "BRCAness" describes a group of tumors mimicking BRCA1 or BRCA2 loss, due to a deficiency in homologous recombination repair. BRCA-deficient cells utilize defective DNA-repair pathways, which lead to increased genomic instability, conferring them sensitivity to DNA damaging agents (16). This knowledge is the rationale behind clinical trials focusing on platinum salts, which lead to DNA cross-link strand breaks (7).

Treatment duration

The standard of care is to continue chemotherapy until disease progression or treatment-limiting toxicity occurs (6). This approach is supported by two meta-analysis showing statistically significant modest OS improvement for women randomized to longer durations of chemotherapy (17,18).

The latest meta-analysis to address this question with most contemporary chemotherapy regimens, included 11 randomized controlled trials (RCTs), representing 2,269 patients with metastatic breast cancer (MBC). It demonstrated that extending chemotherapy reduces the risk of death 9% (HR, 0.91; 95% CI, 0.84 to 0.99; P<0.046) and the risk of progression 36% (HR, 0.64; 95% CI, 0.55 to 0.76; P<0.001) when compared with shorter duration of chemotherapy (18).

However, Gennari *et al.* only included three RCTs evaluating taxane-based regimens. More recently, the Stop & Go study compared paclitaxel plus bevacizumab regimen deliver to an intermittent against continuous fashion, in first-line treatment of HER2-negative MBC of which 17% of which were mTNBC. The study authors concluded that to change the tumor biology for long-lasting efficacy more than four successive chemotherapy cycles are needed (18).

MBC is considered an incurable disease. As such, the treatment with a palliative intent focuses on extending survival and improving quality of life. Chemotherapy is aimed at controlling the cancer, rather than eradicating it. Therefore, it is important to carefully weigh the survival benefit against the potential added toxicities and detrimental impact on quality of life when considering a prolonged duration of chemotherapy (17).

Combinations versus single-agent

For more than a decade, single-agent chemotherapy has been the standard of care in the treatment of mTNBC (19). First-line single-agent taxane is offered to patients who have received prior adjuvant anthracyclines or presented anthracycline failure, or as second line in patients who have received prior anthracyclines in the metastatic setting (20).

Anthracycline failure is defined as:

(I) Progression while on an anthracycline-containing regimen,
(II) Relapse within 12 months of discontinuing anthracycline-containing adjuvant therapy, or
(III) Inability to receive further anthracycline-containing treatment because of toxicity, including potential cardiotoxicity (20).

This approach is based on a meta-analysis of 37 trials, which included 7,093 women, intended to investigate the effect of more versus less-intensive chemotherapy comparing single drug regimens (possibly less active) with regimens containing more than one drug (possibly more active). Even though this meta-analysis found an OS and PFS improvement (9% and 22%, respectively) with the use of combination regimens when compared with single agent regimens; in the subgroup analysis, single-agent Taxane appeared to have an advantage in OS, PFS, and ORR when compared with non-taxane, non-anthracycline combination regimens and when added to a combination regimen. Single-agent Taxane showed a statistically significant benefit of 17% on survival, 25% benefit on progression, and 26% on response rate. Importantly, combination chemotherapy was associated with significantly greater nausea and

vomiting (OR 1.65), alopecia (OR 1.55), and leukopenia (OR 1.45) toxicities which would be expected to worsen quality of life (21).

There are some cases in which combination chemotherapy is often considered. For example, in a visceral crisis, which describes a severe organ dysfunction involving rapid disease progression, severe symptoms and alteration in laboratory values (22), combination chemotherapy may be a reasonable option. In this scenario, the use of reliably effective therapies is imperative to obtain significant treatment response or disease stabilization in a short amount of time (6).

Anthracycline-naïve metastatic setting

Standard anthracycline-based chemotherapy is the treatment of choice as first-line chemotherapy for metastatic breast cancer patients not previously treated with anthracyclines (23).

Doxorubicin (Adriamycin)

Doxorubicin inhibits the biosynthesis of macromolecules intercalating itself in the DNA and blocking the enzyme topoisomerase II progression, stopping the replication process. Another mechanism is causing cell membrane and DNA damage due to free-radicals generation. The cardiotoxicity associated with doxorubicin can be acute or chronic, and it is dose-limiting. Acute cardiotoxicity manifests as rhythm disturbances, electrocardiographic abnormalities, and reversible decreased left-ventricular ejection fraction (LEVF). Chronic cardiotoxicity ultimately results in irreversible congestive cardiomyopathy. Cardiac hearth failure incidence is approximately 3% at cumulative dose of 400 mg/m^2, 7% at 550 mg/m^2 and 18% at 700 mg/m^2 (24).

Given concerns regarding cardiotoxicity, the widespread use of anthracyclines in the neoadjuvant and adjuvant setting limits their use as first-line therapy in metastatic disease (25). Its use is preferred in anthracycline-naïve patients and those without risk factors for anthracycline-cardiotoxicity, such as heart disease history, extremes in age, race, exposure to mediastinal radiation, and the cumulative dose received (24).

Doxorubicin is frequently used in combination regimens, paired with Cyclophosphamide (CFA) or Taxanes.

The European Organization for the Research and Treatment of Cancer (EORTC) Breast Group in collaboration with the Early Clinical Study Group evaluated the activity of 6 cycles of Doxorubicin plus Paclitaxel (AT) scheme with Doxorubicin plus CFA (AC) combination as first-line chemotherapy for MBC patients, anthracycline and taxane naïve, in a randomized phase III study. The AT regimen failed to improve the response rate (58% versus 54%), progression-free survival (HR 1.06), or OS (HR 0.90). The patients with Er negative tumors represented 35% of the study population; however, the ER status was not evaluated as a predictor of outcome. Based on these results, standard anthracycline-CFA chemotherapy remains the treatment of choice in this setting (23).

The American Intergroup Trial E1193 tested whether the combination of Doxorubicin plus Paclitaxel (AT) proves superior to sequential, single-agent therapy with the same agents as first-line chemotherapy for MBC patients, anthracycline and taxane naïve. Combination therapy resulted both in a superior overall response rate (47%) and TTF (8 months), but it failed to improve OS (22 months). No difference in cardiotoxicity was noted in patients receiving single-agent doxorubicin and combination therapy. Doxorubicin plus Paclitaxel regimen did not increase the quality of life. 26% of the study population was ER-negative; this feature was a predictor for impaired OS with a RR 1.7, P=0001. In contrast, the treatment regimen did not show to be a significant predictor of survival. This study provided evidence that sequential chemotherapy is a reasonable option for MBC treatment (26).

Looking for a more effective combination, a phase 3 RCT compared Doxorubicin plus Docetaxel (AT-Docetaxel) against Doxorubicin plus CFA (AC) for at least eight cycles in MBC patients with no prior exposure to anthracyclines. The AT-Docetaxel regimen showed significant improvement in response rate (59% versus 47%) and time to progression (37.3 versus 31.9 weeks), but no survival difference (22.5 versus 21.7 months). Patients presented no significant difference in cardiac toxicity between the groups but more myelosuppression with AT-docetaxel. QoL was the same within both regimens. This study proved that Doxorubicin plus Docetaxel combination is an option for first-line therapy for MBC patients with rapidly progressive visceral disease. Biomarkers were not reported in this trial (27).

In the second-line scenario, a phase 3 RCT compared Docetaxel with Doxorubicin in anthracycline and taxane naïve patients after CMF progression. Even though patients in the Docetaxel arm presented a significantly increased response rate (48% versus 33%), the final endpoint time to progression (26 versus 21 weeks) did not reach statistical

significance. No difference in OS was noticed (28).

Epirubicin

Epirubicin is a 4'-epimer of doxorubicin with reorientation of the hydroxyl group in the 4' position of the daunosamine ring (29); that retains antineoplastic activity but presents a reduced potential for cardiac damage, less gastrointestinal toxicity, myelosuppression, and chronic cardiotoxicity.

The last update of the Practice Guidelines Initiative of Cancer Care Ontario in 2010 provided a rationale for the choice between doxorubicin and epirubicin in the MBC setting. They performed a meta-analysis, including eleven published reports and two abstracts. They found no difference in response rate (RR 1.04), complete response rate (RR 1.05), or deaths at one year (RR 1.01) between epirubicin and doxorubicin when given at equal doses. The meta-analysis showed a tendency for less incidence of congestive heart failure (RR, 0.38) and a significant difference in the incidence of another cardiotoxicity (ECG changes, decrease in LVEF, increase in pre-ejection period/LV pre-ejection period ratio) with an RR =0.43 (P=0.004) in patients treated with epirubicin. Epirubicin was also better tolerated with less neutropenia, nausea and vomiting, and alopecia (30).

