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Anti-Tumour Treatment

Nab-paclitaxel for the treatment of triple-negative breast cancer: Rationale, clinical data and future perspectives

Francesco Schettini [a], Mario Giuliano [a,b,*], Sabino De Placido [a], Grazia Arpino [a]

[a] *Medical Oncology, Department of Clinical and Surgical Medicine, University of Naples Federico II, Pansini 5, 80131 Naples, Italy*
[b] *Lester and Sue Smith Breast Center, Baylor College of Medicine, 1 Baylor Plaza, 77030 Houston, TX, USA*

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ABSTRACT

Triple-negative breast cancer (TNBC) accounts for ~10–20% of breast cancers and is associated with relatively poor prognosis, earlier disease recurrence and higher number of visceral metastases. Despite an increasing understanding of the molecular heterogeneity of TNBC, clinical trials of targeted agents have thus far been disappointing; chemotherapy, in particular with anthracycline and taxanes, remains the backbone medical management for both early and metastatic TNBC. *Nab*-paclitaxel is a solvent-free, albumin-bound, nanoparticle formulation of paclitaxel and represents a novel formulation of an established, effective chemotherapeutic agent. *Nab*-paclitaxel has been specifically designed to overcome the limitations of conventional taxane formulations, including the barriers to effective drug delivery of highly lipophilic agents. It has shown significant efficacy and better tolerability than conventional taxanes in metastatic breast cancer and is approved for use in this setting. Increasing evidence suggests that *nab*-paclitaxel is effective in patients with more aggressive tumours, as seen in TNBC. Indeed, results of Phase II/III studies indicate that *nab*-paclitaxel may be effective as neoadjuvant treatment of TNBC. This article reviews the rationale and evidence supporting a role for *nab*-paclitaxel in the treatment of TNBC, including ongoing studies such as ADAPT-TN and tnAcity. In addition, the article reviews ongoing research into targeted therapies and immuno-oncology for the treatment of TNBC, and explores the potential role, current evidence and ongoing studies of *nab*-paclitaxel as the chemotherapy partner in combination with immunotherapy, where the unique properties of this taxane, including the lack of requirement for steroid pre-medication, may present an advantage.

Background

Triple-negative breast cancer (TNBC), which is defined according to a lack of oestrogen receptor (ER) and progesterone (PgR) receptor expression, and human epidermal growth factor receptor 2 (HER2) overexpression, accounts for approximately 10–20% of malignant breast tumours [1–3], and is encountered more frequently in specific patient groups, such as younger women, those of Afro-American origin, and those with BRCA mutations [3]. At presentation, triple-negative (TN) tumours are typically larger in size and of higher grade than other breast cancers; they are also associated with an aggressive clinical behaviour, frequently resulting in early metastatic dissemination, particularly to visceral sites [3]. As such, TNBC is associated with a relatively poor prognosis compared with other subtypes [2]. Indeed, data from clinical reports as well as real world data indicate that the median overall survival (OS) for patients with metastatic TNBC is much shorter than that for patients with other metastatic breast cancer (MBC) subtypes (9–13.3 months vs. 28 months, respectively) [4–11].

Breast cancer tumours are classified into four main intrinsic molecular subtypes according to their gene expression profiles: luminal A, luminal B, HER2-enriched and basal-like [12]. TNBC most closely associates with the basal-like subgroup, but the overlap is not absolute; approximately 72% of TN tumours are basal-like, others share molecular characteristics with the luminal A (5%), luminal B (6%) and HER2-enriched (9%) subtypes, and the remaining 8% are normal-like tumours [13]. TN tumours also often share a gene expression profile that is present in breast cancers with *BRCA1* dysfunction, a feature often referred to as 'BRCAness' [8,14]. In 2011, a seminal study by Lehmann and colleagues sought to sub-classify TNBC using gene expression profiling; based on their results, seven distinct molecular subtypes with differing

* Corresponding author at: Division of Medical Oncology, Department of Clinical and Surgical Medicine, University of Naples Federico II, Pansini 5, 80131 Naples, Italy. Fax: +39 081 2203147.
E-mail addresses: francescoschettini1987@gmail.com (F. Schettini), m.giuliano@unina.it (M. Giuliano), deplacid@unina.it (S. De Placido), grazia.arpino@unina.it (G. Arpino).

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biological features, driver mutations for cell growth, natural history and clinical behaviour were identified: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), luminal androgen receptor (LAR) and unclassified (U) [15]. These subtypes differ in terms of prognosis and *in vitro* response to targeted therapy [15,16]. More recently, a simplified algorithm using small gene sets has been developed that can recapitulate the TNBC subtypes identified by the original 2188-gene model of Lehmann et al. and reliably predict therapeutic response to standard chemotherapy [17].

Clinical trials of targeted agents in TNBC have thus far been disappointing. As such, the mainstay medical management for TNBC remains chemotherapy [18,19]. Taxane/anthracycline-containing regimens are the preferred option in the neoadjuvant and adjuvant settings, with various other agents also listed as options by the main international guidelines [18–21]. There is also increasing support for the use of platinum-based regimens for TNBC based on evidence from several randomized controlled trials [22–31], making them an important treatment option for this patient population [18–21]. However, there is still an urgent need for more effective treatments for patients with this breast cancer subtype.

Nab-paclitaxel is a next–generation taxane that has been specifically designed to overcome the limitations of conventional taxane formulations, including the barriers to effective drug delivery of highly lipophilic agents [32]. In this article, we provide an overview of the pharmacological properties and suggested mechanism of action of *nab*-paclitaxel, and discuss how these features translate into improved clinical efficacy and tolerability, as demonstrated in MBC. In particular, we present the latest data on the use of *nab*-paclitaxel in TNBC and summarize recently completed and ongoing trials of therapeutic agents designed to target the molecular aberrations of TNBC subtypes.

Nab-paclitaxel: a novel tumour-targeted therapy comprising an old chemotherapy drug

Paclitaxel has been available for 25 years and its efficacy in the treatment of breast cancer is well established. However, due to its highly lipophilic nature and the need to formulate using a solvent (Cremophor EL) and ethanol, its use is associated with a number of challenges. These include increased risk of hypersensitivity (requiring pre-treatment of patients with a corticosteroid/antihistamine) and prolonged sensory neuropathy, non-linear pharmacokinetics and a toxicity profile that limits dose escalation. The limitations of traditional taxanes (i.e. paclitaxel and docetaxel) have been reviewed extensively in previous publications [33–36].

