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Cytotoxic chemotherapy: Still the mainstay of clinical practice for all subtypes metastatic breast cancer

Chris Twelves[a,b], Maria Jove[b,*], Andrea Gombos[c], Ahmad Awada[c]

[a] Leeds Institute of Cancer and Pathology, St. James's University Hospital, Leeds, UK
[b] St James's Institute of Oncology, St. James's University Hospital, Bexley Wing, Level 4, Beckett Street, LS9 7TF Leeds, UK
[c] Medical Oncology Clinic, Jules Bordet Institute, Université Libre de Bruxelles, Boulevard de Waterloo 121, B-1000 Brussels, Belgium

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ABSTRACT

Cytotoxic chemotherapy remains central to the treatment of all subtypes of metastatic breast cancer (MBC). We review evidence-based chemotherapy options for women with MBC after an anthracycline and a taxane including re-challenge with anthracycline or taxane, capecitabine, eribulin and ixabepilone as a single agent or combination with capecitabine (not approved in the EU); and the vinca alkaloid vinflunine as single agent or combined with either capecitabine/gemcitabine (also not approved EU or USA). Etirinotecan pegol, comprising irinotecan bound to polyethylene glycol by a biodegradable linker, is a new cytotoxic agent for patients with MBC that has achieved encouraging response rates in phase II studies; it has been further evaluated in the phase III BEACON trial. New cytotoxics should address novel targets or modes of delivery, achieve meaningful improvements in outcomes and seek to identify predictive biomarker(s).

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Abbreviations: 5FU, 5-fluorouracil; A, anthracycline; BEACON, BrEAst Cancer Outcomes with NKTR-102; BRCA, breast cancer gene; CALGB, cancer and leukemia Group B; CTCs, circulating tumor cells; CI, confidence interval; CHF, congestive heart failure; DFI, disease-free interval; EMBRACE, Eisai Metastatic BReast Cancer study Assessing physician's Choice vs E7389; EPR, enhanced permeability and retention; NKTR-102, etirinotecan pegol; EMA, European Medicines Agency; EU, European Union; q21d, every 3 weeks; FDA, Food and Drug Administration; 1L, first-line; HFS, hand–foot syndrome; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ITT, intention-to-treat; MBC, metastatic breast cancer; nab-P, nab-paclitaxel; NPLD, non-pegylated doxorubicin; NR, not reported; NS, not statistically significant; ORR, overall response rate; OS, overall survival; PPE, palmer-plantar erythrodysesthesia; PLD, pegylated liposomal doxorubicin; PN, peripheral neuropathy; PFS, progression free survival; QOL, quality of life; T, taxanes; TTP, time to tumor progression; TOP1, topoisomerase I; T-DM1, trastuzumab emtansine; TPC, treatment of physicians' choice; TNBC, triple-negative breast cancers; US, United States.

* Corresponding author. Fax: +44 113 206 8474.
E-mail addresses: C.J.Twelves@leeds.ac.uk (C. Twelves), M.Jove@leeds.ac.uk (M. Jove), andrea.gombos@bordet.be (A. Gombos), ahmad.awada@bordet.be (A. Awada).

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1. Introduction

Despite advances in the diagnosis and treatment of women with early breast cancer, globally more than 500,000 women die annually from the disease, reflecting the ongoing need for better treatment for women with metastatic breast cancer (MBC) (World Health Organization, 2014). Increasingly, we appreciate the heterogeneity of MBC in terms of its biology, but when making systemic treatment decisions, there are four main subgroups: hormone receptor (HR)-positive (≥65% of invasive breast cancers), which comprise luminal A cancers that are human epidermal growth factor receptor 2 (HER2)-negative and low Ki 67 and luminal B cancers that are HER2-positive or high Ki 67; HER2-positive (15–20%); and HR- and HER2-negative or triple-negative breast cancers (TNBC; 15–20%) (Lakhani et al., 2012). The median survival of patients with MBC is approximately 24 months, but is better in patients with HR-positive and HER2-positive tumors than those with TNBC (André and Zielinski, 2012; Kennecke et al., 2010; Bonotto et al., 2014).

While there are major differences in the treatment of patients with MBC, chemotherapy remains fundamental to the management of women with all molecular subtypes. For those with TNBC, chemotherapy offers the only systemic treatment option, but they are not the only group in whom chemotherapy is important. Patients with HR-positive disease, the biggest MBC subgroup, usually receive successive lines of endocrine therapy as long as they respond (Fedele et al., 2012). Everolimus appears to delay endocrine resistance (Baselga et al., 2012); palbociclib also enhances the efficacy of endocrine therapy (letrozole or fulvestrant) (Finn et al., 2014). Ultimately, when endocrine options have been exhausted, or the patient develops more aggressive disease, chemotherapy becomes relevant. Similarly, patients with HER2-positive MBC receive targeted therapies (*e.g.*, trastuzumab, pertuzumab, lapatinib) usually in combination with chemotherapy; trastuzumab emtansine (T-DM1) is given as monotherapy, but is a conjugate that includes the cytotoxic agent maytansine (Krop et al., 2014). Independent of the molecular phenotype, chemotherapy will, therefore, be an option at some point for most patients with MBC. Early reports of immunotherapy targeting PD-1/PD-L1 and antiandrogens are encouraging in subsets of TNBC, but these are not ready to replace chemotherapy (Emens et al., 2015; Traina et al., 2015).

Improving overall survival (OS) and/or quality of life (QOL) are key aims in treating patients with MBC. A perception may exist when considering chemotherapy: that the choice is between efficacy with treatment or better QOL without treatment. This misconception ignores the complications of the underlying disease on QOL. Our aim should, therefore, be to improve both quantity and quality of life for women with MBC.

Another guiding principle in treating patients with MBC is that single-agent sequential treatment is usually preferable to combination treatments (Fedele et al., 2012). The latter frequently achieves higher response rates, but at the cost of increased toxicity and little impact on OS. Although single-agent sequential treatment is accepted as "standard," the evidence from randomized trials regarding which drug to use following anthracycline and taxane has been surprisingly limited, especially for "old" agents such as vinorelbine and gemcitabine (Oostendorp et al., 2011). As a result, guidelines do not specify the sequence in which drugs should be given.

In contrast to the use of endocrine and HER2 targeted therapies, where biomarkers predictive of efficacy (*e.g.*, ER, HER2 status) are integral to treatment decisions, similar biomarkers are not well defined in the context of specific chemotherapy. The data are arguably strongest for patients with BRCA-mutated MBC in whom carboplatin was substantially more effective and better tolerated than docetaxel as first-line treatment (Tutt et al., 2014a). The ability to "personalize" the choice of cytotoxic to the individual patient and her cancer more widely would represent a major paradigm shift.

Drug resistance is, without doubt, the primary impediment to successful treatment of patients with MBC (Perez, 2009). With the increased use of anthracyclines (although with less cumulative doses) and taxanes in the (neo) adjuvant setting, a growing proportion of patients with MBC have pretreated and/or drug-resistant disease (Perez, 2009). Usual practice after an anthracycline and taxane has been to favor agents from a class not previously administered, with the expectation that the cancer is less likely to be cross-resistant to such treatment. The need remains, therefore, for new and better chemotherapy for women with MBC, almost half (43%) of whom receive >3 lines of chemotherapy (Ribeiro et al., 2012). New agents should preferably belong to a novel class, or have a novel mechanism of action, improve OS while maintaining or improving QOL when given as monotherapy, and be well tolerated and supported by sound evidence that would ideally include a predictive biomarker.

This article does not attempt to be a comprehensive review of chemotherapy in MBC. Rather, we focus on single-agent treatment following an anthracycline and a taxane, limiting ourselves to the most widely used drugs and emerging chemotherapy options.