Epirubicin has been evaluated in combination with CFA and Docetaxel (31) with success, but the scheme epirubicin plus paclitaxel, it is not recommended outside of a clinical trial (32).

Pegylated liposomal doxorubicin (PLD)

PLD is doxorubicin encapsulated in sterically stabilized liposomes by grafting polyethylene glycol onto the surface. PLD has a longer circulation half-life than doxorubicin (73.9 hours versus 10 minutes), leading to greater tumor tissue uptake and reduced free doxorubicin plasma levels, which reduce toxicity.

PLD is a therapeutic option for MBC patients with increased cardiac risk or who have received anthracyclines in the past; it can minimize some of the acute adverse effects of the non-liposomal anthracyclines with a convenient q4w infusion schedule.

PLD use is support by a phase 3 non-inferiority RCT, which compared PLD 50 mg/m^2 every four weeks with Doxorubicin 60 mg/m^2 every three weeks in patients with IIIB or IV BC previously untreated, prior anthracycline adjuvant CT was permitted, with a cumulative doxorubicin (or doxorubicin-equivalent) dose of posomal a^2. Patients with a history of ischemic heart disease or arrhythmia on current treatment, a valvular disease with clinical signs or abnormal LVEF, were excluded. The study included patients with cardiac risk factors defined as prior mediastinal irradiation, age ≥65 years, history of heart disease (previous myocardial infarction, arrhythmia or angina, not requiring treatment), or had hypertension or diabetes requiring medical treatment.

The risk of developing cardiotoxicity was significantly lower for patients receiving PLD (Doxo versus PLD, HR =3.16). The risk of developing cardiotoxicity. For patients with prior exposure to anthracyclines as adjuvant therapy was seven-fold higher with doxorubicin. OS (HR 0.94), progression-free survival (HR 1), overall response rate, and median DoR were similar in both study arms. Confirming that PLD and doxorubicin have comparable efficacy, with different safety profiles, PLD showed a significantly reduced cardiac toxicity compared with doxorubicin (33) (*Table 1*).

Anthracycline-pretreated or anthracycline-contraindication metastatic setting

Taxanes

Paclitaxel

A National Cancer Institute (NCI) program screening natural compounds discovered Paclitaxel, isolated from Pacific yew tree (Taxus brevifolia) bark. Paclitaxel binds to tubulin stabilizing the microtubules and arresting the cell cycle in G2M (34). Paclitaxel is highly hydrophobic, and thus the synthetic solvents, Cremophor (polyethylated castor oil) and ethanol, are used to enable its parenteral administration (35). Single-agent Paclitaxel is considered standard first or second-line chemotherapy in MBC patients who either have failed or are not eligible to receive Anthracycline-based regimens.

Paclitaxel antitumor activity is influenced by its dosing schedule and is delivered weekly. The weekly administration of paclitaxel is based on evidence from a phase 3 RCT, the Cancer and Leukemia Group B protocol 9840, which showed that weekly compared to every three week infusion significantly improved overall response rates from 29% to 42%, extended time to progression from 5 to 9 months, and led to almost a doubling of OS from 12 to 24 months. Although this efficacy improvement resulted in an increase in the development of grade 3 sensory and motor neuropathy, overall quality-of-life was not affected. This trial began in 1998, included 735 women, of which 25% were ER-negative, 29% were PR-negative, and 24% were HER 2-positive, but the outcomes were not evaluated in biomarkers subgroups (36).

Table 1 Randomized clinical trials for metastatic breast cancer anthracyclines-treatment

Author	Trial	Primary objective	Patients characteristics	Experimental arm	Control arm	Toxicity (experimental *vs.* control arm)	Progression (experimental *vs.* control arm)	Response (experimental *vs.* control arm)	Survival (experimental *vs.* control arm)
Chan, 1999 (28)	Phase 3 RCT. Multicentre open-label	TTP	326 patients with MBC who had received previous alkylating agent CT (CMF). 2nd line Prior anthracyclines or taxanes were not allowed. Biomarkers not reported	Docetaxel 100 mg/m^2 every 3 weeks for a maximum of seven treatment cycles (46% of patients completed 7 cycles, P=0.027)	Doxorubicin 75 mg/m^2 for a maximum of seven treatment cycles (34% of patients completed 7 cycles)	TRAEs discontinuation: 12% *vs.* 16%. Toxic death: 3% *vs.* 1.2%. CHF: 0 *vs.* 3.7%. LVEF decrease: 8% *vs.* 29%. g3–4 neutropenia: 94% *vs.* 89% (P≤0.05). FN: 6% *vs.* 12% (P≤0.05). Fluid retention: 60% *vs.* 4%. g3–4 GI toxicity (nausea, vomiting, stomatitis, diarrhea): 22% *vs.* 40% (P≤0.05). g3–4 neuropathy: 10% *vs.* 0	mTTP: 26 *vs.* 21 weeks (NS)	ORR: 48% *vs.* 33% (P=0.008)	mOS: 15 *vs.* 14 mos
Biganzoli, 2002 (23)	Phase 3 RTC. Multicentre Open-Label	PFS	275 patients with MBC. 1st line. Anthracycline and taxane naïve. ≥ ntmos since prior adjuvant CMF allowed % ER (–) AT 39; AC 31. % PR (–) AT 38: AC 33	AT. Doxorubicin 60 mg/m^2 plus Paclitaxel 175 mg/m^2 every 3 weeks for a maximum of six cycles	AC. Doxorubicin 60 mg/m^2 plus Cyclophosphamide 600 mg/m^2 every 3 weeks for a maximum of six cycles	FN: 32% *vs.* 9% (P=0.001). g4 Neutropenia: 89% *vs.* 81%. GI (nausea, vomiting, stomatitis): 17% *vs.* 27%. Neurotoxicity: 3% *vs.* 0. CHF: 2% *vs.* 1%. LVEF decline: 27% *vs.* 14%. Toxic death: 0 *vs.* 1%	mPFS: 6 *vs.* 6 mos, HR 1.06 (P=0.65)	ORR: 58% *vs.* 54% (P=0.51). mDoR: 5.4 *vs.* 5 mos	mOS: 20.6 *vs.* 20.5 mos, HR 0.90 (P=0.49)
Nabholtz, 2003 (27)	Phase 3 RCT. Multicentre Open-Label	TTP	429 patients with previously untreated MBC. 1st line. (neo)-adjuvant CT non-anthracycline-containing allowed; Prior taxane not allowed; Biomarkers not reported	AT. Doxorubicin 50 mg/m^2 plus Docetaxel 75 mg/m^2 on day 1, every 3 weeks for up to eight cycles (55.4% of patients completed 8 cycles)	AC. Doxorubicin 60 mg/m^2 plus Cyclophosphamide 600 mg/m^2 on day 1, every 3 weeks for up to eight cycles (47.6% of patients completed 8 cycles)	TRAEs discontinuation: 14% *vs.* 13%. LVEF decline: 4% *vs.* 8%. g3–4 Neutropenia: 97% *vs.* 88% (P=0.01). FN: 33% *vs.* 10% (P<0.001). Toxic death 1 *vs.* 4 patients. Prophylactic G-CSF: 37% *vs.* 13%. Diarrhea: 8% *vs.* 1%. CHF: 3% *vs.* 4%. LVEF decrease ≥20% from baseline: 6% *vs.* 13% (P=0.03)	TTP: 37.3 *vs.* 31.9 weeks (P=0.014); HR 1.32	ORR: 59% *vs.* 47% (P=0.009)	Mos: 22.5 *vs.* 21.7 mos (P=0.26)
O'Brien, 2004 (33)	Phase 3 RCT. Multicentre Open-Label Non- inferiority	PFS	509 patients with IIIB or IV MBC previously untreated 1st line. >12 mos since prior adjuvant anthracycline therapy was permitted. Cumulative doxorubicin (or doxorubicin-equivalent) dose of ≤300 mg/m^2. Patients with cardiac risk factors (?) were allowed. % ER (–) PDL 21.2; Dox 23.1	(PLD) Pegylated liposomal doxorubicin 50 mg/m^2 every 4 weeks	Doxorubicin 60 mg/m^2 every 3 weeks	Cardiotoxicity risk of Doxorubicin. HR 3.16, (P<0.001). LVEF 3.9% *vs.* 18.8%. Symptomatic CHF: 0 *vs.* 3.9%. g3 HFS: 17 *vs.* 0. g3 Gastrointestinal (nausea, vomiting, mucositis, stomatitis, diarrhea) 13% *vs.* 13%. g3–4 Neutropenia 2% *vs.* 7%. Prophylactic G-CSF: 5.1% *vs.* 8.6%. FN: 2 *vs.* 8 patients. Death: 2 *vs.* 3 patients	mPFS: 6.9 *vs.* 7.8 mos, HR 1.00	ORR: 33% *vs.* 38%. mDoR: 7.3 *vs.* 7.1 mos	mOS 21 *vs.* 22 mos; HR 0.94