Nab-paclitaxel is a novel formulation of paclitaxel, consisting of a colloidal suspension of albumin-bound paclitaxel nanoparticles with a mean diameter of 130 nm [37]. The paclitaxel particles are associated with albumin through non-covalent, hydrophobic interactions, allowing for rapid dissociation of the paclitaxel nanoparticles when administered intravenously [36]. Importantly, *nab*-paclitaxel is not formulated using a solvent and, thus, is devoid of solvent-associated hypersensitivity reactions, toxicities and dosing complications; its use does not require pre-medication [36,38,39]. *Nab*-paclitaxel is pharmacologically distinct from solvent-based paclitaxel, having linear pharmacokinetics and a higher maximum tolerated dose than paclitaxel [32,40–44]. In addition, by exploiting the natural interactions between albumin and the gp60/caveolin-1 receptor pathway, *nab*-paclitaxel is associated with rapid and preferential delivery and accumulation of paclitaxel at the tumour site [32,36,38,45]. Indeed, pharmacokinetic studies have shown that, compared with paclitaxel, *nab*-paclitaxel is associated with a 9-fold greater penetration of paclitaxel into tissues via transporter-mediated pathways, a 33% higher intratumoural drug concentration, a 10-fold higher mean maximal concentration of free paclitaxel, and a 4-fold lower elimination rate [38,45,46].

The suggested mechanism of action of *nab*-paclitaxel is shown in Fig. 1. Briefly, *nab*-paclitaxel binds to the albumin-specific receptor glycoprotein, gp60, on the endothelial cell surface, which activates caveolin-1 leading to the creation of vesicles (caveolae) that transcytose across the cell cytoplasm. The caveolae then fuse with the cell membrane and release their contents into the tumour interstitial space; there, the drug binds to albumin-binding proteins, which may include SPARC (secreted protein acidic and rich in cysteine), although data are inconsistent [47–53], with no correlation between SPARC expression and clinical efficacy demonstrated in recent Phase III clinical trials [54,55]. The accumulation of *nab*-paclitaxel via albumin-binding proteins at the tumour cell membranes allows for diffusion of paclitaxel into the intracellular compartment and subsequent induction of tumour cell death [36].

Nab-paclitaxel for the management of TNBC: ongoing and completed clinical trials

Nab-paclitaxel has demonstrated superior efficacy compared with paclitaxel in Phase III trials in unselected breast cancer populations, both in the early [56] and metastatic setting [57]. In MBC, findings from a systematic review have shown that *nab*-paclitaxel is the only agent to demonstrate a survival benefit as second line therapy in a clinical trial setting [58]. Moreover, exploratory analyses conducted using data from Phase II [59] and III [57] trials suggest that *nab*-paclitaxel is an effective treatment strategy in patients with poor prognostic factors, such as a short disease-free interval, a higher number of metastatic sites ($\geqslant 3$) and predominantly visceral disease [60,61]. As TNBC is often characterized by poor prognosis, visceral metastasis and early recurrence [3–7], *nab*-paclitaxel may be considered as an option for these patients. Indeed, exploration of the role of *nab*-paclitaxel in patients with TNBC is an area of much interest and active research, with trials undertaken in both the metastatic (Table 1) and neoadjuvant (Table 2) settings. Many of these studies have exclusively recruited patients with TNBC, although some have been conducted in a broader population and included a subgroup analysis of those with TNBC. Of note, *nab*-paclitaxel is dosed on a weekly basis for 3 weeks out of every four (QW 3/4) in most of the studies. The rationale for this approach is based on the increased efficacy observed with weekly paclitaxel, both for metastatic [62–64] and early breast cancer [65,66]. Furthermore, findings from several Phase II studies of *nab*-paclitaxel indicate significant efficacy in MBC with weekly schedules of 100 mg/m^2, 125 mg/m^2, 130 mg/m^2 and 150 mg/m^2 in first and subsequent lines [59,67,68], although concerns remain about the toxicity of weekly doses of 150 mg/m^2 [69]. In the early breast cancer setting, data from the Phase III GeparSepto study have shown that 12 continuous weekly doses of *nab*-paclitaxel 125 mg/m^2 given as the taxane component of neoadjuvant therapy is both well tolerated and associated with superior pathologic complete response (pCR) rates vs. weekly paclitaxel 80 mg/m^2 [56]. In this trial, the original *nab*-paclitaxel dose was 150 mg/m^2, but this was reduced to 125 mg/m^2 in a protocol amend after 464 patients had been treated following toxicity concerns with the higher dose. Another Phase III study (ETNA) evaluated treatment with four cycles of *nab*-paclitaxel 125 mg/m^2 QW 3/4 vs. paclitaxel 90 mg/m^2 QW 3/4 as the taxane component of neoadjuvant therapy [70]. This trial provided important information regarding the required dose intensity for *nab*-paclitaxel as neoadjuvant therapy, since it included a less dose-intense *nab*-paclitaxel regimen compared with the GeparSepto trial [70].

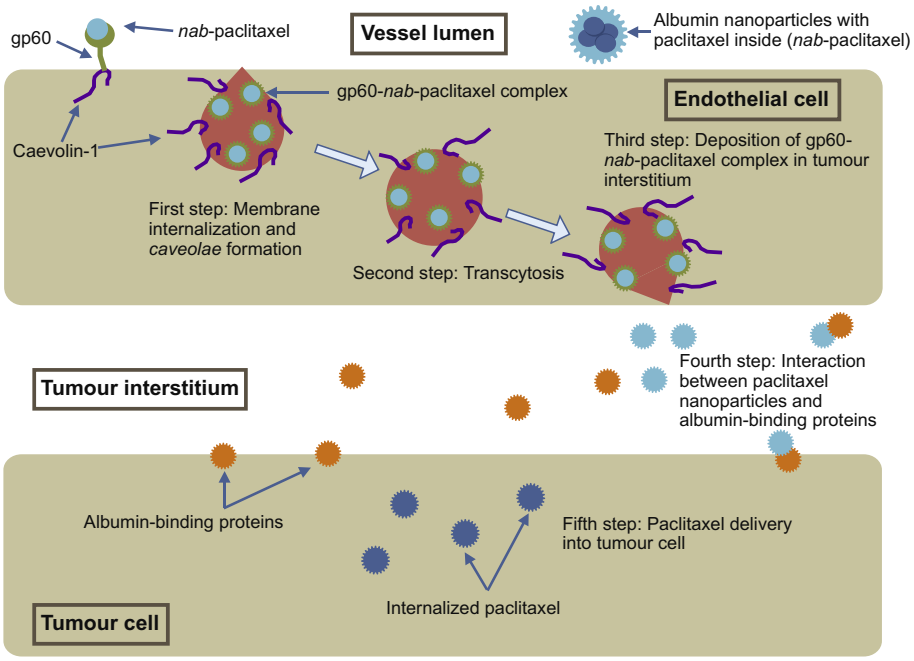

Fig. 1. *Nab*-paclitaxel delivery to tumour cells via albumin-binding proteins.

Results from ETNA were presented at the 2016 ASCO annual meeting [71] and will be discussed later in this article.

It is notable that several studies evaluating *nab*-paclitaxel in TNBC include a platinum agent in the treatment regimen. This is likely because several randomized trials conducted in patients with basal-like TN breast cancer have shown that cisplatin and carboplatin were associated with greater pCR rates (neoadjuvant setting) and improved overall response rates (ORR) and/or slightly longer OS (metastatic setting) compared with non-platinum-based therapies [23,25–28,30,31]. This likely reflects the fact that basal-like TN tumours are frequently associated with *BRCA* mutations or homologous recombination deficiency (HRD) [72–74], which appear to be more sensitive to platinum agents [28,75–78].