2. Current therapeutic options for anthracycline- and taxane pretreated MBC

Until recently, therapeutic options after failure of anthracycline and taxane were limited (André and Zielinski, 2012). Currently, widely approved monotherapies for later-line treatment of MBC include capecitabine, eribulin, nanoparticle albumin-bound (*nab*)-paclitaxel, and ixabepilone (in the U.S.); vinorelbine is approved after an anthracycline (but not specifically a taxane) in Europe. Pegylated liposomal doxorubicin (PLD) and single agents such as gemcitabine, platinum agents, and irinotecan are also used (Table 1). There is no agreement regarding the preferred agents and their sequence; a recent consensus report recognized that evidence is strongest for eribulin and capecitabine (Partridge et al., 2014). Likewise, carboplatin/cisplatin chemotherapy seems to be especially active in patients with BRCA 1/2 mutations or for TNBC with DNA repair deficiency (Isakoff et al., 2015). The TNT randomized phase III trial compared carboplatin with docetaxel in 376 patients with metastatic/locally recurrent advanced TNBC and/or BRCA1/2 positive tumors (Tutt et al., 2014b). In the 43 BRCA positive patients the ORR was 68% *vs* 33% and PFS of 6.8 *vs* 3.2 months in the carboplatin vs docetaxel arms, respectively. Such differences were not, however, seen in the overall population (ORR of 31.4 vs 35.6% and PFS of 3.1vs 4.5 months in the carboplatin vs docetaxel arms, respectively). Indeed, many of the current options after anthracycline and taxane have not been compared in randomized clinical trials, and cross-trial comparisons can be difficult. Consequently, treatment decisions are frequently based on personal experience, prior therapy, adverse event profiles, and patient preference (Ribeiro et al., 2012).

2.1. Rechallenge with, or reformulation of, an anthracyclines or taxane

There is a paucity of evidence documenting the efficacy of rechallenge with a conventional anthracycline or taxane in patients with MBC (Ribeiro et al., 2012; Partridge et al., 2014; Isakoff et al., 2015; Tutt et al., 2014b; Venturini et al., 1996). Although responses have been described, most studies are single-center cohorts, small phase II trials, or retrospective analyses of phase III studies; such trials often do not specify previous adjuvant chemotherapy, and patients with anthracycline- and taxane-resistant or refractory dis-

Table 1
At a glance: most common agents used in anthracycline- and taxane-pretreated metastatic breast cancer.

Drug	Differentiating characteristics related to mechanism or class	Key messages from clinical trials	Gaps	Role and issues in clinical practice
Pegylated (PLD) and non-pegylated liposomal doxorubicin	Doxorubicin hydrochloride encapsulated in liposomes with or without surface-bound pegylation	• Similar efficacy but less cardiotoxicity than conventional anthracyclines in first-line setting • Myelosuppression, stomatitis, and PPE major toxicities associated with use	Limited data to suggest role of anthracycline rechallenge in MBC and in later stage MBC	• May consider use after non-anthracycline–containing adjuvant therapy or after limited doses of anthracycline-based adjuvant therapy • Cumulative cardiotoxicity precludes or limits the use in patients with cardiac risk or near threshold doses
nab-paclitaxel	Paclitaxel in albumin-bound complexes *via* nanotechnology platform (nab-technology)	• Until recently, thought to be associated with improved ORR and PFS over that of conventional taxanes (q 3 week schedule) • Activity suggested in taxane-resistant MBC (*i.e.*, not complete cross-resistance) • Less neutropenia but greater PN than paclitaxel (albeit possibly shorter-lived) • Significant alopecia	Recent trial (CALGB 40502 trial) shows no better efficacy and more toxicity than paclitaxel; limited data to suggest role of taxane rechallenge in MBC	• Advantage of short infusion time and "lack" of premedication (especially in diabetic patients and those with prior history of paclitaxel-induced infusion reaction) but neuropathy, alopecia, and cost preclude its broad use • Cumulative PN precludes its use in patients with residual (baseline) neuropathy or history of severe PN with previous agent
Capecitabine	Prodrug that is enzymatically converted to the antimetabolite 5FU	• Convenient oral therapy devoid of appreciable alopecia • Dosage adjustments often necessary even at recommended reduced dose of 2000 mg/m^2/day • HFS (20%) may be treatment limiting; fatigue and diarrhea other common toxicities • Dose reduction required in patients with renal dysfunction	Role in specific molecular subtypes unclearbenefit possibly limited to hormone receptor-positive MBC	• Approved as monotherapy for the treatment of MBC after failure of both A and T • Cumulative PPE may limit duration of therapy or require dose modification and treatment delays over time • Option in women who want to avoid alopecia or concerned about lifestyle interruptions and in elderly patients
Ixabepilone	Epothilone (new class)—non-taxane tubulin polymerizing agent	• Modest phase II activity noted in A-/T- and capecitabine resistant (ORR, 11–12%; TTP/PFS, 2.2–3.1 months) • Toxicity profile not all that different than taxanes in resistant population (most common grade 3/4: neutropenia (50%), neuropathy (14%), and, alopecia (>80%); fatigue also an issue) • Neuropathy is major dose-limiting AE and can be permanent in some • Important to adjust dose in patients with mild to moderate hepatic dysfunction	Recent trial (CALGB 40502 trial) suggests less effective than paclitaxel with greater neuropathy	• Approved as monotherapy for the treatment of metastatic or locally advanced breast cancer after failure of A, T, and capecitabine • Approved in combination with capecitabine for treatment of metastatic or locally advanced breast cancer resistant to A and T or T and A contraindicated • Possible role in TNBC (ORR, 18%) • Not approved by EMA as benefit thought not to outweigh risk (specifically neuropathy) • Cumulative PN precludes its use in patients with residual (baseline) neuropathy or history of severe PN with previous agent
Eribulin	Synthetic analog of natural murine product; binds to a unique site on tubulin	• Survival benefit in late-line regimen after treatment with A, T (and usually capecitabine) compared to TPC; TTP and ORR also favored eribulin • Eribulin at least as effective as capecitabine when compared as single agents • PN and fatigue generally manageable • Neutropenia and fatigue (all grades) in ~50% of patients, but febrile neutropenia uncommon • Dose reductions, delays, and interruptions somewhat common in clinical trials mainly due to neutropenia	• Benefits of eribulin maintained across molecular subtypes, but most robust in patients with HER2-negative disease; efficacy appears greatest in patients with TNBC • Efficacy retained in older patients	• Approved for use in US after A and T and two previous therapies for MBC; in EU, positive opinion for use earlier in MBC (after one previous chemotherapy) • Unsure how to best incorporate agent into standard algorithms but provides evidenced base support for treatment after A, T, and as an alternative to capecitabine • Pre-existing PN does not preclude use of eribulin

Table 1 (*Continued*)