Table 1 (*continued*)

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Author	Trial	Primary objective	Patients characteristics	Experimental arm	Control arm	Toxicity (experimental *vs.* control arm)	Progression (experimental *vs.* control arm)	Response (experimental *vs.* control arm)	Survival (experimental *vs.* control arm)
Sledge, 2003 (26) Intergroup trial E1193	Phase 3 RCT. Multicentre Open-Label Non-inferiority	ORR	731 patients with MBC. 1st line. No prior anthracycline or taxane allowed. ≥6 mos since prior adjuvant CT. % ER (–)/unknown A:25/29; T: 27/26 and AT 26/30	(AT) Doxorubicin 50 mg/m^2 plus Paclitaxel 150 mg/m^2/ 24 hours	Doxorubicin 60 mg/m^2 or Paclitaxel 175 mg/m^2/24 hours (patients on single-agents were crossed over to the other agent at progression)	AT *vs.* T *vs.* A. Leukopenia: 55% *vs.* 60% *vs.* 50%. Infection: 12.5% *vs.* 8.3% *vs.* 4.1%. Cardiac: 8.6% *vs.* 3.7% *vs.* 8.7%. Neurologic: 10.7% *vs.* 3.7% *vs.* 1.6%. GI (vomiting, diarrhea, stomatitis): 13.5% *vs.* 7% *vs.* 16%. Death: 1.6% *vs.* 1.6% *vs.* 2.5%	AT *vs.* T *vs.* A. mTTF: 8 *vs.* 6 *vs.* 5.8 mos. A *vs.* T (P=0.68). A *vs.* AT (P=0.003). T *vs.* AT (P=0.009)	AT *vs.* T *vs.* A. ORR: 47% *vs.* 34% *vs.* 36%. A *vs.* T (P=0.84). A *vs.* AT (P=0.007). T *vs.* AT (P=0.004)	AT *vs.* T *vs.* A. mOS: 22 *vs.* 22.2 *vs.* 18.9 mos (all NS)
Langley, 2005 (32) AB01 trial	Phase 3 RCT. Multicentre Open-Label	PFS	705 patients with previously untreated MBC. 1st line. ≥6 mos since prior adjuvant CT allowed. Limited anthracycline cumulative dose (*)	(EP) Epirubicin 75 mg/m^2 and Paclitaxel 200 mg/m^2 every 3 weeks for 6 cycles	(EC) Epirubicin 75 mg/m^2 and Cyclophosphamide 600 mg/m^2 every 3 weeks for 6 cycles (71% of patients in both arms received 6 cycles)	TRAEs discontinuation: 18% *vs.* 7% (P=0.025). g3–4 toxicity: 48% *vs.* 38%. g3–4 mucositis: 6% *vs.* 2% (P=0.0006). g3–4 neurotoxicity: 5% *vs.* 1%, (P<0.0001). Cardiotoxicity 10 *vs.* 4 patients (P=0.088)	mPFS: 7.0 *vs.* 7.1 mos HR 1.07, (P=0.41). 1-year PFS: 16% *vs.* 20%	ORR: 65% *vs.* 55% (P=0.015)	mOS: 13 *vs.* 14 mos, HR 1.02, (P=0.8). 2-year OS: 26% *vs.* 27%
PEBC-CCO, 2011 (30)	Meta-analysis and guideline		11 RTC. MBC patients	Epirubicin	Doxorubicin	CHF: RR 0.38, (P=0.059). Another cardiotoxicity ($) RR 0.43, (P=0.0044)	NR	Response rate: RR 1.04, (P=0.51). Complete response rate RR 1.05, (P=0.77)	1-year OS: RR 1.01 (P=0.87)

(*) Previous exposure to anthracyclines was limited to a cumulative dose of ≤300 mg/m^2 of doxorubicin or ≤400 mg/m^2 of epirubicin; ($) ECG changes, decrease in LVEF, increase in pre-ejection period/left ventricular pre-ejection period ratio; (?) Cardiac risk factors defined as prior mediastinal irradiation, age ≥65 years, history of heart disease (previous myocardial infarction, arrhythmia or angina, not requiring treatment) or had hypertension, or diabetes requiring medical treatment. (–), negative; CHF, congestive heart failure; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; CT, chemotherapy; DoR, duration of response; ECG, electrocardiogram; ER, estrogen receptor; FN, febrile neutropenia; G-CSF, granulocyte-colony stimulator factor; g, grade; GI, gastrointestinal; HFS, hand–foot syndrome; HR, hazard ratio; LVEF, left ventricular ejection fraction; m, median; MBC, metastatic breast cancer; mos, months; NR, not reported; NS, not statistically significant; ORR, overall response rate (percentage of patients who achieved an objective confirmed overall complete response or partial response); OS, overall survival; PEBC, Program in Evidence-based Care, Cancer Care; PFS, progression free survival; PR, progesterone receptor; RCT, randomized clinical trial; RR, risk ratio; TRAEs, treatment related adverse effects; TTF, time to treatment failure; TTP, time to disease progression.

Following this trial, a meta-analysis including 11 trials provided evidence of OS (HR 0.78) and response (RR 1.20) benefit for the weekly administration compared to the every-three-week regimen. Weekly Taxane schedules also showed fewer toxicities such as neutropenia, neutropenic fever, and peripheral neuropathy (37).

Docetaxel

An extensive search for taxane derivatives to improve paclitaxel's potential led to Docetaxel synthesis from extracts of Taxus baccatas' needles (European yew tree). Given that both have similar chemical structures, they share the mechanism of action and cause cell cycle arrest. Docetaxel has greater tubulin-binding site affinity, different microtubule polymerization patterns, higher intracellular concentration, and more potent apoptosis induction, resulting in enhanced antitumor activity (34). Docetaxel vehicles are polysorbate 80 and an ethanol diluent (35).

Fifteen years ago, Jones *et al.* performed a head to head study to compare Docetaxel 100 mg/m^2 with Paclitaxel 175 mg/m^2, both drugs given every 21 days. This phase 3 study demonstrated docetaxel superiority in time to progression (2 months benefit), response duration (2.9 months increase), overall response rate (from 25% to 32%), and OS (2.7 months improvement). Even though treatment discontinuation due to adverse effects was three times more frequent with Docetaxel, no significant differences in quality of life were noticed (34).

Nanometer sized albumin-bound (nab)-Paclitaxel

Solvents are directly responsible for the rarely fatal hypersensitivity reactions and the sometime irreversible neurotoxicity associated with demyelination and axonal degeneration. In addition, polyethylated castor oil can contribute to myelosuppression. Solvents form micelles in plasma, entrapping the active drug and the co-administered drugs, enhancing drug exposure, decreasing clearance, finally affecting efficacy. nab-Paclitaxel was developed to avoid the solvent-associated toxicities. Paclitaxel dose-limiting toxicities (sensory neuropathy, stomatitis, and superficial keratopathy) occurred at a dose of 375 mg/m^2. Albumin is a human natural carrier of lipophilic molecules that allows safe delivery of higher doses of Paclitaxel in 30 minutes of infusion schedules with no premedication (35).

As single-agent, nab-Paclitaxel has been compared with Paclitaxel and Docetaxel three-weekly regimens in the MBC setting. In both studies, biomarkers were not reported, and no subgroup analysis was made to evaluate the impact of the ER status as predictor of outcome.

In a phase 3 RCT, nab-Paclitaxel 260 mg/m^2 displayed an ORR of 33% and 23 weeks of TTP, both outcomes significantly superior to Paclitaxel, both drugs delivered each 21 days. The subgroup analysis of patients receiving it as a second-line or more showed an improvement in OS (HR, 0.73). Moreover, this drug exhibits a favorable safety profile, with significatively less grade 4 neutropenia (9%), grade 3 sensory neuropathy (2%), and hypersensitivity reactions (<1%) (35).