Of the eleven studies in the advanced/metastatic setting (Table 1), four have been completed [79–82] and, of these, three have reported results. One of these was a Phase II trial which evaluated the combination of *nab*-paclitaxel with gemcitabine and bevacizumab as first-line treatment in metastatic HER2-negative breast cancer [79]. In a subgroup analysis of patients with TNBC in this trial ($n = 13$), the ORR was 69%, compared with 75.9% in the overall population ($n = 29$). PFS and OS at 18 months were 10.6% and 82.5%, respectively; values that were not significantly different from those in patients with hormone receptor-positive disease. The authors described the clinical benefit rate (CBR; ORR + stable disease [SD]) in the TNBC subgroup (84.6%) as exceptionally high [79]. In the second completed Phase II study, which was comprised exclusively of patients with metastatic TNBC ($n = 34$), first-line treatment with *nab*-paclitaxel, carboplatin and bevacizumab was associated with an ORR of 85%, a CBR of 94%, and a median PFS of 9.2 months [81]. The third was a Phase III randomized controlled trial which compared first-line treatment with bevacizumab 10 mg/kg on Days 1 and 15 Q4W combined with either paclitaxel 90 mg/m^2 (arm A), *nab*-paclitaxel 150 mg/m^2 (arm B) or ixabepilone 16 mg/m^2 (arm C), all QW 3/4, in 799 women with MBC [82]. Arm C was closed for futility at the first interim analysis and arm A and arm B were also closed for futility at the second interim analysis. Without considering ixabepilone results, *nab*-paclitaxel was not superior to paclitaxel (PFS 9.3 vs. 11.0 months; hazard ratio (HR) 1.20; 95% confidence interval (CI) 1.00–1.45; $p = 0.054$). Similar results were seen in terms of OS. In an unplanned, exploratory subset analysis of patients with TNBC, there was also no significant difference in terms of PFS between *nab*-paclitaxel and paclitaxel (median PFS 7.4 and 6.5 months, respectively; HR 0.86; 95% CI 0.60–1.25; $p = 0.43$). Despite the possible confounder of the addition of bevacizumab, this is the only Phase III trial comparing weekly *nab*-paclitaxel with weekly paclitaxel in the advanced setting that also provides data for the TN subgroup. Although results from this trial confirmed good activity with *nab*-paclitaxel, albeit without demonstrating superiority to paclitaxel, this trial also showed that *nab*-paclitaxel 150 mg/m^2 QW 3/4 in combination with bevacizumab was too toxic in this patient population, as revealed by the higher rates of Grade $\geqslant 3$ toxicity, dose reductions and discontinuations in the *nab*-paclitaxel/bevacizumab arm compared with the paclitaxel/bevacizumab arm [82].

Amongst the ongoing studies, data are available from a Phase II study which compared *nab*-paclitaxel monotherapy with *nab*-paclitaxel plus the anti-death receptor 5 monoclonal antibody, tigatuzumab, in 64 patients with TNBC (any line) [83]. Although the combination was well tolerated, the addition of tigatuzumab did not improve the ORR or PFS compared with *nab*-paclitaxel alone. However, there was prolonged clinical benefit in four patients treated first-line with the combination. Although it was not the aim of the trial, the results support the activity of *nab*-paclitaxel in advanced TNBC.

Other ongoing studies in the advanced setting have yet to report data. The largest of these exclusively in patients with TNBC is tnAcity (Triple-Negative Albumin-bound paclitaxel Combination International Treatment Study), which is a Phase II/III trial evaluating *nab*-paclitaxel 125 mg/m^2 QW for 2 weeks out of every three (2/3) in combination with either gemcitabine or carboplatin vs. gemcitabine plus carboplatin [84,85]. Recruitment to the 3-arm, Phase II part of this trial is complete, and results will determine which of the *nab*-paclitaxel doublet combinations will be compared with gemcitabine plus carboplatin in the Phase III part of the trial. Considering the results of the Phase III TNT (Triple Negative Trial), which showed no difference in efficacy between carboplatin and docetaxel for the first-line treatment of metastatic

Table 1
Nab-paclitaxel studies in the advanced/metastatic setting.

Authors/trial	Phase	Trial population	Regimen(s)	Line	ORR	PFS	OS	Status
Lobo et al. [79]	II	HER2− (subgroup analysis for TNBC)	• Gemcitabine 1500 mg/m^2 + *nab*-P 150 mg/m^2 + bevacizumab 10 mg/kg D1, 15 Q4W	I	69%	10.6% (95% CI, 0.6–36.8%) at 18 months	82.5% (95% CI, 46.1–95.3%) at 18 months	Published
Hamilton et al. [81]	II	TNBC	• *Nab*-P 100 mg/m^2 QW 3/4 + carboplatin AUC2 QW 3/4 + bevacizumab 10 mg/kg Q2W	I	85%	Median 9.2 months	–	Published
NCT00472693 [80]	II	TNBC	• *Nab*-P 100 mg/m^2 QW 3/4 + bevacizumab 10 mg/m^2 D1,15 Q4W	II	–	–	–	Completed, but not yet published
Forero-Torres et al. [83]	II	TNBC	• *Nab*-P 100 mg/m^2 QW 3/4 + tigatuzumab Q2W • *Nab*-P 100 mg/m^2 QW 3/4	Any line	28% vs. 38%	Median 3.6 months (both arms)	–	Ongoing Interim data published
tnAcity (NCT01881230) [85]	II/III	TNBC	Phase II: • *Nab*-P 125 mg/m^2 + gemcitabine 1000 mg/m^2 • *Nab*-P 125 mg/m^2 + carboplatin AUC2 • Gemcitabine 1000 mg/m^2 + carboplatin AUC2 • Phase III: • *Nab*-P + gemcitabine or carboplatin • Gemcitabine + carboplatin • All doses given QW 2/3	I	–	–	–	Ongoing
NCT00733408 [87]	II	TNBC	• *Nab*-P QW 3/4 + bevacizumab D1, 15 Q4W × 6 *Patients achieving CR, PR or SD will receive bevacizumab Q2W or Q3W and erlotinib QD*	I	–	–	–	Ongoing
SNAP (NCT01746225) [89]	II	HER2−	*Nab*-P 125 mg/m^2 QW 3/4 × 3 cycles then maintenance with: • *Nab*-P 150 mg/m^2 D1, 15 Q4W, or • *Nab*-P 100 mg/m^2 QW 3/4, or • *Nab*-P 75 mg/m^2 weekly	I	–	–	–	Ongoing
ABRAMYO (2013-005134-38) [90]	I/II	HER2−	Phase I: • *Nab*-P 100 mg/m^2 + L-doxorubicin 20 mg/m^2 (Step 1); *nab*-P 125 mg/m^2 + L-doxorubicin 20 mg/m^2 (Step 2); *nab*-P 125 mg/m^2 + L–doxorubicin 25 mg/m^2 (Step 3) All doses given QW 3/4 Phase II: • *Nab*-P + L-doxorubicin at recommended dose from Phase I All doses given QW 3/4	I	–	–	–	Ongoing
NCT01463072 [88]	II	All types of BC	• *Nab*-P QW 3/4	I	–	–	–	Recruiting
NCT01207102 [130]	II	TNBC	• *Nab*-P 100 mg/m^2 QW 3/4 + carboplatin AUC2 QW 3/4	I	–	–	–	Terminated because of low enrollment
CALGB 40502/NCCTG N063H (Alliance) [82]	III	All types of BC (subgroup analysis for TNBC)	• *Nab*-P 150 mg/m^2 QW 3/4 ± bevacizumab 10 mg/kg D1, 15 Q4W • Paclitaxel 90 mg/m^2 QW 3/4 ± bevacizumab 10 mg/kg D1, 15 Q4W • Ixabepilone 16 mg/m^2 QW 3/4 ± bevacizumab 10 mg/kg D1, 15 Q4W	I	34% vs. 38%	9.3 vs. 11.0 months; $p = 0.054$ (7.4 vs. 6.5 months in TNBC; $p = 0.43$)	23.5 vs. 26.5 months; $p = 0.20$	Completed

