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ORIGINAL ARTICLE

Metastatic or locally advanced breast cancer patients: towards an expert consensus on nab-paclitaxel treatment in HER2-negative tumours—the MACBETH project

Marina E. Cazzaniga[1,2] · E. Ciruelos[3] · A. Fabi[4] · J. Garcia-Saenz[5] · H. Lindman[6] · D. Mavroudis[7] · C. Schem[8] · G. Steger[9] · E. Timotheadou[10] · K. Zaman[11] · V. Torri[12] · on behalf of the MACBETH Group

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Abstract

Introduction Despite the large use of nab-paclitaxel as a treatment option in metastatic breast cancer (MBC) across different countries, no definitive data are available in particular clinical situations.

Areas covered Efficacy, safety and schedule issues concerning available literature on nab-paclitaxel in advanced breast cancer and in specific subgroups of patients have been discussed and voted during an International Expert Meeting. Ten expert specialists in oncology, with extensive clinical experience on Nab-P and publications in the field of MBC have been identified. Six scientific areas of interest have been covered, generating 13 specific Statements for Nab-P, after literature review. For efficacy issues, a summary of research quality was performed adopting the GRADE algorithm for evidence scoring. The panel members were invited to express their opinion on the statements, in case of disagreement all the controversial opinions and the relative motivations have been made public.

Expert opinion Consensus was reached in 30.8% of the Nab-P statements, mainly those regarding safety issues, whereas ones regarding efficacy and schedule still remain controversial areas, requiring further data originated by the literature.

Keywords Expert meeting · Nab-paclitaxel · Breast cancer · Weekly schedule · Neuropathy

Introduction

The currently available taxanes, paclitaxel and docetaxel, play a central role in the treatment of metastatic breast cancer (MBC). Although paclitaxel and docetaxel proved to have significant activity against breast cancer and other solid tumours, emerging data indicate that the polyethylated castor oil–ethanol solvents and polysorbate 80 directly contribute to potentially severe toxicities observed in patients treated with paclitaxel or docetaxel. Among the well-characterized, solvent-related toxicities are hypersensitivity reactions, which can rarely be fatal even with corticosteroid premedication,

✉ Marina E. Cazzaniga
marina.cazzaniga@asst-monza.it

1 Phase 1 Trials Research Unit and Oncology Unit, ASST Monza and Milano Bicocca School of Medicine, Via GB Pergolesi 33, 20900 Monza, MB, Italy

2 Oncology Unit, ASST Monza, Monza, Italy

3 Unidad de Cáncer de Mama del Centro Integral Oncológico Clara Campal HM CIOCC, Madrid, Spain

4 Medical Oncology, Regina Elena National Cancer Institute, Rome, Italy

5 Department of Medical Oncology, IdISSC. CIBERONC-ISCIII, Hospital Clínico San Carlos, Madrid, Spain

6 Department of Immunology, Genetics and Pathology, University of Uppsala, Uppsala, Sweden

7 Department of Medical Oncology, University Hospital of Heraklion, Heraklion, Crete, Greece

8 Mammazentrum, Hamburg, Germany

9 Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria

10 Aristotle University of Thessaloniki School of Medicine, Papageorgiou Gen. Hospital, Thessaloníki, Greece

11 Breast Center, Department of Oncology, University Hospital CHUV, Lausanne, Switzerland

12 Istituto IRCCS Istituto Mario Negri, Milan, Italy

and prolonged, sometimes irreversible, peripheral neuropathy associated with demyelination and axonal degeneration [1]. Nab-paclitaxel (Nab-P) is a novel, biologically interactive, nanometre-sized albumin-bound paclitaxel particle initially developed to avoid the toxicities associated with polyethylated castor oil. It is the first of a new class of anticancer agents that incorporate albumin particle technology and exploit the unique properties of albumin, a natural carrier of lipophilic molecules in humans. Administered as a colloidal suspension of 130-nm particles, Nab-P allows the safe infusion of significantly higher doses of paclitaxel than the doses used with standard paclitaxel therapy, with shorter infusion schedules (30 min versus 3 h, respectively) and no premedication. In addition, the albumin-bound nanoparticle was designed to preferentially deliver paclitaxel to tumours by biologically interacting with albumin receptors that mediate drug transport; in vitro studies have demonstrated a 4.5-fold increase in paclitaxel transport across endothelial cells for Nab-P compared to standard paclitaxel.