In a phase 2 trial, three different nab-Paclitaxel regimens were analyzed against Docetaxel 100 mg/m^2 q3w. The primary outcome was the overall response, but despite all nab-Paclitaxel schedules being numerically superior, these differences did not reach statistical significance. PFS was a secondary outcome, and the regimen of weekly nab-Paclitaxel 150 mg/m^2 noticed significant improvement from 7.5 to 12.9 months, with an increase in grade 4 neutropenia and neurotoxicity development. Suggesting that weekly nab-paclitaxel may be an appropriate alternative to docetaxel in the first-line treatment of patients with MBC (38).

Taxane-based combinations (doublets)

As previously stated, the optimal regimen for the front-line treatment of MBC remains unknown. In tailoring treatment for the individual patient, prior therapy history, and specific disease features guide the therapy selection. The use of sequential single-agents is an appropriate alternative for most patients. However, combination therapy may be preferred in rapidly progressive or symptomatic metastatic disease, where the higher response rates achieved with combination regimens impact the outcome (31). Some phase 3 clinical trials confirmed the superior efficacy of taxane-containing doublets over single-agent taxane in women with MBC after adjuvant anthracycline therapy or for whom the cardiotoxic effects of anthracyclines preclude its use.

Gemcitabine is an attractive drug to combine with a taxane, given the different mechanisms of action, synergistic activity, non-overlapping toxic profile, and lack of cardiotoxicity. A pivotal phase 3 study proved that gemcitabine added to q3w paclitaxel is an effective first-line therapy for MBC in patients who previously had neoadjuvant or adjuvant anthracycline-based CT when compared with paclitaxel alone. Patients receiving the combination therapy presented significantly increased time to progression (HR 0.70), overall response rate (41.4%), the median duration of response (9.89 months), and a tendency to improve OS (HR 0.82). An independent predictor of outcome was the ER status; the patients' subgroup with ER-negative or unknown, noted a significantly increased risk of death (HR 1.39 and 1.50, respectively). 38% of the

study population was ER-negative and 30% unknown. The doublet was a well-tolerated choice; despite increased toxicity, with a favorable global QOL (25).

Another attractive treatment option when combination chemotherapy is chosen as the optimal approach for patients with anthracycline-pretreated MBC is Capecitabine 1,250 mg/m^2 twice daily for 14 days added to docetaxel 75 mg/m^2 on day one, in a 21-days cycle. A phase 3 clinical trial compared this regimen with single-agent docetaxel 100 mg/m^2 q3w, in the first and second-line setting, demonstrating significant superiority in time to progression (HR 0.65) and OS (HR 0.77), with increased response rates (42%) and toxicity profile (71% of grade 3 adverse effects) mostly gastrointestinal toxicity and hand-foot syndrome, a cutaneous condition affecting the palms and soles. Thirty percent of the study population was ER-negative but this was not evaluated as a predictor of outcome (39).

Taxanes are the partner of anthracycline-based combined therapy. Docetaxel and Epirubicin combination, both at 75 mg/m^2 on day 1 in 21-day cycles, is considered by many as a 'standard' regimen for women with rapidly progressive visceral disease. A multicenter randomized study substitutes Epirubicin for Capecitabine in this regimen as first-line therapy, aiming to increase efficacy and reduce cardiotoxicity associated with anthracycline re-administration. This trial enrolled 272 previously untreated patients with MBC or ABC relapsing after one year since completing previous anthracycline-based neoadjuvant or adjuvant CT, but docetaxel plus capecitabine did not reach the primary objective, PFS. ER and PR negative tumors were represented in around 40% of the study population, but the outcomes were not evaluated by subgroups (31).

A doublet containing Paclitaxel and Carboplatin AUC 6 was evaluated against the Paclitaxel and Epirubicin 80 mg/m^2 combination, in the first-line scenario for patients with MBC in which anthracycline administration had the potential of being harmful; but was unable to fulfill the primary endpoint of the study, OS. Even though numerically improved survival from 22.4 to 27.8 months, this difference did not reach statistical significance (40).

Nevertheless, the prior discussed trials included all types of MBC, and just one analyzed ER status as a predictor of outcome, showing that patients with ER-negative tumors presented a significantly increased risk of death.

The phase 2 tnAcity study evaluated two different combination regimens containing nab-Paclitaxel contrasted with a non-taxane based combined therapy, Gemcitabine plus Carboplatin (G/Cp), for first-line treatment in mTNBC. The study population needed to be treatment-naïve for MBC, must have prior neoadjuvant or adjuvant anthracycline-based chemotherapy; if newly diagnosed MBC, the patient needed to be not eligible for anthracyclines. 6 months or more should pass since completion of prior neo/adjuvant CT; or ≥12 months if taxane, gemcitabine, or platinum agents were used. First-line nab-Paclitaxel 125 mg/m^2 plus Carboplatin 2 AUC (nab-P/Cp), given on days 1 and 8 of a 21-day cycle, demonstrated a significantly longer PFS (8.3 months) compared with either nab-Paclitaxel plus Gemcitabine (HR 0.59) or G/Cp (HR 0.58). Further, treatment with nab-P/Cp resulted in a numerically longer OS (16.8 months) and higher ORR (73%) than the other regimens. nab-P/Cp was well tolerated, with patients presenting 80% of adverse effects grade 3 or more (41,42) (*Table 2*).

Eribulin

Eribulin mesylate included in the halichondrin class is a non-taxane antineoplastic agent that inhibits the microtubule dynamics and generates an irreversible mitotic blockade and long-term loss of cell viability (43). In vitro and *in vivo* data suggest that eribulin may promote TNBC cells transition from a mesenchymal to an epithelial phenotype, decreasing its ability to migrate and metastasize (44).

Two phase-3 RTCs reported eribulin efficacy in women diagnosed with MBC who have previously received anthracycline and taxane chemotherapy. In the EMBRACE trial, eribulin was compared with physician's choice treatment (TPC), showing improved survival (median 13.1 versus 10.6 months, HR 0.81, P=0.041) in patients who had received two to five lines of systemic therapy, including an anthracycline and a taxane regimen (45). The Study 301 compared eribulin with capecitabine, with no survival benefit (15.9 versus 14.5 months, HR 0.88, P=0.056) from the first to the third-line setting (43).

European Medicines Agency (EMA) requested a pooled analysis of both studies to provide more information on the eribulin efficacy concerning the biomarkers' status. This pooled analysis confirmed the significant survival benefit of eribulin compared with control. Furthermore, in patients with TNBC, median survival was longer in patients treated with eribulin (12.9 versus 8.2 months; HR 0.74; P=0.006). Patients with more than two organs involved with metastasis, non-visceral disease, and disease not refractory to taxane presented a benefit from eribulin treatment (44).

Another pooled analysis using updated data from both trials specifically assessed the efficacy of eribulin in the patient population defined according to the EU label: MBC patients

Table 2 Randomized clinical trials for metastatic breast cancer taxanes-treatment