BC, breast cancer; CI, confidence interval; CR, complete response; *nab*-P, *nab*-paclitaxel; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

Table 2
Nab-paclitaxel studies in the neoadjuvant setting.

Authors/trial	Phase	Trial population	Treatments	pCR rates	Status
Mrozek et al. [91]	II	HER2– (subgroup analysis for TNBC)	• *Nab*-P 100 mg/m^2 + carboplatin AUC2 QW 3/4 + bevacizumab 10 mg/kg D1, 15 Q4W	50% (pCR achieved only in TNBC)	Completed
Matsuda et al. [92]	II	Inflammatory BC (subgroup analysis for TNBC)	• *Nab*-P 100 mg/m^2 + carboplatin AUC2 + panitumumab 2.5 mg/kg QW × 4 followed by 5-fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2 QW × 4	36% (60% in TNBC subgroup)	Completed
GeparSepto (NCT01583426) [56,131]	III	All types of BC (subgroup analysis for TNBC)	• *Nab*-P 150 mg/m^2 weekly for 12 w • Paclitaxel 80 mg/m^2 weekly for 12 w *Both followed by epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 Q3W × 4*	*Nab*-P: 48.2% Paclitaxel: 25.7% ($p < 0.001$)	Ongoing (primary endpoint data published)
ADAPT-TN (NCT01815242) [96,110]	II/III	TNBC	• *Nab*-P 125 mg/m^2 + gemcitabine 1000 mg/m^2 D1, 8 Q3W × 4 • *Nab*-P 125 mg/m^2 + carboplatin AUC2 D1, 8 Q3W × 4	Overall: 36% *Nab*-P + gemcitabine: 25% *Nab*-P + carboplatin: 49.2% ($p = 0.006$)	Ongoing
ETNA (NCT01822314) [70] [71]	III	HER2– (subgroup analysis for TNBC)	• *Nab*-P 125 mg/m^2 QW 3/4 × 4 • Paclitaxel 90 mg/m^2 QW 3/4 × 4 *Both followed by standard EC, AC or FEC Q3W × 4*	Overall: *Nab*-P 22.5%, Pac 18.1%; $p = 0.127$ (TNBC: *Nab*-P: 41.3%, 35.5%; $p = 0.376$)	Ongoing (primary endpoint data presented)
NCT01525966 [98]	II	TNBC	• Carboplatin D1 Q4W + *nab*-P weekly × 4	–	Recruiting
Sachdev et al. [97]	II	TNBC	• *Nab*-P 100 mg/m^2 QW 3/4 + carboplatin AUC6 Q3W × 4 followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 Q3W × 4 *Bevacizumab 10 mg/kg D1, 15 Q4W during first six cycles of preoperative CT and post-operatively to complete 1 year of treatment*	Breast: 56% Breast and nodes: 53%	Closed due to slow accrual

AC, doxorubicin + cyclophosphamide; BC, breast cancer; CT, chemotherapy; EC, epirubicin + cyclophosphamide; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; *nab*-P, *nab*-paclitaxel; pCR, complete pathological response; TNBC, triple-negative breast cancer.

TNBC in the overall study population, but superior efficacy for carboplatin in the subgroup of patients with germline *BRCA* mutations [86], tnAcity will provide interesting information on the specific efficacy of a first-line taxane-platinum regimen in the TN setting.

Another ongoing study that exclusively includes patients with advanced TNBC is evaluating induction therapy with six courses of weekly *nab*-paclitaxel plus bevacizumab, with responders receiving bevacizumab or erlotinib until disease progression or unacceptable toxicity [87]. The remaining ongoing studies are evaluating *nab*-paclitaxel in broader breast cancer populations. These include a Phase II study of weekly *nab*-paclitaxel monotherapy in patients ⩾65 years with all types of breast cancer [88], the Phase II SNAP study comparing three different *nab*-paclitaxel regimens in HER2-negative disease [89], and the Phase I/II ABRAMYO study evaluating the combination of *nab*-paclitaxel and liposomal doxorubicin, also in HER2-negative MBC [90].

Many of the trials evaluating *nab*-paclitaxel in the neoadjuvant setting have reported data (Table 2). Four of these studies [56,71,91,92] were conducted in a broader range of breast cancer subtypes, with data also reported for the TNBC subgroup. In a Phase II study conducted by Mrozek and colleagues, which evaluated the combination of weekly *nab*-paclitaxel and carboplatin plus bevacizumab in 33 patients with HER2-negative breast cancer, pCR was achieved only in the subgroup of patients with TNBC ($n = 12$), with a pCR rate in this subgroup of 50% (6/12) [91]. Similarly, in a Phase II study of weekly *nab*-paclitaxel and carboplatin plus panitumumab in 24 patients with inflammatory breast cancer, a higher pCR rate was achieved in the TNBC subgroup of patients (56% vs. 20% in the non-TNBC subgroup) [92]. Notably, in the large Phase III GeparSepto study, pCR rates were significantly greater with *nab*-paclitaxel compared with paclitaxel in the overall patient population (38.4% vs. 29.0%; $p = 0.001$) and were doubled for those with TNBC (48% vs. 26%; $p < 0.001$) [56]. Although long-term outcomes data from GeparSepto are yet to be reported, these results are encouraging given that patients who achieve a pCR seem to achieve a survival benefit compared with those who do not [4,93–95]. Indeed, in a pooled analysis of data from over 6000 patients treated with neoadjuvant anthracycline-taxane-based chemotherapy in seven randomized trials, pCR was associated with improved disease-free survival (DFS) in a number of breast cancer subtypes, including TNBC, and the authors concluded that pCR is a suitable surrogate endpoint for TNBC [95]. A more recent analysis of data from nearly 12,000 women with breast cancer also showed that the association between pCR and long-term outcomes was particularly strong in those with aggressive tumour subtypes; in TNBC, the HR (95% CI) for event-free survival (EFS) and OS were 0.24 (0.18–0.33) and 0.16 (0.11–0.25), respectively [94]. However, there is insufficient data to validate pCR as surrogate endpoint for survival.