Drug	Differentiating characteristics related to mechanism or class	Key messages from clinical trials	Gaps	Role and issues in clinical practice
Vinorelbine	Second-generation vinca alkaloid	• Phase III trial (vs gemcitabine-capecitabine combination) in A-/T-resistant MBC provided 25% ORR and median PFS of 4 months • Relatively well tolerated; however, significant neutropenia (>50% grade 3/4; ~11% febrile neutropenia risk) • Often require central venous line due to its vesicant properties • Inconvenient dosing regimen (weekly regimen)	Majority of data in anthracycline-resistant disease; wide range of ORR in phase II studies; only one phase III trial *vs* combination (not other monotherapy)	• Cumulative PN precludes its use in patients with residual (baseline) neuropathy or history of severe PN with previous agent • Constipation and abdominal complaints can be particularly bothersome side effects
Gemcitabine	Pyrimidine nucleoside analogue	• Most effective when administered with a taxane (first-line) or carboplatin (later-lines) • Myelosuppression (neutropenia and thrombocytopenia) most common grade 3/4 toxicities; thrombocytopenia may be dose limiting • Liver enzyme elevation may limit the dose intensity	Lack of demonstrable activity as monotherapy in A-/T-resistant MBC	• Limited data supporting use as monotherapy in MBC • Use caution in patients with history of significant myelosuppression, in particular thrombocytopenia, from prior therapies
Platinum agents	Induces DNA adduct formation	• Activity in patients with MBC associated with germline BRCA mutations • Activity in combination (gemcitabine, 5FU, vinorelbine)	Lack demonstrable activity as monotherapy in A-/T-resistant MBC	• Little, if any, role as single agents in MBC as both drugs (carboplatin and cisplatin) perform poorly in previously treated patients • Possible exception is TNBC
Vinflunine	Third-generation vinca alkaloid (novel bi-fluorinated derivative of vinorelbine); possible additional anti-angiogenic properties	• Activity noted in A-/T-resistant MBC (~30% ORR); importantly, 7 of 18 responding patients failed a taxane within 3 months • Phase II trial showed modest activity in patients resistant to vinorelbine • Superior preclinical activity *vs* other vinca alkaloids • Less frequent and milder neurotoxicity than vinorelbine but significant neutropenia, fatigue, and constipation • Difficult to use in combination due to neutropenia • Combination with capecitabine associated with prolonged PFS over capecitabine alone but associated with significant grade 3/4 neutropenia and HFS; combination with gemcitabine less neurotoxic than paclitaxel/gemcitabine; awaiting OS data for both trials	Wide range of ORR in phase II studies; unsure if superior activity over other vinca alkaloids will translate into significant clinical outcome differences	• Pending approval • Less frequent and milder neurotoxicity than earlier generation vinca alkaloids • More grade 3/4 neutropenia although febrile neutropenia was not frequent (2.1–4.8% in combination studies) • It might have a role in some patients in combination with capecitabine (improve PFS and QoL and a trend • to OS)
Irinotecan	Topoisomerase I inhibitor—interferes with DNA coiling	• Broad range of activity; lack cross resistance and overlapping toxicity • Data suggest cytotoxicity dependent upon exposure time with phase II trial demonstrating weekly dosing associated with better tolerability and improved outcomes over every 3 week dosing (due to prolonged SN38, active metabolite) • Myelosuppression and diarrhea (dose limiting) are most frequent toxicities	No randomized data in A-/T-resistant MBC; wide range of ORR in phase II studies	• Not approved for use in MBC • Limited data to support its use as monotherapy in MBC

Table 1 (*Continued*)

Drug	Differentiating characteristics related to mechanism or class	Key messages from clinical trials	Gaps	Role and issues in clinical practice
Etirinotecan pegol	Unique, long-acting polymer engineered molecule consisting of irinotecan bound to polyethylene glycol core by a biodegradable linker (proprietary polymer conjugate technology)	• Pharmacokinetic profile of drug associated with reduced peak SN38 concentrations and long (50 days) half-life providing continuous and sustained exposure of active drug • Phase II trial suggests highly active agent in A-/T- (and capecitabine) resistant MBC (ORR 29%; median PFS 4.9 months for ITT population and 5.6 months for every 21 day regimen) • Most frequent AE is delayed onset diarrhea (77% all grades; 23% grade 3; no grade 4); delayed neutropenia can occur	Awaiting results of phase III *vs* TPC (BEACON trial); trial will also provide additional information regarding biomarkers based on circulating tumor cells and further elucidation on frequency and severity of diarrhea (strict protocol defined guidelines regarding dose modification and treatment)	• BEACON results reported in 2015 and if positive will provide a statistically significant improvement in OS over TPC comparator • Exploratory analysis include poor prognostic subgroups (brain metastases and TNBC) and translational biomarker studies • Lacks common cumulative and/or overlapping toxicities (*e.g.* low bone marrow reserves, neurotoxicity, and cardiotoxicity) with other established agents in MBC • Due to long half-life of SN38, treatment can be delayed to allow for resolution of toxicity (*e.g.*, diarrhea) without interruption of continuous exposure to the active moiety

Abbreviations: 5FU, 5-fluorouracil; A, anthracycline; BEACON, BrEAst Cancer Outcomes with NKTR-102; BRCA, breast cancer gene; CALGB, cancer and leukemia Group B; EMA, European Medicines Agency; HFS, hand–foot syndrome; ITT, intent-to-treat; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PN, peripheral neuropathy; PPE, palmer-plantar erythrodysesthesia; T, taxane; TNBC, triple negative breast cancer; TPC, therapy of physicians' choice.

ease may be excluded (Venturini et al., 1996; Falkson et al., 1994; Bontenbal et al., 1998; Perez et al., 2001; Valero et al., 1998). Nevertheless, patients with disease progression after a "substantial" period following adjuvant anthracycline or taxane treatment may benefit from rechallenge with a conventional anthracycline or taxane in particular if a limited number of cycles of adjuvant anthracyclines and taxanes was received. Although cardiac toxicity can be a concern, the cumulative anthracycline dose in standard adjuvant regimens frequently leaves scope for rechallenge, especially with epirubicin (Ryberg et al., 1998).

Another strategy is to rechallenge with a novel anthracycline or taxane formulation. Most such clinical trials exclude patients with resistant or refractory disease (Table 2) (Keller et al., 2004; Al-Batran et al., 2006; Sparano et al., 2009; Gradishar et al., 2005; Blum et al., 2007a; Roy et al., 2009; Lobo et al., 2010; Gradishar et al., 2012; Rugo et al., 2015; Yardley et al., 2013; Hamilton et al., 2013; Sun et al., 2014). It is also difficult to determine whether rechallenge of new formulations is superior to conventional formulations as data are limited, and direct comparisons were not made. Nevertheless, liposomal anthracyclines as pegylated (PLD) and non-pegylated (NPLD) doxorubicin have different pharmacokinetic profiles (*i.e.*, longer circulating half-life, enhanced drug accumulation) from those of conventional anthracyclines and appear less cardiotoxic whilst demonstrating similar efficacy (Keller et al., 2004; Al-Batran et al., 2006; Sparano et al., 2009). With the availability of multiple other active cytotoxics, PLD or NPLD re-challenge is, however, likely to be limited to patients with a long relapse-free interval following anthracycline-based adjuvant therapy, without significant cardiac impairment and limited access to alternative drugs. Data to support PLD or NPLD rechallenge in later lines of therapy are lacking.

Nab-paclitaxel is an albumin-based paclitaxel delivery system developed as an alternative to solvent-based taxanes and exploiting enhanced albumin uptake in tumors (Table 2) (Ribeiro et al., 2012; Gradishar et al., 2005; Blum et al., 2007a; Roy et al., 2009; Lobo et al., 2010; Gradishar et al., 2012; Rugo et al., 2015; Yardley et al., 2013; Hamilton et al., 2013; Sun et al., 2014). *Nab*-paclitaxel achieved superior overall response rate (ORR) and time to tumor progression (TTP) with less myelosuppression compared to 3-weekly paclitaxel in a phase III trial (Gradishar et al., 2005); it also compared favorably with docetaxel in a randomized phase II trial (Gradishar et al., 2012). In the phase III Cancer and Leukemia Group B (CALGB) 40502 study, however, *nab*-paclitaxel was not superior to weekly paclitaxel but did increase neurotoxicity (Rugo et al., 2015). In terms of efficacy after failure of a conventional taxane, defined as metastatic disease progression during taxane therapy or relapse within 12 months of adjuvant taxane, responses to *nab*-paclitaxel have been reported (Yamamoto et al., 2011); other phase II/III trials have demonstrated activity (Table 2). Despite recent disappointing results, *nab*-paclitaxel is certainly an option in patients who experience hypersensitivity reactions with conventional paclitaxel (Table 1) (Yamamoto et al., 2011).