A phase II trial [2] evaluating Nab-P at 300 mg/m^2 3 weekly in patients with MBC demonstrated an overall response rate (ORR) of 48%, with a response rate of 64% for patients who received Nab-P as the first-line therapy. Time to tumour progression (TTP) was 26.6 weeks for all patients and 48.1 weeks for patients with confirmed tumour responses; median overall survival (OS) was 63.6 weeks. The observed adverse events (AEs) of myelosuppression and peripheral neuropathy were less frequent and less severe than what would be expected with comparable doses of standard paclitaxel.

In a phase III trial [3], 3-weekly Nab-P demonstrated significantly higher response rates compared to 3-weekly standard paclitaxel (33% vs 19%, respectively; $p=0.001$) and significantly longer TTP (23.0 vs 16.9 weeks, respectively; hazard ratio 0.75; $p=0.006$). The incidence of grade 4 neutropenia was significantly lower for Nab-P compared to standard paclitaxel (9% vs 22%, respectively; $p<0.001$) despite a 49% higher paclitaxel dose. Febrile neutropenia was uncommon (< 2%), and the incidence did not differ between the two study arms. Grade 3 sensory neuropathy was more common in the Nab-P arm than in the standard paclitaxel arm (10% vs 2%, respectively; $p<0.001$) but was easily managed and improved rapidly (median, 22 days) to grade 1 or 2. No hypersensitivity reactions occurred with Nab-P despite the absence of premedication and shorter administration time.

A subsequent randomized phase II study [4], conducted to evaluate the safety and efficacy of three Nab-P dosing regimens—weekly (w) vs every 3 weeks (Q3w) vs Docetaxel administered at the highest standard dose in the first-line setting, indicated that Nab-P at the dose of 150 mg/m^2/week produces a significantly longer progression-free survival (PFS) than docetaxel by both independent radiologist assessment (12.9 vs 7.5 months, respectively; $p=0.0065$) and investigator assessment (14.6 v 7.8 months, respectively; $p=0.012$), as well as a higher ORR, although this did not reach statistical significance. Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all Nab-P arms in comparison with the docetaxel arm. The frequency and grade of peripheral neuropathy were similar in all arms.

Different real-life studies [5–7] explored the activity and safety of Nab-P in the clinical practice, reporting results similar to those shown in the clinical randomized trials.

However, despite the large use of Nab-P as a treatment option in MBC across different countries since many years, no consensus is available regarding the potential use in specific subgroups of patients, or after new endocrine strategies in combination with biological agents.

While current guidelines provide general recommendations on the use of Nab-P for MBC [8], they do not provide guidance on the most appropriate patient profile for the drug, mainly in special clinical situations, for example, elderly patients.

In September 2017, a group of 10 International Experts in the management of breast cancer, with extensive experience in cancer treatment, convened to develop an expert report aimed at describing the most appropriate use of Nab-P in the clinical practice.

Aim of the MACBETH (metastatic or locally advanced breast cancer patients: towards a consensus on Nab-P treatment in HER2-negative tumours) project is to reach a European Consensus regarding the use of Nab-P for the treatment of advanced breast cancer, based on the literature evidence and International Expert opinion.

This paper aims to complement the information provided in existing guidelines and to provide clinically relevant suggestions for Nab-P use in daily practice.

Materials and methods

Expert selection

Experts from 6 different European Countries (Italy 2, Spain 2, Greece 2, Switzerland, Austria and Sweden) were selected to participate in the panel; requirements were oncology specialist extensive clinical experience of Nab-P, defined as experience in the daily use of the drug, involvement in clinical research or academic work in the field of MBC and fluent English speakers.

Countries where Nab-P is not available or reimbursed have been excluded.

Literature review

Ahead of the expert panel meeting, a literature review (details provided in Table 1) was performed to establish the current evidence about the use of Nab-P, by identifying key areas in which data or guidelines are lacking, as well as areas of inconsistency within these. This broad review was undertaken before the development of consensus statements. The terms used for this literature search were "Nab-P" AND "chemotherapy" AND "breast cancer" AND "locally advanced or metastatic".