Author	Trial	Primary objective	Patients characteristics	Experimental arm	Control arm	Toxicity (experimental *vs.* control arm)	Progression (experimental *vs.* control arm)	Response (experimental *vs.* control arm)	Survival (experimental *vs.* control arm)
O'Shaughnessy 2002 (39)	Phase 3 RCT Multicentre	TTP	511 patients with MBC. 1st and 2nd line. After anthracycline failure (#). Prior Paclitaxel allowed. Prior Docetaxel not allowed. ER (–) DC 32%, D 28% (HER 2 no evaluated)	(DC) Docetaxel 75 mg/m^2 on day 1 every 3 weeks in combination with Capecitabine 1,250 mg/m^2 bid days 1 to 14 every 3 weeks	(D) Docetaxel 100 mg/m^2 day 1 every 3 weeks	g3 TRAEs: 71% *vs.* 49%. FN: 15% *vs.* 21%. g3–4 neutropenia: 16% *vs.* 15%. g3 hyperbilirubinemia: 6.8% *vs.* 2%. g3–4 GI (stomatitis, diarrhea, nausea): 38% *vs.* 12%. g3–4 HFS: 24% *vs.* 1%	mTTP: 6.1 *vs.* 4.2 mos, HR 0.65, (P=0.0001)	ORR: 42% *vs.* 30% (P=0.006). mDoR: 7.3 *vs.* 7 mos	mOS: 14.5 *vs.* 11.5 mos, HR 0.775, (P=0.012)
Fountzilas, 2004 (40)	Phase 3 RCT	OS	332 patients with ABC. 1st line. ≥12 since prior adjuvant CT and first relapse was c Breast Allowed anthracycline cumulative doses in pretreated patients (@). ER (–) PCp 27%, PE 36%. PR (–) PCp 40%, PE 45%. HER 2-positive: PCp 26%, PE 30%	(PCp) Paclitaxel 175 mg/m^2 in combination with Carboplatin AUC 6, on day 1 q3w for 6 cycles	(PE) Paclitaxel 175 mg/m^2 in combination with Epirubicin 80 mg/m^2 on day 1 q3w for 6 cycles	g3–4 TRAEs: 29% *vs.* 24%. Neutropenia: 12% *vs.* 11%. FN: 8 *vs.* 9 patients	mTTF: 10.8 *vs.* 8.1 mos (P=0.04)	ORR: 41% *vs.* 47% (P=0.32). mDoR: 13.8 *vs.* 8.98 mos (P=0.01)	mOS: 27.8 *vs.* 22.4 mos (P=0.25)
Jones, 2005 (34)	Phase 3 RCT Multicentre Open-Label	OS	449 patients with ABC or MBC. 2nd line. Progression <12 mos after (neo)-adjuvant CT. Required prior anthracycline. Prohibited prior taxanes. ER or PR (–)/unknown D 44%, P 50%	Docetaxel 100 mg/m^2 every 21 days	(P) Paclitaxel 175 mg/m^2 every 21 days	Discontinuation due to TRAEs: 26% *vs.* 8%, (P=0.001). Sensory neuropathy: 8% *vs.* 4%. Motor neuropathy: 5% *vs.* 1%. Deaths: 4 patients *vs.* 0	mTTP: 5.7 *vs.* 3.6 mos, HR 1.64, (P<0.0001)	ORR: 32% *vs.* 25% (P=0.1). mDoR: 7.5 *vs.* 4.6 mos (P=0.01)	mOS: 15.4 *vs.* 12.7 mos, HR 1.41, (P=0.03). 2-years OS: 33% *vs.* 22% (P=.009)
Gradishar, 2005 (35)	Phase 3 RCT Multicentre Open-Label	ORR	460 patients with MBC. 1st and atnd line. Candidates for single-agent paclitaxel therapy Not Paclitaxel or Docetaxel for MBC or relapse <1 year after adjuvant Paclitaxel or Docetaxel allowed. Biomarkers not reported	(nab-P) nab-Paclitaxel 260 mg/m^2 q3w	Paclitaxel 175 mg/m^2 every 21 days	g4 neutropenia: 9% *vs.* 22% (P<0.001). FN: <2% both arms. Sensory neuropathy g3: 2% v 10% (P<.0001). Hypersensitivity reactions: <1% *vs.* 2%	mTTP: 23 *vs.* 16.9 weeks, HR 0.75, (P=0.006). 1st line: 24 *vs.* 19.7 weeks (NS). 2nd line: 20.9 *vs.* 16.1 weeks, HR 0.73, (P=0.020)	ORR: 33% *vs.* 19%, (P=0.001). 1st line: 42% *vs.* 27%, (P=0.029). ≥2nd line: 27% *vs.* 13%, (P=0.006)	mOS: 65 *vs.* 55.7 weeks (P=0.374). ≥2nd line: 56.4 *vs.* 46.7 weeks, HR 0.73, (P=0.024)

Table 2 (*continued*)

Table 2 (*continued*)

Author	Trial	Primary objective	Patients characteristics	Experimental arm	Control arm	Toxicity (experimental *vs.* control arm)	Progression (experimental *vs.* control arm)	Response (experimental *vs.* control arm)	Survival (experimental *vs.* control arm)
Seidman, 2008 CALGB 9840 (36)	Phase 3 RCT Multicentre	ORR	735 patients with MBC or ABC. 585 patients CALGB9840. 158 patients CALGB9342. 1st line or 2nd line. >1 year since prior adjuvant taxane allowed. >6 mos since adjuvant CT. ER (–) 29% *vs.* 20%. PR (–) 34% *vs.* 23%. HER 2-positive 24% (*)	Paclitaxel 80 mg/m^2 weekly via 1-hour infusion	Paclitaxel 175 mg/m^2 every 3 weeks via 3-hour infusion	Granulocytopenia ≥ g3: 9% *vs.* 15%, (P=0.017). FN: 4% *vs.* 3%. Sensory neuropathy g3: 24% *vs.* 12% (≥ g2; P=0.0046). Motor neuropathy g3: 9% *vs.* 4% (≥ g2; P=0.013)	mTTP: 9 *vs.* 5 mos, HR 1.43, (P<0.0001)	ORR: 42% *vs.* 29%, OR 1.75, (P=0.0004)	mOS: 24 *vs.* 12 mos, HR 1.28, (P=0.0092)
Albain, 2008 (25)	Phase 3 RCT Multicentre Open-Label	OS	529 patients with locally recurrent or MBC. 1st line. After one (neo)-adjuvant Anthracycline-based regimen. Prior Gemcitabine or taxane was not allowed. ER (–) GP 34.6%, P 39.2%	(GP) Gemcitabine 1,250 mg/m^2 days 1 and 8 plus Paclitaxel, 175 mg/m^2 on day 1 every 21 days	Paclitaxel 175 mg/m^2 on day 1 every 21 days	g3–4 neutropenia: 47.9% *vs.* 11.5% FN: 5% *vs.* 1.2%. g2–4 fatigue: 19.2% *vs.* 12.4%. g2–4 sensory neuropathy: 24.1% *vs.*21.6%. g2–4 Motor neuropathy: 8.8% *vs.* 3.1%. 1 patient died in each arm	mTTP: 6.14 *vs.* 3.98 mos, HR 0.70, (P=0.0002). mPFS: 5.9 *vs.* 3.9 mos, HR 0.73, (P=0.0005)	ORR: 41.4% *vs.* 26.2% (P=0.0002). mDoR: 9.89 *vs.* 8.44 mos, HR 0.82, (P=0.2333). Visceral *vs.* non-visceral disease: 36.5% *vs.* 21.9%, (P=0.0030)	mOS: 18.6 *vs.* 15.8 mos, HR 0.82, (P=0.0489). ER (+) *vs.* (–): HR 1.39, (P=0.0103)
Gradishar, 2009 (38)	Phase 2 RCT Multicentre Open-Label	ORR	302 patients with previously untreated MBC. 1st line. ≥l year since prior (neo)-adjuvant CT was allowed. Biomarkers not reported	nab-Paclitaxel 300 mg/m^2 q3w, or 100 mg/m^2 weekly, or 150 mg/m^2 weekly	Docetaxel 100 mg/m^2 q3w	g4 neutropenia: D 75%. nab-Paclitaxel 300: 5%; 150: 9%; 100: 5%; all (P<0.001). FN: D 8% *vs.* 1% in each nab-P arm. Sensory neuropathy g2–3: D 31%. nab-Paclitaxel 300: 39%; 150: 40%; 100: 20%; all (NS)	mPFS: nab-P 150 *vs.* D: 12.9 *vs.* 7.5 mos, HR 0.49, (P=0.0065). nab-P 300 *vs.* D: 11 *vs.* 7.5 mos (NS)	ORR: nab-Paclitaxel: 300: 37% (NS); 150: 49% (NS); 100: 45% (NS); D: 35%. DCRs: nab-Paclitaxel: 300: 68% (NS); 150: 80% (P=0.017); 100: 75% (P=0.009); D: 58%	Not reported
Mavroudis, 2009 (31)	Phase 3 RCT Multicentre Open-Label	TTP	272 previously untreated patients with ABC. 1st line. >1 year since previous anthracycline-based (neo)-adjuvant CT was allowed. ER and PR (–) 39.6%	(DC) Docetaxel 75 mg/m^2 on day 1 plus Capecitabine 950 mg/m^2 orally twice daily on days 1–14 in 21-day cycles (&)	(DE) Docetaxel 75 mg/m^2 plus Epirubicin 75 mg/m^2 on day 1 in 21-day cycles (&)	g3–4 neutropenia: 46% *vs.* 57%, (P=.07). FN: 8% *vs.* 11%, (P=0.4). g2–3 anemia: 7% *vs.* 20% (P=0.001). g3 HFS: 4% *vs.* 0%, (P=0.02). 1 patient died due to TRAEs (DE arm)	mTTP: 11 *vs.* 10.6 mos, (P=0.735)	ORR: 52.9% *vs.* 51.5% (P=0.808). mDoR: 13.7 *vs.* 10.4 mos (P=0.602)	mOS: 35.7 *vs.* 37.6 mos (P=0.744)

Table 2 (*continued*)

Table 2 (*continued*)