Finally, there are some data for taxane rechallengerechallange combined with targeted therapy. The phase III AVADO trial of bevacizumab plus docetaxel as first-line therapy for MBC included a small percentage of patients pretreated with adjuvanta taxane (Miles et al., 2010). Although response rate and PFS were significantly superior in the bevacizumab arm, the combination did not improve OS and is not, therefore, approved by the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) for MBC. Similarly, the CLEOPATRA clinical trial combined trastuzumab and docetaxel with pertuzumab or placebo as first line for HER-2 positive MBC included 23.2% and 22.6% of patients pretreated with taxanes (Swain et al., 2015). Recently reported positive OS results have established the triplet as the recommended first-line treatment of choice for women with HER2-positive MBC.

2.2. Capecitabine

Capecitabine, usually given as monotherapy, is commonly used in patients with anthracycline- and taxane-refractory or –resistant MBC, having been extensively evaluated in phase II trials in pretreated MBC and to a lesser extent in randomized trials (Blum et al., 1999; Blum et al., 2001; O'shaughnessy et al., 2001; Talbot et al., 2002; Reichardt et al., 2003; Fumoleau et al., 2004; Blum et al., 2007b; Miller et al., 2005). In a 2011 systematic review of

Table 2
Anthracycline/taxane reformulations: clinical study outcomes.

Author/study phase	Agents	Patients	Previous therapy				ORR	PFS	OS	Grade 3/4 toxicity	Comments
			≥2 MBC (%)	A	T	Resistant					
Keller et al. (2004) Phase III	PLD *vs* Vinorelbine or Mitomicin C + vinblastine	150 129 22	38%	√/-	√	A/T	10% *vs* 12%	2.9 *vs* 2.5 mo $p = 0.11$	11 *vs* 9 mo $p = 0.71$	PLD arm had more HFS (37%)	• Disease progression ≤6 mo of previous T for MBC • 17% of patients in both arms were A-naïve • 39% (arm A) and 35% (arm B) were resistant to A
Al-Batran et al. (2006) Phase II	Single-arm PLD	79	35.4%	√	√/-	A	12.7%	3.6 mo; 95% CI (2.7–6.4)	12.3 mo; 95% CI (7.7–16.3)	HFS 5% Neutropenia 17.1%	• Overall clinical benefit rate was 16.1% for patients documented as A resistance
Sparano et al. (2009) Phase III	PLD + docetaxel *vs* Docetaxel	378 373	0%	√	NR	No	35% *vs* 26% $p = 0.0085$	[a]9.8 *vs* 7 mo $p < 0.001$	20.5 *vs* 20.6 mo $p = 0.81$	HFS: 24% *vs* 0% CHF: 5% *vs* 1%	• One previous chemotherapy regimen for MBC allowed • 100% received (neo) adjuvant A
Gradishar et al. (2005) Phase III	*nab*-P *vs* Paclitaxel	229 225	17% *vs* 18%	√/-	√ (adju-vant)	No	33% *vs* 19% $p = 0.001$	[a]23 *vs* 16.9 wk $p = 0.006$	NR	Grade 4 neutropenia: 9% *vs* 22% PN: 10% *vs* 2%	• Eligibility criteria of previous adjuvant T > 1 year • 77% received previous A
Blum et al. (2007a) Phase II	*nab*-P 100 mg/m^2 *vs* nab-P 125 mg/m^2	106 75	NR (median 3 for MBC)	√/-	√/-	T (89%; 78% in MBC)	14% *vs* 16%	3 *vs* 3.5 mo	9.2 *vs* 9.1 mo	Neutropenia: 18% *vs* 34% PN: 8% *vs* 19%	• Only Nab-P study with T resistant patients (progressed while receiving T for MBC or within 12 mo of adjuvant) • ~67% received A in adjuvant setting • 55% received T in MBC
Roy et al. (2009) Phase II	*nab*-P + gemcitabine	50	0% (1L)	√/-	√/-	No	50%	7.9 mo	92% (6 mo)	Neutropenia: 54% Fatigue: 28%	• 2% HER2-positive patients • 48% received previous A • 30% received previous T
Lobo et al. (2010) Phase II	*nab*-P + gemcitabine + bevacizumab	30	0% (1L)	NR	NR	No	75.9%	10.4 mo	77.2% (18 mo)	PN: 3% Grade 3/4 neutropenia: 0%	• HER2-negative patients • ≥6 mo from (neo)adjuvant therapy • 62% chemo-naïve

Table 1 (*Continued*)

Author/study phase	Agents	Patients	Previous therapy				ORR	PFS	OS	Grade 3/4 toxicity	Comments
			≥2 MBC (%)	A	T	Resistant					
Gradishar et al. (2012) Phase II	*nab*-P 100 mg/m^2 or 150 mg/m^2 weekly vs *nab*-P 300 mg/m^2 q21d vs Docetaxel	76 74 76 74	0% (1L)	NR	NR	No	nab-P 150 49% *vs* docetaxel 35%	nab-P 150 12.9 *vs* docetaxel 7.5 mo $p = 0.0065$	nab-P 150 33.8 *vs* docetaxel 26.6 mo $p = 0.688$	Neutropenia: nab-P 150 44% *vs* docetaxel 94%; $p = 0.001$ PN: nab-P 22% *vs* docetaxel 12%; p = NS	• No prior chemo for MBC allowed • At least 1 year from prior (neo)adjuvant therapy • 39–
Rugo et al. (2015) Phase III	Paclitaxel +/- bevacizumab *nab*-P +/-bevacizumab Ixabepilone +/- bevacizumab	283 271 245	0% (1L)	NR	√/-	No (~20% DFI ≤1 year)	NR	10.6 vs 9.2 *vs* 7.6 mo (Ixabepilone *vs* paclitaxel; $p < 0.0001$)	NR	More adverse events (PN, fatigue, GI) in nab-P arm; least hematologic events in ixabepilone arm	• Bevacizumab planned to all patients but optional in 3/2011 (98% patients received bevacizumab) • 44% received previous T - At interim analysis, ixabepilone failed in comparison to paclitaxel; accrual was closed
Yardley et al. (2013) Phase II	*nab*-P + lapatinib	60	0% (25% received 1 prior regimen)	NR	√/-	No	53%	39.7 wk	Not reached	Diarrhea: 22% Neutropenia: 22% PN: 3%	HER2-positive • One previous chemotherapy regimen for MBC allowed; previous T ≥12 mo • Previous T-containing regimens(Neo)adjuvant: 37%MBC: 7% • (Neo)adjuvant + MBC: 3%
Hamilton et al. (2013) Phase II	*nab*-P + carboplatin + bevacizumab	38	0% (1L)	√	√	NR	85%	9.2 mo	NR	Neutropenia: 53% Thrombocyto-penia: 18% PN: 6%	• Only triple-negative MBC allowed • 65% received previous adjuvant A • 62% received previous adjuvant T
Sun et al. (2014) Phase II	*nab*-P + cisplatin	73	~38% as 2L; 12% as ≥3L	√	√	No	67.1%	9.3 mo	26.9 mo	Neutropenia: 84% PN: 26%	• Eligibility criteria of previous (neo)adjuvant T > 12 mo • Previous T-containing regimens -(Neo)-adjuvant: 50% (>12 mo) - MBC: 32% (> 3 mo) • Previous A-containing regimens: - (Neo)-adjuvant: 73% - MBC: 16% • Longer OS if no previous T

Abbreviations: A, anthracyclines; CHF, congestive heart failure; CI, confidence interval; DFI, disease-free interval; HFS, hand–foot syndrome; MBC, metastatic breast cancer; *nab*-P, *nab*-paclitaxel; NR, not reported; NS, not statically significant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PN, peripheral neuropathy; q21d, every 3 weeks; T, taxanes.
[a]Reported as time to progression.

trials in which at least 80% of patients had received prior anthracycline and taxane, 1494 patients from 8 randomized phase II trials and 2 phase III trials were treated with single-agent capecitabine; the response rate was 18%, median PFS 4.2 months, and OS 13.5 months (Oostendorp et al., 2011). Results from more recent phase III trials of capecitabine monotherapy as the control arm in similar populations reported comparable outcomes (Thomas et al., 2007a; Sparano et al., 2010; Kaufman et al., 2015; Baselga et al., 2014). For historical reasons, most capecitabine trials in MBC are from molecularly-unselected populations. Recent data suggest that capecitabine may be more active in patients with HR-positive MBC (Glück et al., 2009).