The research generated 37 unique References which were identified from PubMed Central. References useful for the Panel Meeting were selected using the exclusion criteria detailed in Table 1. In all, 12 unique references were included in the final list and served as support to develop the Nab-P guidance in this publication.

Drawing up guidelines

The recommendations included in this publication are intended to fill the gaps identified in the current ground rules and were established based on findings from the literature review, as well as the experts' experience and opinions.

After a preliminary web meeting done in December 2016, the panelists decided to include at the beginning of each area of interest some general statements generated from International guidelines, to put the sub-statements specific for the drug into the context.

Eight topics of interest and 20 statements, of which 13 specific for Nab-P, were identified (Table 2), and shared among all the participants before the expert meeting by e-mail. Subsequently, each topic has been assigned by the Chairman to each participant for analysis and subsequent presentation. Everyone had been asked to review the selected literature and to present three to four slides supporting the topic during the live meeting, which took place on 8th September 2017 in Madrid.

Table 1 Literature review exclusion criteria

Search conducted matching the terms "nab-paclitaxel" and "breast cancer" and "metastatic" and "locally advanced" Exclusion criteria	Number excluded
Studies in other settings (neo-adjuvant)	2
Phase I studies	16
Reviews	15
No trial data, letter to the editor, case reports	4

The final literature search was performed on 14th June 2017, ahead of the guidance group meeting. To capture all phase II–IV trials with nab-paclitaxel reference product, no cut-off date was selected

After each presentation, the related statement(s) was discussed by all the experts and voted according to a five-score scale (Fig. 1).

Methods

A preliminary discussion aimed at finalizing the statements based on unmet clinical need and a subsequent expert meeting was held to determine the wording and supporting content.

Prior to the meeting, a set of preliminary recommendation statements was prepared, basing on available published data and following the ESMO guideline methodology. These recommendations were circulated to all panel members by email for comments and corrections on content and wording. A final set of recommendations was presented, discussed, and voted upon during the meeting. All panel members were instructed to vote on all questions. Additional changes in the wording of statements were made during the session. For questions related to efficacy, a summary of research quality was also performed adopting the GRADE algorithm for scoring the evidence [9].

The level (strength) of evidence for each recommendation was evaluated in line with widely used grading criteria:

I. Evidence obtained from meta-analysis of multiple, well-designed, controlled studies or from high-power randomized, controlled clinical trials
II. Evidence obtained from at least one well-designed experimental study or low-power randomized, controlled clinical trial
III. Evidence obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-group, pre–post, cohort, time, or matched case–control studies
IV. Studies such as comparative and correlational descriptive and case studies
V. Evidence obtained from case reports and clinical examples

The ESO-ESMO second international consensus guidelines for advanced breast cancer (ABC2) were used as a source document for grading recommendations [8].

The panel members were invited to express their opinion on the statements; in case of disagreement, all the controversial opinions and the relative motivations were made public.

Results

Results concerning all the specific statements for Nab-P are listed in Table 3.

Table 2 Areas of interest and statements

Area of interest	Statements
TNBC patients	
General statements	Taxane-based chemotherapy is the standard of treatment
	Paclitaxel + bevacizumab is the most used regimen
Specific statements	Nab-paclitaxel could be a valid option in second line for pts previously treated with paclitaxel + bevacizumab
	Nab-paclitaxel could be an option of treatment in the presence of visceral and symptomatic disease after any kind of taxane-based regimen
	Nab-paclitaxel has a specific efficacy activity in advanced TNBC
HR + patients	
General statements	First-line therapy is usually an endocrine treatment alone
	First-line therapy usually includes endocrine therapy in combination with CDK4/6 inhibitors
	In intermediate-/low-risk patients, endocrine agents + everolimus is the referral second-line treatment
	HR + patients are considered at high risk in the presence of visceral and symptomatic disease
	In high-risk patients without visceral crisis, endocrine agents + CDK inhibitor is usually the first-line choice
Specific statements	In high-risk patients, nab-paclitaxel is considered one of the possible options of treatment after failure of endocrine agents
	Nab-paclitaxel has a specific efficacy profile in the advanced stage HR + BC
Elderly patients	
General statements	Single-agent chemotherapy is preferred for elderly patients to guarantee QoL
Specific statements	The low impact on daily life and the avoidance of steroids are the key values for nab-paclitaxel
	Single-agent chemotherapy with nab-paclitaxel is an option
Nab-paclitaxel—efficacy	
	Nab-paclitaxel in taxane-pre-treated patients is feasible and supported
	Increase in overall survival is determinant for nab-paclitaxel choice over other options
Nab-paclitaxel—safety	
	Rapid recovery from peripheral neuropathy makes the difference in comparison to other taxane-based treatments
	Haematological toxicity is lower
Nab-paclitaxel—schedule and regimens	
	Optimal schedule and dose have been defined