Author	Trial	Primary objective	Patients characteristics	Experimental arm	Control arm	Toxicity (experimental *vs.* control arm)	Progression (experimental *vs.* control arm)	Response (experimental *vs.* control arm)	Survival (experimental *vs.* control arm)
Mauri, 2010 (37)	Meta-analysis		2,540 patients with ABC 11 trials	q1w taxane-based regimens	q3w taxane-based regimens	q3w > q1w. Neutropenia, FN, and peripheral neuropathy	PFS: Paclitaxel q3w = q1w, HR 1.02 (P=0.860). Docetaxel q3w = q1w, HR 1.08	ORR: Paclitaxel q3w > q1w, RR 1.20 (P<0.001). Docetaxel q3w = q1w, HR 0.92	OS: Paclitaxel q1w > q3w, HR 0.78 (P=0.001). Docetaxel q3w = q1w, HR 1.25
Yardley, 2018 (42)	Phase 2/3 RCT Multicentre Open-Label	PFS	Phase 2: 191 patients, 1:1:1 randomization (open-label). Planned Phase 3I: 550 patients, 1:1 randomization. Triple Negative MBC. 1st line. Treatment naïve for MBC. Must have prior (neo)-adjuvant anthracycline CT; or new diagnosed MBC not eligible for anthracycline. ≥6 mos prior (neo)-adjuvant CT; or ≥12 mos if taxane, gemcitabine, or platinum agents	(nab-P/G) nab-Paclitaxel 125 mg/m^2 plus Gemcitabine 1,000 mg/m^2. (nab-P/Cp) nab-Paclitaxel 125 mg/m^2 plus Carboplatin 2 mg/min/mL	(G/Cp) Gemcitabine 1,000 mg/m^2 plus Carboplatin AUC 2 mg/min/mL. All given on days 1 and 8 of a 21-day cycle	≥ g3 TRAEs: nab-P/Cp: 80%; nab-P/G: 77%; G/Cp: 84%. ≥ 8 neutropenia: nab-P/Cp: 42%; nab-P/G: 27%; G/Cp: 52%. FN: nab-P/Cp: 5%; nab-P/G: 2%; G/Cp: 0. Peripheral neuropathy ≥ g3: nab-P/Cp: 5%; nab-P/G: 7%; G/Cp: 2%. Death: nab-P/Cp: 2%; nab-P/G: 3%; G/Cp: 3%	mPFS: nab-P/Cp v nab-P/G: 8.3 *vs.* 5.5 mos, HR 0.59, (P=0.02). nab-P/Cp *vs.* G/Cp: 8.3 *vs.* 6 mos, HR 0.58, (P=0.02). 12-mos PFS: nab-P/Cp: 30%; nab-P/G: 13%; G/Cp: 11%	ORR: nab-P/Cp: 73%; nab-P/G: 39%; G/Cp: 44%. mDoR: nab-P/Cp: 6.2 mos; nab-P/G: 5.8 mos; G/Cp: 5 mos. ORR: DFI ≤1 *vs.* >1 year; nab-P/Cp: 69% *vs.* 75%; nab-P/G: 41% *vs.* 37%; G/Cp: 35% *vs.* 47%	mOS: nab-P/Cp *vs.* nab-P/G: 16.8 *vs.* 12.1 mos, HR 0.73, (P=0.16). nab-P/Cp *vs.* G/Cp: 16.8 *vs.* 12.6 mos, HR 0.80, (P=0.29)

(#) Anthracycline failure, defined as: (I) progression while receiving anthracycline-based CT without experiencing any transient improvement; (II) no response after administration of ≥4 cycles of anthracycline-based CT; (III) relapsing <2 years of completing (neo)-adjuvant anthracycline-based CT; or (IV) a brief objective response to anthracycline-based CT with subsequent progression while receiving the same therapy or <12 months after the last dose. (@) Allowed anthracycline cumulative doses in pretreated patients; ≤360 mg/m^2 for doxorubicin, ≤450 mg/m^2 for EPI, or ≤72 mg/m^2 for mitoxantrone. (*) Received weekly trastuzumab 2 mg/kg via 30-minute infusion following a 4-mg/kg loading dose administered over 90 minutes. (&) 6 cycles scheduled, continuation was allowed in responding patients. (–), negative; ABC, advanced breast cancer; AUC, area under the curve; CALGB, Cancer and Leukemia Group B; CT, chemotherapy; DCR, disease control rate (stable disease for ≥16 weeks or confirmed overall response); DFI, disease free interval; DoR, duration of response; ER, estrogen receptor; FN, febrile neutropenia; g, grade; HER 2; human epidermal growth factor receptor; HFS, hand–foot syndrome; HR, hazard ratio; m, median; MBC, metastatic breast cancer; mos, months; NS, not statistically significant; OR, odds ratio; ORR, overall response rate (percentage of patients who achieved an objective confirmed overall complete response or partial response); OS, overall survival; PFS, progression free survival; PR, progesterone receptor; q1w, weekly; q3w, each three weeks; RCT, randomized clinical trial; RR, relative risk; TRAEs, treatment related adverse effects; TTF, time to treatment failure; TTP, time to disease progression.

who had received one or more prior systemic lines. Treatment with eribulin was associated with a significantly longer OS versus the control arm (15 versus 12.6 months, HR 0.85); and a significantly longer PFS (3.9 versus 3.2 months, HR 0.87). With no difference in the objective response rate. Three hundred fifty-two patients with TNBC, representing 21% of the study population, presented significantly longer OS with eribulin versus the control arm (12.4 versus 8.1 months HR 0.72) and PFS (2.8 versus 2.5 months, HR 0.77). Compared with capecitabine, eribulin significantly prolonged OS (15.2 versus 13.3 months, HR 0.84). This benefit was observed in the TNBC subgroup analyzed as well. ($P<0.05$) (46).

Capecitabine

Capecitabine is an oral prodrug that is transformed to 5-fluorouracil (5-FU) by an enzymatic process mediated by thymidine phosphorylase. Some human tumor tissues, including breast, present significantly higher TP activity than normal tissue surrounding the tumor, allowing this prodrug to be preferentially converted in 5-FU at the tumor site (47).

Single-agent capecitabine is indicated for treating patients MBC after taxanes and anthracycline-chemotherapy failure or when further anthracycline-therapy is not indicated (48). Capecitabine can be an option for women who are not candidates to more aggressive regimens as first-line systemic therapy due to significant comorbidities and indolent disease with low tumor burden. Patients with high tumor burden, rapidly progressing, or life-threatening visceral disease may require more intensive treatment (49). Capecitabine is one of the most common physician's choices as second-line regimens in mTNBC (8).

A phase 3 RTC trial evaluated capecitabine efficacy against the classical CMF regimen. Capecitabine was administered continuously (650 mg/m^2, twice daily) or intermittently (1,000 mg/m^2, twice daily, 14 of every 21 days), achieving the same total dose. The study enrolled women diagnosed with MBC, not previously treated, unsuited to more intensive chemotherapy. Even though capecitabine did not reach the primary endpoint, quality-adjusted-PFS against CMF did show significantly increased survival of 4 months (22 versus 18 months, HR 0.72). 36% of the study population presented ER and PR-negative or unknown. Patients with hormonal receptor-positive tumors showed a significantly better OS when treated with capecitabine (HR 0.69). Patients treated with capecitabine presented more grade 3 or 4 hand-foot syndrome but less grade 3 or 4 neutropenia, febrile neutropenia, and stomatitis. Capecitabine, when given continuously or intermittently, displays the same efficacy and toxicity profile (49).

The PELICAN study compared PDL with Capecitabine 1,250 mg/m^2 twice daily, for 14 days every 21 days in patients with MBC, ineligible for endocrine or trastuzumab therapy, not previously treated, without anthracycline-resistant disease defined as developing of metastatic disease during or in the first 12 months after completion adjuvant therapy with anthracyclines. Capecitabine presented a time to progression of 6.1 months, a survival of 26.8 months, and a response rate of 13.8%. PDL could not demonstrate superiority over capecitabine. Patients treated with capecitabine presented more diarrhea (43%) and thromboembolic events (17%) (50).

Although both studies bring evidence about capecitabine activity in the first-line metastatic setting, additional data are needed before concluding its real impact. In the first trial, capecitabine was compared with a non-standard-of-care regimen, and the hormonal receptor-negative population presented worse survival than the hormonal receptor-positive population. The study population in the PELICAN trial is considered HER 2-negative, but the status of the biomarkers was not reported or evaluated as predictor of outcome.