Experience with capecitabine-based combinations has been mixed. The addition of capecitabine to docetaxel improves OS *vs* docetaxel alone, but at the cost of greater toxicity (O'shaughnessy et al., 2002). Although this is one of the few regimens that significantly improve OS in MBC, and does so without sacrificing QOL, the combination was not widely adopted in clinical practice due to concerns over toxicity. The addition of ixabepilone to capecitabine increased ORR and PFS, but not OS, and caused substantially more neuropathy and neutropenia (Table 3) (Thomas et al., 2007a; Sparano et al., 2010). Nevertheless, the combination of capecitabine and ixabepilone was approved by the FDA but not by the EMA. Despite initial encouraging results with the combination of capecitabine and sorafenib, a subsequent double-blind, placebo-controlled phase III trial in patients with previously-treated MBC comparing the combination with single-agent capecitabine failed to meet its primary endpoint of improved PFS[515] Finally, a phase II study of capecitabine and eribulin in 42 patients with previously-treated MBC reported an ORR of 42% and PFS of 7.2 months; this efficacy was almost identical to that previously reported with capecitabine and docetaxel, but with superior tolerability and no unexpected toxicities (Twelves et al., 2014a). Of note, the median number of cycles was 8 (range 1–46) and seven patients (16.2%) received >30 cycles of the combination.

3. Newer antimicrotubule agents

3.1. Ixabepilone

The epothilones are structurally distinct from taxanes and represent a new class of microtubule inhibitors; importantly, they have preclinically promising activity in taxane-resistant tumors (Table 3) (Thomas et al., 2007a; Sparano et al., 2010; Perez et al., 2007; Thomas et al., 2007b; Aogi et al., 2013; Smith et al., 2013). Ixabepilone, a semi-synthetic analog of epothilone B, is the first epothilone to be approved by the FDA as a single agent after failure of anthracycline, taxane, and capecitabine; it was also approved by the FDA in combination with capecitabine in patients with previously-treated MBC as described above. Ixabepilone has not, however, been approved by the EMA due to concerns about its therapeutic index, especially the risk of neuropathy (European Medicines Agency, 2014). Some support for the combination of ixabepilone and capecitabine comes from a pre-planned pooled analysis of 2 trials (Thomas et al., 2007a; Sparano et al., 2010), in which patients with TNBC ($n = 443$) had superior ORR (31% *vs* 15%), longer PFS (4.2 *vs* 1.7 months), and a trend toward longer survival (10.3 *vs* 9.0 months) *vs* single-agent capecitabine (Rugo et al., 2008).

In an attempt to improve its therapeutic index in MBC, the standard 3-weekly regimen of ixabepilone was compared to weekly treatment (days 1, 8, 15 every 28 days); 3-weekly ixabepilone was more effective than weekly treatment, albeit with considerably more toxicity and patient withdrawals due to toxicity (Smith et al., 2013). In the first-line setting, a large randomized trial comparing 3-weekly ixabepilone to weekly paclitaxel and weekly *nab*-paclitaxel, each combined with bevacizumab, closed recruitment to the ixabepilone arm at the first interim analysis when the comparison of ixabepilone *vs* paclitaxel crossed the boundary for futility (Table 2) (Rugo et al., 2015). Ixabepilone was significantly less effective than paclitaxel (median PFS 7.6 *vs* 10.6 months, respectively; hazard ratio (HR), 1.53 [95% CI, 1.24–1.90]; $p < 0.0010$); weekly paclitaxel caused less peripheral sensory neuropathy (16% and 25%, respectively) but more grade 3/4 neutropenia (47% and 7% with paclitaxel and *nab*-paclitaxel, respectively). Questions remain, including whether the regimens chosen (based on phase II trials) were optimal; whether toxicity and consequent dose reductions (45% of patients in the *nab*-paclitaxel arm) account for reduced efficacy; and whether bevacizumab may have had a differential effect between the treatment arms. Overall, the role of ixabepilone as single agent or combined with capecitabine as treatment of MBC remains unclear and the risk-benefit balance challenging.

3.2. Eribulin

A more significant addition to the list of novel agents for the treatment of chemotherapy-resistant/pretreated MBC is eribulin mesylate. As a structurally simplified synthetic analog of the natural marine product halichondrin B, eribulin distinguishes itself from other antimicrotubule agents by its unique interaction with tubulin, inhibiting microtubule growth with no apparent effect on depolymerization, unlike other cytotoxic agents directed at the microtubule (Kuznetsov et al., 2004). This novel mechanism of action may explain the activity of eribulin in taxane-resistant tumor cell lines (Kuznetsov et al., 2004). Encouraging activity was seen in an initial phase II study, but at the price of frequent neutropenia leading to frequent dose omissions (Vahdat et al., 2009). Modification of the regimen from administration on days 1, 8, and 15 every 28 days to a days 1 and 8 every 21-day regimen reduced treatment omissions and maintained activity, although neutropenia remained common (Vahdat et al., 2009; Cortes et al., 2010).

The global multicenter phase III trial, EMBRACE (Eisai Metastatic BReast Cancer study Assessing physician's Choice *vs* E7389) randomized patients with locally recurrent or MBC previously treated with 2–5 prior chemotherapy regimens, including anthracycline and taxane, to eribulin or single-agent "treatment of physicians' choice" (TPC) (Cortes et al., 2011). The study achieved its primary endpoint with a statistically and clinically significant increase in OS of 2.5 months with eribulin; TTP and ORR supported the clinical benefit of eribulin over TPC. The most common grade 3–4 toxicities were neutropenia, although febrile neutropenia was uncommon (8% of patients), as was reversible peripheral neuropathy (Table 3). An updated survival analysis after 77% of events, requested by regulators, confirmed the primary analysis with eribulin benefits being maintained across all molecular subtypes of MBC. EMBRACE established eribulin as the only cytotoxic to significantly prolong survival in patients with MBC previously treated with both anthracycline and taxane and led to its approval as third-line or later treatment in this setting. The novel study design, with a TPC control arm and OS primary endpoint, was commended by the FDA (Donoghue et al., 2012).

A second phase III trial, Study 301, compared eribulin with capecitabine in a less heavily pretreated population, who had nevertheless received anthracycline and taxane (Kaufman et al., 2015).The trial failed to meet its co-primary endpoints of improved OS, although there was a trend favoring eribulin (HR 0.88 [95% CI, 0.77–1.00]; $p = 0.056$). Neutropenia was common, but febrile neutropenia was seen even less frequently (<3%) than in the EMBRACE trial; QOL was similar in both arms (Cortes et al., 2015a,b). Of note, there was no difference in PFS between the two arms. Recent preclinical work has suggested that eribulin may alter tumor biol-

Table 3
New-agent chemotherapy outcomes in pretreated metastatic breast cancer.