The final literature search was performed on 14th June 2017, ahead of the guidance group meeting. To capture all phase II–IV trials with nab-paclitaxel reference product, no cut-off date was selected

STATEMENT				
1 Totally disagree	2 Partially disagree	3 Neutral	4 Partially agree	5 Totally agree

Fig. 1 Five-score scale used for the vote

At the beginning of each topic, one or more general statements were identified and discussed to put the specific Nab-P statements for the area and the related literature into context.

1. TNBC setting

General statements on TNBC

1.1 Taxane-based CHT is the standard of treatment as the first-line therapy in unselected TNBC patients

Experts' recommendation

The experts consider of strategic importance the clear identification of the role of taxanes in the first-line setting, because of the important consequences that the choice of first line has on subsequent lines of therapy.

The treatment of triple-negative breast cancer (TNBC) still remains the largest unmet need within MBC. No specific recommendations can be done for this advanced breast cancer subtype, with the possible exception of platinum compounds for BRCA-mutated patients [8].

Table 3 Results of statement vote

Results of agreement	Statements
TNBC patients	
	Taxane-based chemotherapy is the standard of treatment
	Paclitaxel + bevacizumab is the most used regimen
Consensus NOT reached Totally + partially agree 50% Neutral 10% Totally + partially disagree 40%	Nab-paclitaxel could be a valid option in the second line for pts previously treated with paclitaxel + bevacizumab
Consensus NOT reached Totally + partially agree 60% Neutral 20% Totally + partially disagree 20%	Nab-paclitaxel could be an option of treatment in the presence of visceral and symptomatic disease after any kind of taxane-based regimen
Consensus NOT reached Totally + partially agree 40% Neutral 10% Totally + partially disagree 50%	Nab-paclitaxel has a specific efficacy activity in advanced TNBC
HR + patients	
	First-line therapy is usually an endocrine treatment alone
	First-line therapy usually includes endocrine therapy in combination with CDK4/6 Inhibitors
	In intermediate-/low-risk patients, endocrine agents + everolimus is the referral second-line treatment
	HR + patients are considered at high risk in the presence of visceral and symptomatic disease
	In high-risk patients without visceral crisis, endocrine agents + CDK inhibitor is usually the first-line choice
Consensus NOT reached Totally + partially agree 70% Neutral 10% Totally + partially disagree 20%	In high-risk patients, nab-paclitaxel is considered one of the possible options of treatment after failure of endocrine agents
Consensus NOT reached Totally + partially agree 20% Neutral 10% Totally + partially disagree 70%	Nab-paclitaxel has a specific efficacy profile in the advanced stage HR + BC
Elderly patients	
	Single-agent chemotherapy is preferred for elderly patients to guarantee QoL
Consensus NOT reached Totally + partially agree 70% Neutral 10% Totally + partially disagree 30%	The low impact on daily life and the avoidance of steroids are the key values for nab-paclitaxel
Consensus reached Totally + partially agree 80% Totally + partially disagree 20%	Single-agent chemotherapy with nab-paclitaxel is an option
Nab-paclitaxel—efficacy	
Consensus NOT reached Totally + partially agree 50% Neutral 20% Totally + partially disagree 30%	Nab-paclitaxel in taxane-pre-treated patients is feasible and supported
Consensus NOT reached Totally + partially agree 10% Neutral 30% Totally + partially disagree 60%	Increase in overall survival is determinant for nab-paclitaxel choice over other options
Nab-paclitaxel—safety	
Consensus reached Totally + partially agree 80% Neutral 10% Totally + partially disagree 10%	Rapid recovery from peripheral neuropathy makes the difference in comparison to other taxane-based treatments
Consensus reached Totally + partially agree 90% Totally + partially disagree 10%	Haematological toxicity is lower