Platinum

Cisplatin binds the genomic or mitochondrial DNA, creating DNA lesions that block DNA, mRNA, and protein production, leading to arrest DNA replication, which activates further transduction pathways, leading to apoptosis (51). BRCA-mutated, sporadic triple-negative or basal-like breast cancer display aberrant DNA repair and genomic instability, conferring the rationale for using platinum that provokes more DNA damage (52).

A phase 2 study was designed to explore the efficacy of single-agent cisplatin or carboplatin in mTNBC and to determine the response rate of defined genetic and molecular disease subsets, showing that BRCA1/2 mutation-carriers exhibited a significantly higher response (54.5% versus 19.7%) but no difference in progression-free survival (3.3 versus 2.8 months) or survival (13.7 versus 10.9 months), compared with BRCA1/2 wild-type. This trial added to evidence suggesting that BRCA1/2 mutated breast cancer presents platinum sensitivity due to a defect in DNA repair (53).

The TNT trial was designed to study the responses to DNA-crosslinking agent carboplatin compared to microtubule-disrupting agent docetaxel in unselected mTNBC as a first-line treatment. The overall response rate

(29.3% versus 25.5%) and PFS (4.4 versus 3.1 months) were numerically larger for docetaxel but not reach statistical significance. 11.4% of the study population presented germline BRCA1/2 mutation. In the prespecified subgroup analysis, the mTNBC with BRCA1/2 mutation showed a statistically increased response (68% versus 33.3%) and PFS (6.8 versus 4.4 months) to carboplatin first-line chemotherapy. The carboplatin response was contrasted between the BRCA1/2 mutation-carriers against non-carriers (68% versus 28.1%) being significant. The putative BRCAness evaluation did not show significative difference between the subgroups of BRCA1 methylation, BRCA1 mRNA-low, high HRD score, and basal-like core-basal when compared response to carboplatin versus docetaxel. Only the non-basal-like subgroup presented a statistically significant increase response to docetaxel (72.2% versus 16.7%), which prevailed when compared with the basal-like subgroup (72.2% versus 31%, P=0.003). No difference in OS was found across the groups, but this interpretation can be confounded by the crossover design, as 56% of these patients received carboplatin at progression. This study provides evidence the TNBC biology can select a population that could benefit from the biologically targeted use of platinum chemotherapy rather than the current licensed standard-of-care chemotherapies for metastatic breast cancer (54).

Gemcitabine

Gemcitabine is an antimetabolite. This pyrimidine analog inhibits DNA synthesis and can be used as a single-agent or in combinations. Gemcitabine plus cisplatin combination is considered an optional treatment for MBC in the first- or second-line setting. The rationale for this combination is to exploit the synergistic mechanism of cisplatin, which induces the formation of DNA adducts damaging the DNA structure, and gemcitabine causes defective synthesis of nucleic acids (55).

A phase 3 RCT used the gemcitabine and carboplatin combination as a control arm when evaluated the addition of iniparib to the doublet as a treatment for patients with mTNBC progressing to no more than two lines. This doublet showed an ORR of 30%, median progression-free survival, and OS of 4.1 and 11 months, respectively, without any benefit from adding iniparib, being another treatment choice for these patients (56) (*Table 3*).

As mentioned before, the gemcitabine and cisplatin combination in first-line MBC increased response rates, duration of responses, and time to progression, but in the ER-negative or unknown subgroup, a significantly increased risk of death was noticed (25).

Conclusions

Standard anthracycline-based CT is the treatment of choice as first-line for metastatic breast cancer patients not previously treated with anthracyclines. First-line single-agent taxane is offered to patients who have received prior adjuvant anthracyclines or presented anthracycline failure, or as the second line in patients who have received prior anthracyclines in the metastatic setting. TNBC tumors that carry the germline BRCA1/2 mutations can benefit from the targeted use of platinum. Other drugs as eribulin, capecitabine, platinum, and gemcitabine, that have proven efficacy as single-agents or in combination as further lines, but the sequencing is not established. Combination chemotherapy can be considered when the patient presents a severe organ dysfunction aiming to achieve disease stabilization.

CT remains the cornerstone treatment for mTNBC which not express targetable receptors or defective molecular pathways, and as a counterpart for targeted or immune therapies; given the limited access to these last in

Table 3 Randomized clinical trials for metastatic breast cancer

Author	Trial	Primary objective	Patients characteristics	Experimental arm	Control arm	Toxicity (experimental *vs.* control arm)	Progression (experimental *vs.* control arm)	Response (experimental *vs.* control arm)	Survival (experimental *vs.* control arm)
Twelves, 2014 (44)	Pool Analysis of Study 305/ EMBRACE and Study 301	OS	2 phase 3 RCTs. 1,864 patients. Prior anthracycline and taxane was allowed. Study 305/EMBRACE. 3rd-5th line. Study 301 <3rd line. mTNBC: Eri (22.9%) *vs.* control (23.1%)	1,062 patients. Study 305/ EMBRACE: Eribulin (Eri) 1.4 mg/m^2 on days 1 and 8 every 21 days; Study 301: Eribulin 1.4 mg/m^2 on days 1 and 8 every 21 days	802 patients. Study 305/ EMBRACE treatment of physician's choice. Study 301: Capecitabine 250 mg/m^2 bid on day 1–14 every 21 days	Serious TRAEs: 21.1% *vs.* 22.6%. Discontinuation due to TRAEs 10.5% *vs.* 12%	mPFS: 4 *vs.* 3.4 mos, HR 0.9, (P=0.046). mTNBC: 2.8 *vs.* 2.6 mos, HR 0.78, (P=0.018)	ORR: 14.9% *vs.* 16.4% (NS). CBR: 30.9% *vs.* 30.3% (NS)	mOS: 15.2 *vs.* 12.8 mos, HR 0.85, (P=0.003). mTNBC mOS: 12.9 *vs.* 8.2 mos HR 0.74, (P=0.006)
Pivot, 2016 (46)	Pool Analysis of Study 305/ EMBRACE and Study 301 (updated data)	OS	1,644 MBC patients with criteria matching the EU label: who had received ≥1 prior systemic line, prior anthracycline and taxane chemotherapy was allowed. mTNBC 21% of the study population	Eribulin: n=946	Treatment of physician's choice/ capecitabine: n=698	Serious TEAEs: 21.4% *vs.* 22.5%. Discontinuation: 11.3 % *vs.* 13.6%	mPFS: 3.9 *vs.* 3.2 mos, HR 0.87, (P<0.05). mTNBC: 2.8 *vs.* 2.5 mos, HR 0.77, (P=0.028)	CBR: 30% *vs.* 27%, (P<0.05)	mOS: 15 *vs.* 12.6 mos, HR 0.85, (P<0.01). mTNBC mOS: 12.4 *vs.* 8.1 mos, HR 0.72, (P<0.01). Eri *vs.* Cape: 15.2 *vs.* 13.3 mos, HR 0.84, (P<0.05)
Stockler, 2011 (49)	Phase 3 RCT Multicentre Open-Label	PFS	323 patients. MBC 1st line where more intensive chemotherapy is not considered more appropriate. ≥w since adjuvant CT. ER and PR (–) or unknown: C(i) 38%, C(c) 33%, CMF 36%, all 36%	Capecitabine. Cape (i) Intermittently 1,000 mg/m^2 bid for 14 of every 21 days or Cape (c) continuously 650 mg/m^2 bid for 21 of every 21 days	CMF: oral CFA 100 mg/m^2 days 1 to 14 with intravenous Methotrexate 40 mg/m^2 and Fluorouracil 600 mg/m^2 on days 1 and 8 every 28 days	(# of patients). g3–4 HFS: 15 *vs.* 17 *vs.* 0, P<0.001. g3–4 neutropenia: 1 *vs.* 1 *vs.* 28, P<0.001. g3–4 FN: 0 *vs.* 0 *vs.* 11, P<0.001. g3–4 stomatitis: 0 *vs.* 0 *vs.* 6, P=0.001. Serious adverse events: 21% *vs.* 35%, P=0.02	Quality-adjusted PFS: Cape *vs.* CMF: 8.8 *vs.* 7.6 mos (P=0.20). mPFS: Cape (i) *vs.* (c): 6 mos both, HR 0.97, (P=0.8). Cape *vs.* CMF: 6 mos both, HR 0.86, (P=0.20). Hormonal receptor (+) *vs.* (–): HR 0.89, (P=0.3)	Cape (i) *vs.* Cape(c) *vs.* CMF. ORR: 22% *vs.* 20% *vs.* 18% (NS). Objective disease control (*): 49% *vs.* 50% *vs.* 42% (NS)	mOS: Cape(i) *vs.* (c): HR 0.86, (P=0.4). Cape *vs.* CMF: 22 *vs.* 18 mos, HR 0.72, (P=0.02). Hormonal receptor: (+) *vs.* (–): Univariate HR 0.74, (P=0.03); multivariate Cape *vs.* CMF: HR 0.69, (P=0.006)
Harbeck, 2017 (50) The PELICAN Study	Phase 3 RCT Multicentre Open-Label	TTP	210 patients ineligibles for endocrine or trastuzumab therapy. 1st Line. Cumulative adjuvant anthracyclines of 360 mg/m^2 doxorubicin or equivalent were allowed. Excluded anthracycline-resistant disease (&)	(PLD) Pegylated liposomal doxorubicin 50 mg/m^2 every 28 days	Capecitabine 1,250 mg/m^2 bid for 14 days every 21 days	g3–4 neutropenia: 3% *vs.* 2% (P=0.19). g3–4 HFS: 39% *vs.* 26% (P=0.08). g3–4 Stomatitis: 6% *vs.* 0, (P=0.0007). g3–4 Diarrhea: 0 *vs.* 13%, (P<0.0001). Pulmonary embolism: 0 *vs.* 6%, (P=0.04). Any type of thromboembolism: 17% *vs.* 2%. All cardiac events 10% *vs.* 13%, (P=0.50)	mTTP: 6 *vs.* 6.1 mos, HR 1.08, (P=0.67)	ORR: 7.3% *vs.* 13.8% (P=0.17)	mOS: 23.3 *vs.* 26.8 mos, HR 1.12, (P=0.53)