Author/study phase	Agent	Patients	Prior therapy					ORR	PFS	OS	Grade 3/4 toxicity
			≥2 MBC (%)	Median for MBC (no.)	A	T	C				
Perez et al. (2007)/Phase II	Ixabepilone	126	88%	NR	√	√	√	11%	3.1 mo	8.6 mo	Neutropenia: 54% PN: 14% FN: <1%
Thomas et al. (2007b)/Phase II	Ixabepilone	49	86%	NR	√	√	NR	12%	2.2 mo	7.9 mo	Neutropenia: 53% FN: 6% PN: 12%
Aogi et al. (2013)/Phase II (Japan)	Ixabepilone	52	73%	NR	√	√	NR	11.5%	2.8 mo	12.4 mo	Neutropenia: 83% FN: 6% PN: 19%
Smith et al. (2013)/Phase II	Ixabepilone q21d vs day 1,8,15 q28d	91 85	NR	2	√/-	√/-	√/-	13.5% vs 7.6%	5.3 vs 2.9 mo	16.1 vs 13.9 mo	Neutropenia: 38% *vs* 6% FN: 2% *vs* 0% PN: 16% *vs* 9%
Thomas et al. (2007a)/Phase III	Ixabepilone + capecitabine vs Capecitabine	369 368	46% 43%	NR	√	√	NR	35% vs 14% ($p < 0.0001$)	5.8 vs 4.2 mo ($p = 0.0003$)	NR	Neutropenia: 68% *vs* 11% PN: 23% *vs* 0% Fatigue: 9% *vs* 3% Toxic deaths: 3% *vs* 1% HFS: 18% *vs* 17%
Sparano et al. (2010)/Phase III	Ixabepilone + capecitabine *vs* capecitabine	609 612	18.3% 17.5%	NR (48% received 1 previous regimen for MBC[85])	√	√	–	43% *vs* 29% ($p < 0.0001$)	6.2 *vs* 4.2 mo ($p = 0.0005$)	16.4 *vs* 15.6 mo ($p = 0.116$; $p = 0.023$ with Cox regression)	Neutropenia: 73% vs 9% FN: 7% *vs* <1% PN: 25% *vs* 1% HFS: 21% *vs* 20%
Cortes et al. (2010)/Phase II	Eribulin	299	NR	NR (median 4 reported includes adjuvant)	√	√	√	9.3%	2.6 mo	10.4 mo	Neutropenia: 54% FN: 6% PN: 7%
Cortes et al. (2011)/Phase III	Eribulin *vs* TPC	508 254	100% (per eligibility criteria)	NR (median 4 reported includes adjuvant)	√	√	√/-	12% *vs* 5% ($p = 0.002$)	3.7 *vs* 2.2 mo ($p = 0.137$)	13.1 *vs* 10.6 mo ($p = 0.041$)	Neutropenia: 45% *vs* 21% FN: 5% *vs* 2% PN: 8% *vs* 2%
Kaufman et al. (2015)/Phase III	Eribulin *vs* Capecitabine	554 548	29% 28%	NR	√	√	–	11% *vs* 12%	4.1 *vs* 4.2 mo ($p = 0.3$)	15.9 *vs* 14.5 mo ($p = 0.056$)	Neutropenia: 46% *vs* 4% FN: 2% *vs* <1% PN: 4% *vs* <1% HFS: 0% *vs* 14%
Awada et al. (2013)/Phase II	Etirinotecan q21d[a] *vs* q14d	35 35	71% 49%	2	√	√ (90%)	√/-	29% *vs* 29%	5.6 *vs* 3.3 mo	13.1 *vs* 8.8 mo	q21d regimen: Neutropenia (delayed): 11% FN: <1% Diarrhea (delayed): 21%
Perez et al. 2015	Etirinotecan *vs* TPC	429 423	100% (per eligibility criteria)	3	√	√	√	16% *vs* 17%	2.4 *vs* 2.8 mo	12.4 *vs* 10.3 mo	Neutropenia 10% *vs* 31% Diarrhea: 10% *vs* 1% Anemia 5% *vs* 5% Fatigue 4% *vs* 4%

Abbreviations: FN, febrile neutropenia; HFS, hand–foot syndrome; MBC, metastatic breast cancer; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PN, peripheral neuropathy; q14d, every 2 weeks; q21d, every 3 weeks; q28d, every 4 weeks; TPC, therapy of physicians' choice.

[a] Dose chosen for phase III study.

ogy in other ways by remodeling the tumor vasculature, reversing epithelial-mesenchymal transition and decreasing the capacity of tumor cells for migration and invasion (Yoshida et al., 2014). These non-classical effects may explain, at least in part, the greater effect of eribulin on OS than PFS or response rates.

The EMA recently requested a joint analysis of the two phase III trials that enabled a more detailed evaluation of eribulin in various subgroups. OS was prolonged by 2.4 months (HR 0.85 [CI, 0.77–0.95]; $p = 0.003$) (Twelves et al., 2014b). The benefits of eribulin were maintained across subgroups, but were most robust in patients with HER2-negative disease and appeared greatest in patients with TNBC who gained an average of almost 5 months in OS (HR 0.74 [CI, 0.60–0.92]; $p = 0.006$). Subsequently, the EMA widened the approval for eribulin, moving it to the second-line setting. The combination of eribulin and capecitabine also appears to be highly effective and remarkably well tolerated as described above (Twelves et al., 2014a).

4. Emerging new agents

Capecitabine and eribulin are currently the "go to" agents for MBC after anthracycline and taxane. Preliminary reports of pivotal studies with etirinotecan pegol and vinflunine have been presented and full publications are awaited (Table 1).

4.1. Vinflunine

Vinflunine is a third-generation, fluorinated vinca alkaloid that has been studied in patients with MBC after first-line anthracycline- and taxane-based chemotherapy. In phase II trials, ORRs ranged from 12.5% to 30%, median PFS from 2.6 to 3.7 months, and OS from 11 to 14 months (Campone et al., 2006; Fumoleau et al., 2009). Tolerability was reported as acceptable; nevertheless, almost two-thirds of patients, experience grade 3/4 neutropenia. In a preliminary report of a large phase III trial single agent vinflunine did not, however, improve survival compared to an alkylator of physician's choice (9.1 and 9.3 months, respectively) (Cortes et al., 2015b).

Two recent MBC trials have assessed vinflunine in combination with capecitabine or gemcitabine(Aapro et al., 2014; Jimenez et al., 2014; Llombart et al., 2014). The addition of vinflunine to capecitabine in women with MBC previously treated with or resistant to an anthracycline and a taxane prolonged PFS by 1.3 months; this improvement was statistically significant and associated with less hand–foot syndrome but grade 3 or 4 neutropenia was increased with the combination (Table 1) (Aapro et al., 2014; Jimenez et al., 2014). Vinflunine was also investigated as an alternative to paclitaxel in combination with gemcitabine as first-line treatment for patients previously receiving anthracycline (Llombart et al., 2014). Non-inferiority with respect to PFS was demonstrated for the vinflunine combination (HR 1.05), which was also less neurotoxic than the paclitaxel-gemcitabine combination. There was, however, no difference in OS (19.1 months and 18.9 months, respectively).

Vinflunine has not been approved by the regulatory authorities for use in MBC.