The previously mentioned Phase III ETNA trial compared *nab*-paclitaxel and paclitaxel in a taxane-anthracycline/cyclophosphamide ± fluorouracil (T-AC/EC/FEC) neoadjuvant regimen in patients with HER2-negative, high-risk breast cancer [70], with patients stratified according to tumour subtype. The primary endpoint of this trial was pCR, with secondary endpoints including a comparison between pCR achieved in luminal vs. TN disease. Unlike GeparSepto, results from the ETNA trial failed to show a statistically significant improvement in pCR rates with *nab*-paclitaxel compared with paclitaxel in either the overall population (22.5% vs. 18.1%, respectively; $p = 0.127$) or in the TNBC subgroup (41.3% vs. 35.5%, respectively; $p = 0.376$), although numerical improvements were apparent. Although it is difficult to compare results from these two trials, one possible explanation for the lack of a significant improvement in pCR in the ETNA trial is the lower dose intensity of *nab*-paclitaxel used (125 mg/m^2 QW 3/4 – equivalent to 93.75 mg/m^2/week, compared with 125 mg/m^2/week in

GeparSepto). Although the dose intensity of paclitaxel was also lower in ETNA (90 mg/m^2 QW 3/4 – equivalent to 67.5 mg/m^2/week, compared with 80 mg/m^2/week in GeparSepto), the relative reduction in dose intensity between the two trials was greater for *nab*-paclitaxel (25% reduction in dose intensity with *nab*-paclitaxel compared with a 16% reduction in dose intensity with paclitaxel) [71].

Amongst the trials evaluating *nab*-paclitaxel in the neoadjuvant setting exclusively in patients with TNBC, data from the ADAPT-TN Phase II trial, which compared 12 weeks of *nab*-paclitaxel 125 mg/m^2 QW 2/3 plus either gemcitabine 1000 mg/m^2 or carboplatin area under the curve (AUC) 2 in 336 patients with TNBC, have recently been reported [96]. Findings from this trial showed that the combination of *nab*-paclitaxel plus carboplatin is associated with a greater pCR than *nab*-paclitaxel plus gemcitabine (ypT0/is, ypN0: 45.2% vs. 25.8%; ypT0, ypN0: 45.9% vs. 28.7%; $p < 0.001$). In another Phase II trial, which evaluated the combination of weekly *nab*-paclitaxel plus carboplatin followed by doxorubicin plus cyclophosphamide with concurrent bevacizumab in 42 patients with TNBC, interim data for the first 30 evaluable patients showed an in-breast pCR rate of 56% and a breast plus node pCR rate of 53% [97]. Unfortunately, this trial was closed early due to slow accrual.

An additional trial of weekly *nab*-paclitaxel in the neoadjuvant setting is currently ongoing. This is a single-arm Phase II study evaluating the combination of *nab*-paclitaxel and carboplatin in TNBC, with a primary endpoint of pCR or Symmans criteria of 0–1 and an estimated completion date of January 2017 [98].

Apart from data from randomized clinical trials, several case reports for the use of *nab*-paclitaxel in patients with TNBC have been published. Although anecdotal, these reports also indicate that treatment with *nab*-paclitaxel, either alone or as part of combination therapy, is feasible and effective with strong and prolonged responses and acceptable toxicity reported [99–102].

Taken together, these data demonstrate that *nab*-paclitaxel is a potent and effective taxane for the management of breast cancer, with impressive efficacy also reported in patients with TNBC. Ongoing trials, particularly tnAcity, will provide further evidence to help define the role of *nab*-paclitaxel in TNBC in the future.

Future perspectives

As clinical trials of targeted agents in TNBC have thus far been disappointing, it is likely that chemotherapy will remain the backbone of TNBC treatment in the near future. For patients with early stage TNBC, greater benefit may be derived from intensive neoadjuvant chemotherapy regimens, since attainment of pCR has been associated with a better prognosis [4,94,95,103]. In this context, data from GeparSepto provide compelling evidence for the preferential use of *nab*-paclitaxel as the taxane component of a 12-week T-AC neoadjuvant regimen in patients with TNBC [56]. However, long-term data are still awaited to see if this improvement in pCR translates into an EFS or OS benefit. Lack of regulatory approval also limits the current use of *nab*-paclitaxel in this setting.

For patients with metastatic TNBC, exploratory data from a randomized, Phase III study in MBC indicate that three-weekly *nab*-paclitaxel is effective in achieving a rapid tumour response in patients with features of aggressive disease [60,104]. As weekly conventional paclitaxel is more effective than a three-weekly regimen, it is conceivable that a weekly approach could also improve outcomes with *nab*-paclitaxel, and there is growing support for its use in selected patients [69]. Indeed, weekly *nab*-paclitaxel is included as an option for MBC in NCCN (but not EU) treatment guidelines [21]; however, the weekly schedule of *nab*-paclitaxel is not currently licensed for use in MBC. Results of the tnAcity trial of weekly *nab*-paclitaxel-containing regimens will therefore provide more robust evidence to clarify the optimal use of *nab*-paclitaxel in metastatic TNBC.

Although *nab*-paclitaxel appears to be a highly effective chemotherapy for the management of TNBC, further work is needed to improve outcomes for this patient population. Indeed, an increased understanding of the molecular heterogeneity of TNBC may pave the way for more successful therapy in the future. The gene expression profiles of different TNBC subtypes and corresponding therapies that may prove useful in these subtypes are summarized in Table 3. Currently, there are several ongoing Phase II and III trials of these therapies in TNBC in the neo/adjuvant and metastatic settings (Table 4), with some evaluating targeted agents in combination with a taxane (including *nab*-paclitaxel) and/or a platinum agent. However, most of these trials have not selected patients according to genetically-defined TNBC subtypes, and it will be interesting to see how these agents fare in overall TNBC populations. In addition to these trials, it is also worth highlighting that there are two ongoing trials of personalized genomic-based therapy, one (the PETREMAC study) in high-risk breast cancer [105] and one in TNBC [106].