Table 3 (*continued*)

Table 3 (*continued*)

Author	Trial	Primary objective	Patients characteristics	Experimental arm	Control arm	Toxicity (experimental *vs.* control arm)	Progression (experimental *vs.* control arm)	Response (experimental *vs.* control arm)	Survival (experimental *vs.* control arm)
Isakoff, 2015 (53) TBCRC 009	Phase 2 RCT Single-Arm Multicentre Open-Label	PFS	86 patients Mtnbc. 1st and 2nd line. BRCA1/2 mutation in 11 out of 77 patients	Cohort 1: (C) Cisplatin 75 mg/m^2 once every 3 weeks; or Cohort 2: (Cp) Carboplatin AUC 6 once every 3 weeks		C *vs.* Cp. Anemia: 81% *vs.* 65%. Neutropenia: 49% *vs.* 35%. Hypomagnesemia: 42% *vs.* 23%. Tinnitus: 37% *vs.* 0%. Anorexia: 26% *vs.* 9%. Thrombocytopenia: 19% *vs.* 47%	mPFS 2.9 mos. BRCA 1/2 mut *vs.* wt: 3.3 *vs.* 2.8 mos, (P=0.92)	ORR: 25.6%. 1st line *vs.* 2nd line. 29% *vs.* 11.8%, (P=0.22). C *vs.* Cp: 32.6% *vs.* 18.6%, (P=.22). BRCA 1/2 mut *vs.* wt: 54.5% *vs.* 19.7%, (P=0.022)	mOS: 11 mos. BRCA 1/2 mut *vs.* wt: 13.7 *vs.* 10.9 mos, (P=0.58)
Tutt, 2018 (54) The TNT trial	Phase 3 RCT Multicentre Open-Label Non-inferiority	ORR	376 patients with mTNBC. 1st line. 338 patients (90%) with mTNBC. and no known BRCA1/2 mutation. 43 patients with germline BRCA1/2 mutation. Prespecified analyses of BRCA1/2 germline mutation carriers and of members of putative BRCAness (*). Crossover at progression	Carboplatin 6–8 cycles	Docetaxel 100 mg/m^2	Serious AEs: total 276 events (102 *vs.* 174)	mPFS: 3.1 *vs.* 4.4 mos (NS). BRCA 1/2 mut: 6.8 *vs.* 4.4 mos (P=0.002). Basal *vs.* non-basal: (P=0.04)	ORR central review: 25.5% *vs.* 29.3% (NS). BRCA 1/2 mut: 68% *vs.* 33.3% (P=0.03). BRCA 1/2 wt: 28.1% *vs.* 34.5% (NS). BRCA 1/2 mut *vs.* wt: (P=0.01). BRCA1 methylation: 21.4 % *vs.* 42.1% (NS). BRCA1 mRNA-low: 28.6% *vs.* 64.7% (NS). High HRD Score: 38.2% *vs.* 40.4% (NS). Basal-like: 32.5% *vs.* 31% (NS). Non-basal-like: 16.7% *vs.* 72.2% (P=0.002). Basal *vs.* non-basal: (P=0.003). Core-basal: 34.3% *vs.* 29.2% (NS)	mOS 12.8 *vs.* 12 mos (P=0.96) BRCA 1/2 mut no difference Basal v non-basal: (P=0.17)
Hu, 2015 (52) CBCSG 006 trial	Phase 3 RCT Multicentre Open-Label	PFS	240 patients with mTNBC. 1st line. ≥6 months since (neo)/ adjuvant taxanes were allowed	Cisplatin 75 mg/m^2 on day 1 plus Gemcitabine 1,250 mg/m^2 on days 1 and 8 every 3 weeks for a maximum of 8 cycles, or until progression or intolerable toxicity	Paclitaxel 175 mg/m^2 on day 1 plus Gemcitabine 1,250 mg/m^2 on days 1 and 8 every 3 weeks for a maximum of 8 cycles, or until progression or intolerable toxicity	g3–4 neutropenia: 57% *vs.* 59%. g3–4 FN: 3% *vs.* 3%. g3–4 peripheral neuropathy: 0 *vs.* 2%	mPFS: 7.73 *vs.* 6.47 mos, HR 0.69, (P=0.009)	ORR: 64% *vs.* 49%, (P=0.018)	HR 0.92, (P=0.61)
O'Shaughnessy 2014 (56)	Phase 3 RCT Multicentre Open-Label	OS/PFS	519 patients with mTNBC. 1st to 2nd line. Prior treatment with Gemcitabine, Carboplatin, Cisplatin, or Iniparib was not allowed	Gemcitabine 1,000 mg/m^2 and Carboplatin AUC 2 (days 1 and 8) plus iniparib 5.6 mg/kg (days 1, 4, 8, and 11) every 3 weeks	Gemcitabine 1,000 mg/m^2 and Carboplatin AUC 2 (days 1 and 8)	≥ g3 TRAEs: 88.6% *vs.* 86.1%. g3–4 neutropenia: 62% *vs.* 53%. g3–4 thrombocytopenia: 29% *vs.* 24%. Toxic deaths: 7% *vs.* 3%	mPFS: 5.1 *vs.* 4.1 mos, HR 0.79, (P=0.027, NS). 1st line: 5.6 *vs.* 4.6 mos, HR 0.88. 2nd–3rd line: 4.2 *vs.* 2.9 mos, HR 0.68	ORR: 33.7% *vs.* 30.2% (P=0.395)	mOS: 12.2 *vs.* 11.1 mos, *vs.* HR 0.85, (P=0.28). 1st line: 12.4 *vs.* 12.6 mos, HR 1.11. 2nd–3rd line: 10.8 *vs.* 8.1 mos, HR 0.65

(&) Anthracycline-resistant disease, defined as developing locally recurrent or metastatic disease during, or relapse <12 months after completion of anthracycline therapy. (*) Putative BRCAness TNBC subgroups with DNA methylation at the BRCA1 promoter and/or low BRCA1 mRNA expression and the basal-like phenotype as defined by gene or protein expression. (–), negative; (+), positive; bid, twice daily; CBCSG, Chinese Breast Cancer Study Group; CBR, clinical benefit rate; CFA, cyclophosphamide; CMF: cyclophosphamide, methotrexate and 5-fluorouracil; CT, chemotherapy; ER, estrogen receptor; FN, febrile neutropenia; g, grade; HFS, hand-foot syndrome; HR, hazard ratio; m, median; MBC, metastatic breast cancer; mos, months; mRNA, messenger RNA, mTNBC, metastatic triple-negative breast cancer; mut, mutated; NS, not statistically significant; ORR, overall response rate (percentage of patients who achieved an objective confirmed overall complete response or partial response); OS, overall survival; PFS, progression free survival; PR, progesterone receptor; RCT, randomized clinical trial; TBCRC, Translational Breast Cancer Research Consortium; TRAEs, treatment related adverse effects; TTP, time to disease progression; wt, wild-type.

most countries, CT will continue in the landscape for much longer.

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Footnote

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