4.2. Etirinotecan pegol (NKTR-102)

Topoisomerase I (TOP1) inhibitors disrupt DNA replication in cancer cells causing single strand, and eventually lethal double strand, DNA breaks leading to cell death (Xu and Villalona-Calero, 2002). TOP1 inhibition is a "validated" target but has been studied only to a limited extent in MBC (Kumler et al., 2013). TOP1 inhibitors have a mechanism of action distinct from, and lack cross-resistance with, cytotoxic agents currently used to treat MBC. No topoisomerase I inhibitors have been approved by the FDA or EMA for the treatment of breast cancer.

In a systematic review of TOP1 inhibitors in 4 trials of 217 patients with refractory MBC treated with single-agent irinotecan, ORR ranged from 5% to 23%; primary grade 3/4 toxicities were neutropenia, diarrhea, and nausea/vomiting (Kumler et al., 2013). Much of the toxicity associated with irinotecan is due to high peak drug concentrations with 3-weekly dosing (Gerrits et al., 1997). This was reflected in a randomized phase II MBC trial in which weekly irinotecan 100 mg/m^2 appeared better tolerated and more active (ORR 23%; median PFS, 2.8 months) than every 3-weekly treatment at a dose of 240 mg/m^2 (ORR 14%; median PFS, 1.9 months) (Perez et al., 2004). This suggests that prolonged exposure to irinotecan, and its active metabolite SN38, might be beneficial.

Etirinotecan pegol is a long-acting polymer-engineered molecule comprising irinotecan bound to a proprietary polyethylene glycol core by a biodegradable linker that slowly hydrolyzes *in vivo* to release SN38, the active moiety of irinotecan (Jameson et al., 2013; Hoch et al., 2014). Etirinotecan pegol is designed to provide continuous exposure to SN38 at the site of the tumor through altered pharmacokinetics and by exploiting the enhanced permeability and retention (EPR) effect. The principle is that the high molecular weight of the parent drug will limit its ability to freely cross the intact vasculature into healthy tissues; however, because of the EPR effect in tumors, the macromolecule should easily traverse the leaky tumor vasculature.

4.2.1. Pharmacology

Preclinical and initial clinical studies demonstrated a marked contrast in the pharmacokinetic profile of SN38 after treatment with etirinotecan pegol compared to irinotecan(Jameson et al., 2013; Hoch et al., 2014). Eritinotecan pegol achieved a maximum plasma concentration (Cmax) of SN38 10-fold less than irinotecan but the half-life of SN38 was much longer (50 days and 12–17 h for etirinotecan and irinotecan, respectively) (Jameson et al., 2013). These pharmacokinetic characteristics would be expected to reduce toxicities associated with the excessively high SN38 concentrations but maintain efficacy with tumor exposure to SN38 throughout the treatment cycle. This was confirmed in preclinical models with etirinotecan pegol achieving higher and more sustained tumor concentrations of SN38 that correlated with greater tumor growth inhibition in comparison to irinotecan (Hoch et al., 2014). Interestingly, etirinotecan pegol penetrates, and is retained in, TNBC brain metastases (Nounou et al., 2014); there was a significant reduction in both the size and number of brain metastases, and etirinotecan pegol-treated animals had prolonged survival (Hoch et al., 2014). These results are notable given the efficacy of etirinotecan pegol in patients with brain metastases in the BEACON trial (see below).

4.2.2. Early clinical trials

Phase I trials of etirinotecan pegol revealed early evidence of antitumor activity, including in MBC, over multiple dosing schedules with significantly different toxicity compared to irinotecan (Hoch et al., 2014). A subsequent open-label randomized phase II trial evaluated etirinotecan pegol 145 mg/m^2 every 2 weeks (q14d) or every 3 weeks (q21d) in patients failing prior taxane and receiving $\leq$2 previous chemotherapy regimens for MBC (Awada et al., 2013). The primary endpoint was ORR. Ten of 35 patients in each arm responded, with an ORR in the intention-to-treat (ITT) population of 29% (95% CI 18.4–40.6). The median PFS was 4.7 months (ITT population; 95% CI, 2.7–5.7 months), with more than a third of patients (35.5%) progression-free at 6 months. Delayed diarrhea was the most common serious toxicity (q14d: 69% all grades, 17% grade 3, 3% grade 4; q21d: 77% all grades, 23% grade 3, no grade 4) and typically occurred after 3 months of therapy. Unfortunately,

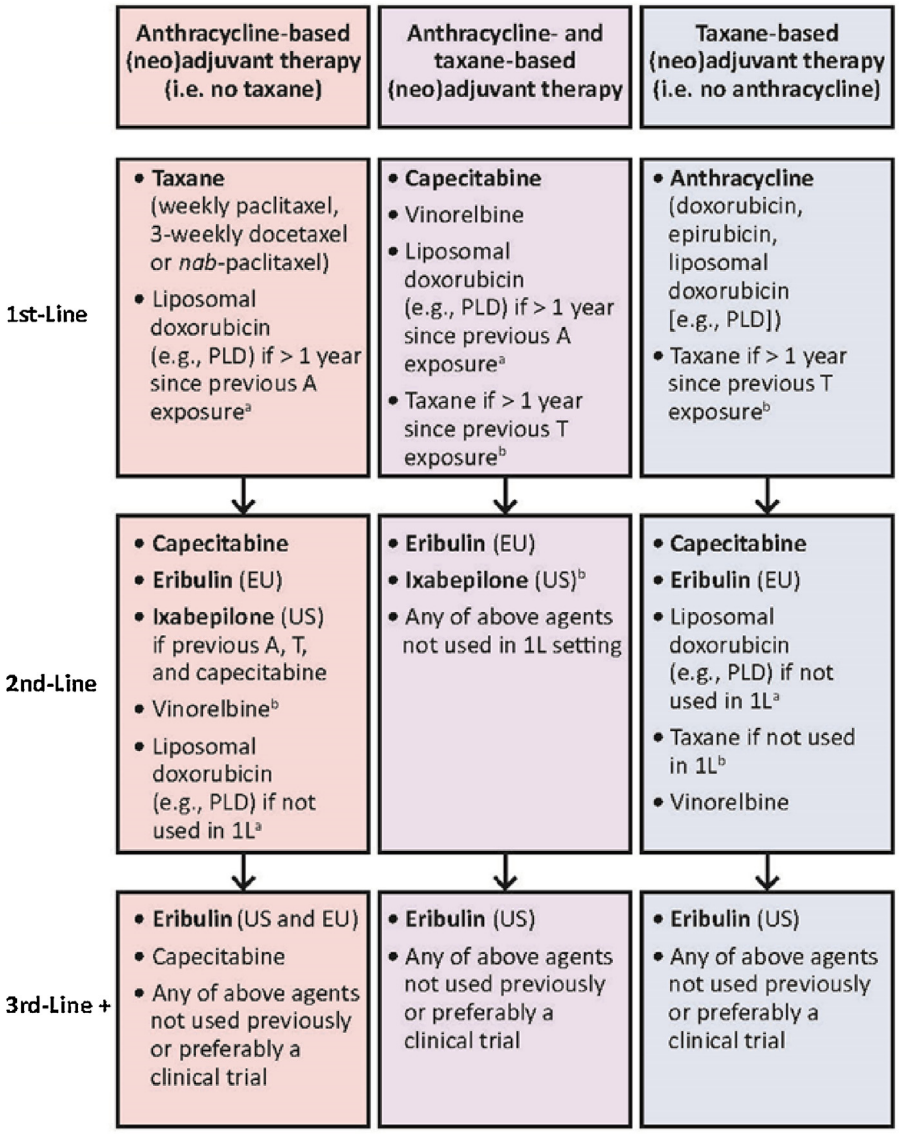

Fig. 1. Algorithmic approach to pretreated metastatic breast cancer utilizing sequential monotherapies.
Abbreviations: 1L, first-line; A, anthracycline; EU, European Union; PLD, pegylated liposomal doxorubicin; T, taxane; US, United States.
Agent(s) with the most supporting documentation in respective treatment line in bold.
[a]Limited if near maximum cumulative dose for cardiotoxicity or if cardiac risk factors.
[b]Limited if important residual neuropathy or history of severe neuropathy with previous therapy.

diarrhea management and dose reduction guidelines were not followed appropriately in more than half (59%) of patients. Other grade 3/4 toxicities observed in >10% of patients across both schedules included fatigue (11%), dehydration (10%), and neutropenia (11%); febrile neutropenia occurred in 1 patient. Comparing the two etirinotecan pegol schedules, both PFS and OS were superior with the q21d schedule (Table 3), which was also associated with less drug-related ≥ grade 3 toxicity and fewer treatment discontinuations. The q21d schedule was, therefore, selected for further study.