Table 3 (continued)

Results of agreement	Statements
Nab-paclitaxel—schedule and regimens	
Consensus NOT reached Totally + partially agree 70% Totally + partially disagree 30%	Optimal schedule and dose have been defined

The most relevant data were those from the TNT study, comparing 'standard' docetaxel to carboplatin in unselected TNBC patients (with pre-specified subgroup analysis of BRCA-mutation carriers). The superiority of carboplatin was demonstrated only among patients with BRCA mutation while it resulted as effective as docetaxel in the basal-like intrinsic subtype; in an unselected TNBC population, docetaxel and carboplatin seem to have similar efficacy [10].

Considering these results, for non-BRCA-associated metastatic TNBC and in the absence of data supporting specific CHT agents, all other recommendations for HER2-negative disease also apply for triple-negative subtype [8].

In the absence of medical contraindications or patients' concerns, anthracycline or taxane-based regimens, preferably as single agents, would usually be considered as the first-line CHT for HER2-ve MBC, in those patients who have not received these regimens as (neo)adjuvant treatment and for whom CHT is appropriate. Alopecia is a major issue for the patients.

For those who are taxane naïve, have anthracycline-resistant or pre-treated MBC, or in whom anthracycline maximum cumulative dose or toxicity (i.e. cardiac) has already been reached, taxane-based therapy, preferably as single agent, would usually be considered as the treatment of choice.

1.2 Paclitaxel + bevacizumab is the preferential option for the first-line treatment

Experts' recommendation

In some countries of the European Union, the combination of paclitaxel + bevacizumab is still approved and available for the treatment of MBC patients.

The experts believe that the use of this combination could sometimes affect, and limit in some cases, the subsequent use of different taxanes, such Nab-P. However, the high ORR observed and the prolonged PFS obtained in the randomized study suggest to consider this treatment in some selected patients.

Most of the experts (50%) disagree with the statement, considering that there are other taxane-based combinations available and that the lack of data concerning supporting OS benefit is the main limitation.

The use of bevacizumab in patients with TNBC has attracted considerable interest, primarily because of the lack of targeted therapy for these patients and because of the failure of drugs developed in this setting, and also because of the observed effect of bevacizumab in the subgroup of patients with TNBC treated in the E2100 trial. In these patients, median PFS was 10.6 months with bevacizumab plus paclitaxel versus 5.3 months with paclitaxel alone (HR 0.49; 95% CI 0.34–0.70), the overall response rate was 43% versus 22%, respectively, and median overall survival (OS) was 20.5 versus 16.3 months (HR 0.89; 95% CI 0.66–1.19) [11]. One recently published meta-analysis included 2447 patients, 1439 receiving bevacizumab-based therapy and 1008 receiving non-bevacizumab treatment, of these, 363 and 258 patients, respectively, had TNBC. The authors reported that the HRs for PFS and OS were 0.63 (95% CI 0.52–0.76) and 0.96 (95% CI 0.79–1.16), respectively. Median PFS was 8.1 months with bevacizumab versus 5.4 months with CHT alone, median OS was 18.9 versus 17.5 months, respectively, and 1-year OS rates were 71% vs 65% [11]. The objective response rate was significantly higher with bevacizumab-containing therapy, compared to CHT alone (42% vs 23%, respectively; $p < 0.0001$). In addition, primary resistant disease (best response was progressive disease) was significantly less common among patients receiving bevacizumab-containing therapy than in those treated with CHT alone (11% vs 28%, respectively; $p < 0.0001$). The HR for OS (unstratified analysis) was 0.96 (95% CI 0.79–1.16; $p = 0.6732$). One-year survival rates were 71% with bevacizumab-containing therapy versus 65% with CHT alone.