Another key area of ongoing research in TNBC is the therapeutic role of platinum agents. High pCR rates were observed when carboplatin was added to paclitaxel/doxorubicin in patients with TNBC in the recent GeparSixto trial (53.2% with carboplatin vs. 36.9% without carboplatin, $p = 0.005$) [28], with early data for long-term outcomes indicating that this improvement in pCR associated with the addition of carboplatin also translates into a benefit in DFS (HR 0.56; $p = 0.0350$) [31]. However, in the CALGB 40603 trial, which also demonstrated an improvement in pCR with the addition of carboplatin to paclitaxel plus dose-dense (dd) AC in patients with TNBC [29], attainment of a pCR was associated with improved OS irrespective of treatment received (HR 0.20; $p < 0.001$) and there was no treatment effect for the addition of carboplatin on EFS (HR 0.84; $p = 0.36$) [30]. In the metastatic setting, the role of platinum agents in an unselected TNBC population, at least as monotherapy, is currently uncertain given the results from the TNT trial, which showed no difference in efficacy between carboplatin and docetaxel for the first-line treatment of metastatic TNBC in the overall study population, but superior efficacy for carboplatin in the subgroup of patients with germline *BRCA* mutations [86]. Given the current evidence base, international guidelines only recommend the routine use of platinum agents for TNBC if patients have known *BRCA* mutations [18–21]. However, several studies are ongoing to further clarify the role of these agents in TNBC. A small number of these studies are evaluating platinum monotherapy,

Table 3
Potential therapeutic approaches for TNBC subtypes according to gene expression profiles [15,132].

TNBC subtype	Gene expression profile	Therapeutic targets
BL1	DNA damage response and cell proliferation	PARP inhibitors
BL2	TP63, EGFR and MET signalling	mTOR, growth factor inhibitors
IM	Immune signalling	PARP inhibitors
M	EMT, Wnt, TGFβ, IG1FR, notch, cell proliferation	mTOR, growth factor inhibitors Src inhibitors
MSL	EMT, Wnt, TGFβ, MAPK, Rac, PI3K, PDGF	mTOR, PI3K, MEK and growth factor inhibitors
LAR	AR signalling, FOXA1 and ERBB4 signalling	AR antagonists, PI3K inhibitors
UNC	DNA damage response and cell proliferation	PARP inhibitors

AR, androgen receptor; BL, basal-like; EGFR, epidermal growth factor receptor; IM, immunomodulatory; LAR, luminal androgen receptor, M, mesenchymal; MSL, mesenchymal stem-like, UNC, unclassified.

Table 4
Key ongoing trials of novel immunotherapy and targeted agents in TNBC.

Agent	Phase	Setting/trial population	Regimen(s)	Line	Status	Trial identifier
Immune checkpoint inhibitors						
Nivolumab [128,129]	I	Metastatic TNBC included in one of three arms of the trial (total $n = 138$)	• Nivolumab + *nab*-paclitaxel	I or II	Recruiting	NCT02309177
Atezolizumab [117,118]	IB	Metastatic TNBC ($n = 32$) included in one of six arms of the trial (total $n = 225$)	• Atezolizumab + *nab*-paclitaxel	I-III	Recruiting	NCT01633970
Atezolizumab [120]	III	Metastatic TNBC ($n = 900$)	• Atezolizumab + *nab*-paclitaxel • Placebo + *nab*-paclitaxel	I	Recruiting	NCT02425891
Atezolizumab [124]	II	Early TNBC ($n = 37$)	• Atezolizumab + *nab*-paclitaxel (4 cycles) then atezolizumab (4 cycles) post-surgery	Neoadjuvant & adjuvant	Recruiting	NCT02530489
Atezolizumab [119]	III	Early TNBC ($n = 272$)	• Atezolizumab + *nab*-paclitaxel + carboplatin then AC/EC or FEC post-surgery • *Nab*-paclitaxel + carboplatin then AC/EC or FEC post-surgery	Neoadjuvant	Not yet recruiting	NCT02620280
Pembrolizumab [121]	III	Previously untreated locally recurrent or inoperable metastatic TNBC ($n = 858$)	• Pembrolizumab + *nab*-paclitaxel • Pembrolizumab + paclitaxel • Pembrolizumab + carboplatin + gemcitabine • Placebo + *nab*-paclitaxel • Placebo + paclitaxel • Placebo + carboplatin + gemcitabine	I	Recruiting	NCT02819518
Pembrolizumab [127]	II	2 cohorts: Metastatic TNBC ($n = 30$) and HER2- MBC ($n = 20$)	• Pembrolizumab + *nab*-paclitaxel	I-III	Recruiting	NCT02752685
Pembrolizumab [126]	I	Early TNBC ($n = 80$)	• Pembrolizumab + *nab*-paclitaxel then AC • Pembrolizumab + *nab*-paclitaxel + carboplatin then AC	Neoadjuvant	Recruiting	NCT02622074
Durvalumab [125]	I/II	Early TNBC ($n = 61$)	• Durvalumab + *nab*-paclitaxel then durvalumab + ddAC	Neoadjuvant	Recruiting	NCT02489448
Durvalumab [123]	II	Early TNBC ($n = 174$)	• Durvalumab + *nab*-paclitaxel then durvalumab + EC • Placebo + *nab*-paclitaxel then placebo + EC	Neoadjuvant	Not yet recruiting	NCT02685059
PARP inhibitors						
Veliparib (ABT-888) [133]	III	Early TNBC ($n = 624$)	• Veliparib + carboplatin + paclitaxel then AC • Placebo + carboplatin + paclitaxel then AC • Placebo + placebo + paclitaxel then AC	Neoadjuvant	Recruiting	NCT02032277
Veliparib (ABT-888) [134]	II	Metastatic TNBC or *BRCA* mutation-associated ($n = 235$)	• Cisplatin + veliparib • Cisplatin + placebo	I or II	Not yet recruiting	NCT02595905
Olaparib [135]	III	Germline BRCA mutated, high risk, HER2 negative primary breast cancer ($n = 1500$)	• Olaparib • Placebo	Adjuvant	Recruiting	NCT02032823
Talazoparib [136]	II	Advanced TNBC or HER2- BC with mutation in homologous recombination pathway genes ($n = 58$)	• Talazoparib	II+	Recruiting	NCT02401347
Rucaparib [137]	II	TNBC with *BRCA*1/2 mutations ($n = 135$)	• Rucaparib + cisplatin • Cisplatin	Adjuvant[a]	Ongoing	NCT01074970
mTOR inhibitors						
Everolimus [138]	II	TNBC ($n = 62$)	• Paclitaxel + everolimus then FEC • Paclitaxel then FEC	Neoadjuvant	Ongoing	NCT00499603
PI3K inhibitors						
BKM120 [139]	II	Metastatic TNBC ($n = 50$)	• BKM120	$\leqslant$III	Ongoing	NCT01629615
Ipatasertib (GDC-0068) [140]	II	Early TNBC ($n = 150$)	• Paclitaxel + ipatasertib • Paclitaxel + placebo	Neoadjuvant	Recruiting	NCT02301988
Ipatasertib (GDC-0068) [141]	II	Inoperable locally advanced or metastatic TNBC ($n = 120$)	• Paclitaxel + ipatasertib • Paclitaxel + placebo	I	Recruiting	NCT02162719
MEK inhibitors						
Cobimetinib [142]	II	Metastatic TNBC ($n = 112$)	• Paclitaxel + cobimetinib • Paclitaxel + placebo	I	Recruiting	NCT02322814
AR antagonists						
Bicalutamide [143]	II	AR + metastatic TNBC ($n = 60$)	• Bicalutamide • Physician's choice of treatment	II + I	Not yet started	NCT02353988