4.2.3. *The BEACON trial*

First results of the phase III BEACON study (BrEAst Cancer Outcomes with NKTR-102) comparing etirinotecan pegol with TPC (defined as active single agent, consisting of eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or *nab*-paclitaxel) in 852 patients with MBC who previously received an anthracycline, taxane, and capecitabine were recently reported (Perez et al., 2015). Stratification factors included geographic region, prior use of eribulin, and receptor status. The primary endpoint was OS; additional endpoints were PFS, ORR, clinical benefit rate, duration of response, pharmacokinetics, safety, health-related QOL, and pharmacoeconomics. Additionally, key exploratory endpoints included specific biomarkers (TOP1, topoisomerase 2, markers of DNA damage/apoptosis) in circulating tumor cells (CTCs) using ApoCell technology (Hoch et al., 2013); prespecified analyses also include efficacy assessments in poor prognostic subgroups (*i.e.*, those with liver and/or stable brain metastases at study entry).

Although median survival was longer in the etirinotecan arm by 2.1 months (12.4 months and 10.3 months, respectively; HR 0.87, $P = 0.08$), the trial did not meet its primary endpoint. Among the prespecified subgroup of 67 patients with preexisting stable brain metastases, there appeared to be particular OS benefit from etirinotecan pegol (10.0 and 4.8 months, respectively; HR 0.51, $P < 0.01$), and 12-month survival was 44.4% and 19.4%, respectively. Similarly, the group with liver metastasis ($n = 456$) also benefited

significantly from etirinotecan pegol (OS 10.9 and 8.3 months, respectively; HR 0.73, $P < 0.002$) (Perez et al., 2015). Analyses of subgroups defined by baseline CTC biomarkers are awaited.

5. Conclusions

Chemotherapy remains a mainstay of treatment for patients with MBC treatment, regardless of the molecular phenotype. Following anthracycline and taxane treatment many patients remain candidates for further chemotherapy. Despite the number of cytotoxic agents available to clinicians, there exists a limited amount of evidence-based randomized data and hence, uncertainty and a lack of consensus on the optimal sequence of agents. Nevertheless, a systematic approach is helpful for identifying which agents may be utilized under what circumstances (Fig. 1).

Notwithstanding the emergence of newer targeted therapies and the emerging promise of immunotherapy, we argue that it would be premature to abandon attempts to develop new cytotoxic chemotherapy for the treatment of patients with MBC. On the other hand, new cytotoxic agents should not be "me too" therapies. Rather, new cytotoxic agents should address specific challenges: (1) either a novel target, a novel interaction with an established target, or a novel mode of delivery; (2) achieve meaningful improvements in clinically relevant endpoints, preferably OS and/or QOL, in well-designed randomized phase III trials; and, (3) ideally should identify biomarker(s) predictive of benefit or resistance.

Conflict of interest

CT, honoraria Roche, Eisai, Nektar; MJ, none; AG, none; AA, Advisory boards Nektar, Roche, Bayer, Eisai, Pfizer.

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Biographies

Chris Twelves is Professor of Clinical Cancer Pharmacology and Oncology and Head of Clinical Cancer Research Groups at the Leeds Cancer Research UK Centre. He is a medical oncologist with a particular interest in new drug development and clinical pharmacology; his clinical practice has been in colorectal and breast cancer. After training as an oncologist in London he was Senior Lecturer, then Reader, in Medical Oncology in Glasgow at the Beatson Oncology Centre before taking up his current post at the University of Leeds and St James's Institute of Oncology. Prof Twelves also heads the Leeds Experimental Cancer Medicine Centre in Leeds and has been a member of the Cancer Research UK New Agents Committee and Chair of the New Drug Development group of the EORTC. He has been involved in the development of several important new agents including capecitabine, and eribulin. Professor Twelves has published over 150 papers in journals including the New England Journal of Medicine, Lancet and Journal of Clinical Oncology and spoken at numerous international meetings. He has also edited, or contributed to, several books.

Maria Jove studied medicine at the University of Barcelona, Spain. She completed her specialization in medical oncology within the Spanish registrar program in 2012 at "Institut Catala d'Oncologia", Barcelona. Maria worked as a Clinical Fellow in this institute for two years in the Lung and the Sarcoma/Genitourinari groups before moving to the UK to take up a position in St James's University Hospital in Leeds as a Clinical Fellow in the Phase 1 unit under the supervision of Professor Christopher Twelves. Maria has also been involved with the Neuro-oncology and the Breast Cancer Groups under the supervision of Professor Susan Short and Professor Twelves, respectively. In April 2015 Maria commenced her PhD project, "Intratumoral drug penetration and distribution", with the Pharmacokinetics Group (Lead, Professor Paul Loadman) at the Institute of Cancer Therapeutics (Hon Clinical Director, Professor Twelves) in Bradford, for which she received a grant from the Spanish Medical Oncology Society. Maria is a certified member of the ESMO and Spanish Medical Oncology Society.

Andrea Gombos is medical oncologist working for five years at the Institut Jules Bordet in Brussles. Her research activity is mainly focused on the coordination as principal investigator of several academic trials and internationally conducted clinical trials, evaluating new treatments and treatment combinations in the management of metastatic and early stage breast cancer. She is involved in the development of some international trials and is coordinator for a multicentre Belgian project including a large translational part aiming to understand resistance to the mTOR inhibitor everolimus in metastatic breast cancer. She is a certified member of the ESMO and full member of AACR.

Ahmad Awada is the Head of Medical Oncology Clinic Jules Bordet Cancer Institute Brussels, Belgium Professor Ahmad Awada was born in Lebanon and studied Medicine at the Université Libre de Bruxelles (ULB), Belgium. He did a specialisation in Internal Medicine and Medical Oncology at Jules Bordet Institute (under the supervision of Professor Jean Klastersky), in Brussels, until 1992 ("La plus grande distinction"). During his specialisation, he also had training in the clinical development of new anticancer drugs. As a research fellow, he worked in the Netherlands (New Drug Development Office, Free University, Amsterdam) and in San Antonio, USA (Institute for Drug Development). He focused on the clinical development of new anticancer agents. Back from the USA at the beginning of 1994, Dr. Awada became Assistant Head of Medical Oncology Clinic, and Head of the New Drugs Development Unit at Jules Bordet Institute, Brussels. Since April 2005, he has been the Head of the Medical Oncology Clinic. In addition and from 1st March 2011, Dr Awada was appointed Associate Head of Medicine Department. He has an important clinical activity in the treatment of solid tumors and in particular breast cancer. Dr. Awada took an active part in the development of new drugs, some of them already widely used, namely molecular-targeted therapies. Dr. Awada is a member of several international scientific (ASCO, EORTC, ESMO) societies and and Professor of Clinical Medicine at the Université Libre de Bruxelles. He published 26 book chapters and, 221 articles in international publications.