(*continued on next page*)

Table 4 (*continued*)

Agent	Phase	Setting/trial population	Regimen(s)	Line	Status	Trial identifier
Enzalutamide [144]	II	AR + advanced TNBC (n = 118)	• Enzalutamide	ND	Ongoing	NCT01889238
EGF inhibitors						
ABX [145]	II	Advanced TNBC (n = 254)	• ABX + cisplatin • Gemcitabine + cisplatin	I	Not yet started	NCT02546934
Nimotuzumab [146]	II	Recurrent/metastatic TNBC (n = 90)	• Nimotuzumab + docetaxel + capecitabine • Docetaxel + capecitabine	I[b]	Recruiting	NCT01939054
VEGF inhibitors						
Bevacizumab [147]	II	Advanced TNBC (n = 304)	• Carboplatin + cyclophosphamide + bevacizumab • Carboplatin + cyclophosphamide • Paclitaxel + bevacizumab • Paclitaxel	I[c]	Recruiting	NCT01898117

AC, anthracycline/cyclophosphamide; AR, androgen receptor; BC, breast cancer; ddAC, dose-dense anthracycline/cyclophosphamide; EC, epirubicin/cyclophosphamide; EGF, epidermal growth factor; FEC, fluorouracil/epirubicin/cyclophosphamide; MBC, metastatic breast cancer; ND, not defined; TNBC, triple-negative breast cancer; VEGF, vascular endothelial growth factor.

Note: This is not an exhaustive list of clinical trials of targeted agents for TNBC; trials were selected for inclusion in the table based on their size, design (inclusion of control arm) and/or population (genetic mutations).

[a] Patients must have completed pre-operative (neoadjuvant) therapy and definitive resection of the primary tumour, but not adjuvant therapy

[b] Previous chemotherapy should include anthracycline or taxane; however, patients must have received no prior chemotherapy after metastasis

[c] Patients must have received no previous cytotoxic therapy for metastatic disease.

either in single-arm studies [107] or vs. other chemotherapies [108] or observation [109]. However, most studies are assessing platinum agents in combination with other chemotherapies, including *nab*-paclitaxel (see Tables 1 and 2). The combination of *nab*-paclitaxel plus carboplatin has been associated with a high ORR in a small Phase II trial in metastatic TNBC [81] and a significant improvement in pCR compared with *nab*-paclitaxel plus gemcitabine in the ADAPT-TN trial [96]. Further information regarding the efficacy of *nab*-paclitaxel plus a platinum agent will be derived from the tnAcity trial [84,85] as well as long-term outcomes data from the ADAPT-TN trial [96,110].

An increasingly important area of current and future research in TNBC is the use of immunotherapy. Indeed, TNBC has a high mutational load which may confer higher immunogenicity compared with other subtypes [111]. Thus, TNBC may respond well to new-generation immunotherapeutic drugs, such as agents that target cytotoxic T-lymphocyte-associated protein 4 (CTLA4) or programmed death ligand 1 (PD-L1) or its receptor, PD-1. Their use in combination with chemotherapies is of particular interest, as cytotoxic agents may help to reinstate anti-tumour immunity via a number of mechanisms, including [112]:

- tumour debulking, which reduces the systemic immunosuppressive activity of malignant cells,
- increased expression or presentation of tumour-associated antigens on the surface of cancer cells,
- stimulation and expression of death receptors on tumour cells which, in the presence of their ligands, induce apoptotic or necrotic cell death and promote the secretion of multiple cytokines and chemokines, including CXCL1, CCL2, interleukin (IL)-6, and IL-8,
- alteration of the surface proteome of cancer cells, making them more susceptible to the cytotoxic activity of various innate and adaptive immune effectors.

Although different chemotherapeutic agents each elicit a discrete effect on the tumour and host immune system, no systematic analysis has been conducted to identify the optimal chemotherapeutic agent to use with immunotherapeutic drugs in order to maximize potential synergistic effects. However, there is emerging evidence to suggest that paclitaxel may be a rational combination partner, as it has been shown to induce secretion of pro-inflammatory cytokines from macrophages, leading to dendritic cell, natural killer cell and T-cell activation; to promote antigen presentation by bone marrow dendritic cells to T cells; and to augment Th1 cellular immunity by increasing the levels of circulating interferon (IFN)-γ-secreting CD8 T-cells and IL-2-secreting CD4 T-cells [113]. However, as *nab*-paclitaxel does not require steroid premedication, which may dampen the immune system and lead to steroid-induced protection of tumour cells against immunotherapy [114], this agent may be preferred over conventional paclitaxel. Indeed, findings from preclinical studies indicate that treatment with *nab*-paclitaxel plus the anti-PD-L1, atezolizumab, shows synergistic antitumour activity [115].

Against this background, there are a number of ongoing trials evaluating the combination of *nab*-paclitaxel with immune checkpoint inhibitors in breast cancer (Table 4). Amongst these, a multicentre, Phase Ib study has recently reported data showing promising activity with the combination of *nab*-paclitaxel plus atezolizumab in 24 patients with metastatic TNBC; the confirmed ORR (defined as $\geqslant$2 consecutive assessments of complete or partial response according to Response Evaluation Criteria in Solid Tumours [RECIST] v1.1 [116]) in all patients was 38% and was higher in patients receiving the combination as first-line (46%, n = 13) vs. second-line (22%, n = 9) or $\geqslant$third-line (40%, n = 10) therapy (Fig. 2 for impact of treatment on tumour burden over time according to line of therapy) [117,118]. Ongoing Phase III trials are NeoTRIPaPDL1 [119], IMpassion130 [120] and KEYNOTE-355 [121], all of which are evaluating *nab*-paclitaxel plus either atezolizumab or pembrolizumab in TNBC. NeoTRIPaPDL1 is evaluating neoadjuvant therapy with *nab*-paclitaxel plus carboplatin ± atezolizumab in locally advanced TNBC [119], whereas IMpassion130 is evaluating *nab*-paclitaxel ± atezolizumab in previously untreated metastatic TNBC and KEYNOTE-355 is evaluating chemotherapy (*nab*-paclitaxel, paclitaxel or carboplatin + gemcitabine) ± pembrolizumab in previously untreated metastatic TNBC [120–122]. In the early breast cancer setting, four other studies of *nab*-paclitaxel with immune checkpoint inhibitors are ongoing. The first is being conducted by the German Breast Group (GBG) and is a randomized Phase II trial (GeparNuevo) to evaluate the addition of durvalumab to a neoadjuvant regimen of *nab*-paclitaxel followed by epirubicin plus cyclophosphamide in

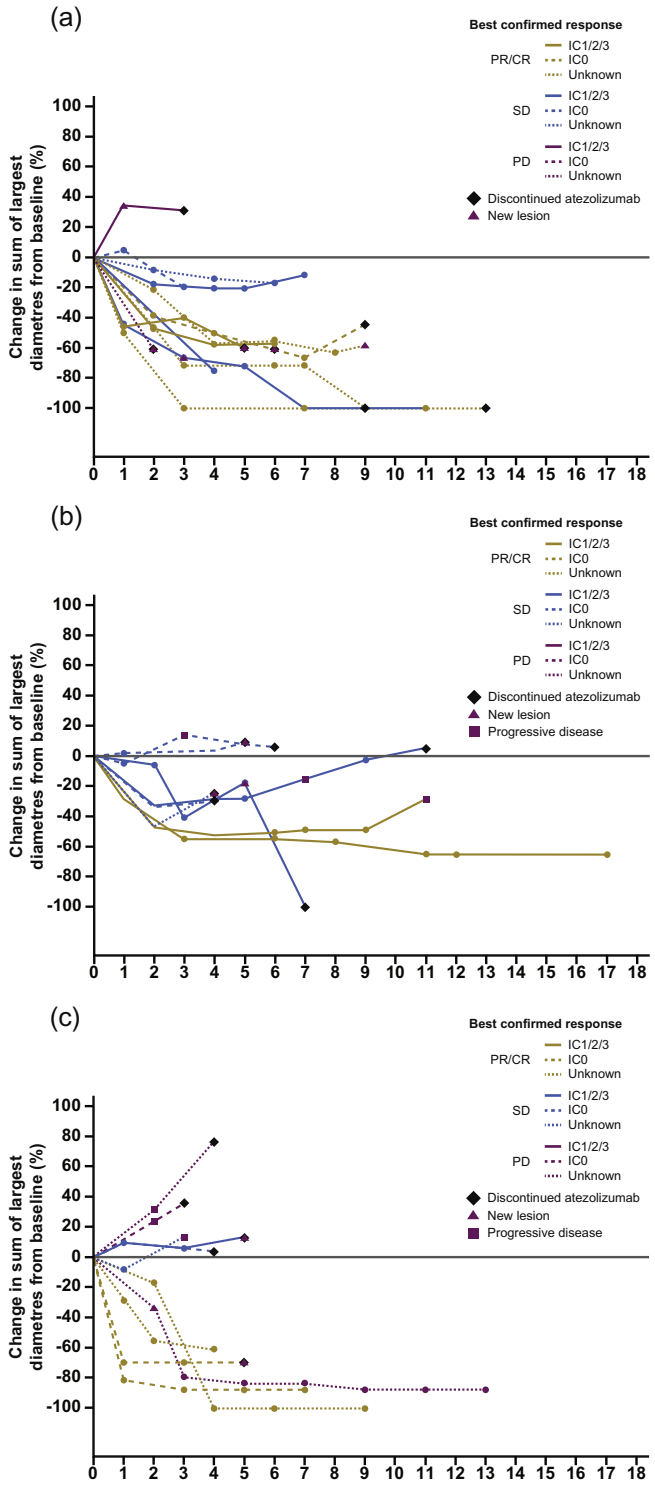

Fig. 2. Changes in tumour burden over time following treatment with *nab*-paclitaxel plus atezolizumab (PD-L1 checkpoint inhibitor) in patients with metastatic TNBC (a) as first-line therapy, (b) as second-line therapy, and (c) as third-line or greater[a] therapy. Reproduced with permission from 'Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC)' by Adams et al., poster presentation at the 2016 ASCO annual meeting [118]. [a]One patient received three prior lines of therapy PD-L1 IC0 defined as <1% IC expressing PD-L1 as a percentage of tumour area. PD-L1 IC1/2/3 defined as ⩾1% IC expressing PD-L1 as a percentage of tumour area. ASCO, American Society of Clinical Oncology; CR, complete response; IC, immune cells; mTNBC, metastatic triple negative breast cancer; PD-L1, programmed death ligand 1; PR, partial response.

TNBC [123]. The other three are smaller trials; one Phase II trial of *nab*-paclitaxel plus atezolizumab as neoadjuvant therapy followed by surgery and adjuvant atezolizumab therapy in 37 patients with TNBC [124], a Phase I/II trial of *nab*-paclitaxel plus durvalumab followed by ddAC plus durvalumab as neoadjuvant therapy in 61 patients with TNBC [125], and KEYNOTE-173, a Phase I trial of *nab*-paclitaxel ± carboplatin plus pembrolizumab followed by AC as neoadjuvant therapy in 80 patients with TNBC [126]. In the metastatic setting, an additional two studies are underway. One is a Phase II trial evaluating *nab*-paclitaxel plus pembrolizumab in two separate cohorts: metastatic TNBC ($n = 30$) and HER2- MBC ($n = 20$) [127], and the other is a Phase I three-arm trial that is evaluating the addition of nivolumab to *nab*-paclitaxel in 138 patients with either metastatic pancreatic cancer (±gemcitabine), non-small cell lung cancer (with carboplatin) or TNBC [128,129]. The results of these trials are awaited with interest, although further biomarker research is required to help predict which patients might benefit more from this therapeutic approach.

Concluding remarks

Given the aggressive nature of TNBC, fast-acting and effective chemotherapy is likely to remain the backbone of therapy for many patients. *Nab*-paclitaxel is a next-generation taxane with a superior therapeutic index to paclitaxel, as demonstrated in Phase III trials [56,57]. It may be a particularly attractive treatment choice in TNBC since it has a better tolerability profile which permits higher dosing, and it is thought to utilize active transport mechanisms to facilitate rapid drug delivery. Indeed, clinical data reported to-date support the preferential selection of *nab*-paclitaxel in TNBC: in the neoadjuvant setting, *nab*-paclitaxel was associated with a doubling in pCR rate (48.2% vs. 25.7%) in GeparSepto [56] and a similarly high pCR rate (49.2%) when combined with carboplatin in the ADAPT-TN trial [96], and there are data from Phase II trials to support its efficacy in metastatic TNBC [79,81], although these data require confirmation from larger, randomized trials such as tnAcity.

There appears to be a strong scientific rationale and impressive early clinical data for *nab*-paclitaxel in combination with new immunotherapies, such as immune checkpoint inhibitors, suggesting that it may represent a valuable chemotherapy combination partner. As such, there is growing enthusiasm for this approach, and results from ongoing trials are awaited with interest. Indeed, it is hoped that results from these trials as well as those evaluating novel agents according to therapeutic targets identified in specific subgroups of TNBC, may help to redefine treatment algorithms in this difficult-to-treat breast cancer subtype, and herald a new era of personalized treatment.

Author contributions

S.F. conducted relevant literature searches and prepared a first draft of the manuscript, which was subsequently revised by G.M., A.G. and D.P.S. All authors approved the final manuscript and are accountable for all aspects of the work.

Conflict of interest

Francesco Schettini has no conflict of interest to declare.
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