Specific statements on Nab-P in TNBC patients

1.3 Nab-P could be a valid second-line option for pts previously treated with paclitaxel + bevacizumab—consensus not reached: (totally + partially agree 50%; totally + partially disagree 40%; neutral 10%)

Half of the experts believe that Nab-P should be used as the second-line treatment, independently of what patients have received as the first-line treatment, even considering the lack of specific data in those who have been treated with paclitaxel–bevacizumab.

Main reasons of disagreement expressed by the experts regarding the use of Nab-P as the second-line treatment in advanced TNBC patients were as follows:

- Absence of data supporting the use of Nab-P after taxane failure, with the only exception of a disease progression occurring after adjuvant taxane-based therapy and DFI > 12 months.
- The amount of evidence is insufficient to originate a recommendation for this specific population, even if some positive data can be drawn from real life and clinical studies.

According to the most recent international guidelines, paclitaxel and docetaxel, the two most commonly used taxanes against breast cancer, are the preferred agents in patients progressing after anthracycline-containing CHT [8]; therefore, being one of the most commonly used first-line therapies.

Till now, no prospective data are available regarding the use of Nab-P as subsequent line of treatment after the failure of the first-line therapy in a pure population of TNBC patients and even more so especially in those pre-treated with bevacizumab + paclitaxel.

Most of the available data in patients pre-treated with taxanes alone are an extrapolation from different studies, which had enrolled all metastatic breast cancer subtypes, or are extracted from the first-line trials.

Blum et al. [12] reported results of a trial which has examined Nab-P (100 mg/m^2 or 125 mg/m^2 administered weekly) to determine the antitumour activity in patients with MBC whose disease progressed despite conventional taxane therapy (PD while receiving taxanes for their metastatic disease, or relapsed within 12 months of taxane-containing adjuvant therapy). Twenty-one TNBC patients were enrolled: ORR was 14% in both schedule arms and DCR was 24% in the 100 mg/m^2 group and 14% in the 125 mg/m^2 one. However, no data have been reported for other clinical outcomes, such as PFS.

The authors concluded that weekly Nab-P was safe and effective, even in heavily pre-treated, taxane-refractory patients. None of the patients have been treated with paclitaxel + bevacizumab.

Palumbo et al. [6] recently reported results of a prospective, multicentre trial designed to assess the activity, safety, and quality of life of Nab-P as the second-line CHT in HER2-negative, taxane-pre-treated metastatic breast cancer. Fifty-two women with HER2-negative metastatic breast cancer have been enrolled. Most of the patients had received taxanes in the metastatic setting (54.2%) and 18 had TNBC (11.6%). The ORR was 48% (95% CI 31.5–61.3%) and included complete responses in 13.5% of the cases. Disease stabilization was obtained in 19 patients and lasted ≥ 6 months in 15 of them; the overall clinical benefit rate (CBR) was 77%. The median time to response was 70 days (range 52–86 days). The median PFS was 8.9 months (95% CI 8.0–11.6 months, range 5–21+ months). A total of 378 CHT cycles were administered to the 52 patients. The median number of courses per patient was six (range 4–26 cycles). Treatment was well tolerated; 92% of the patients received Nab-P at the protocol-specified dose throughout the study, and 40% of them received ≥ 9 cycles. Unfortunately, no data have been reported for the TNBC group, nor in the group of patients treated with paclitaxel + bevacizumab, if any.

Table 4 summarizes Nab-P data in the TNBC setting.

1.4 Nab-P could be an option of treatment in the presence of visceral and symptomatic disease after any kind of taxane-based regimen—consensus not reached (totally + partially agree 60%; totally + partially disagree 20%; neutral 20%)

More than half of the experts, even in the absence of specific supporting data, believe that Nab-P could be considered as an option of treatment after Taxanes, especially in this particular category of patients, who remain at high risk of rapidly progressive disease.

Main reasons of disagreement expressed by the experts regarding the role of Nab-P as the second-line treatment in the presence of visceral and symptomatic disease after any kind of taxane-based regimen were as follows:

- Lack of prospective data supporting the use of Nab-P after taxane failure, with the only exception of disease progression occurring after adjuvant taxane-based therapy and DFI > 12 months, for the potential sensitiveness to taxanes the cells have retained.
- Other treatment options are available for this setting of patients, thus leaving the choice very wide.

Even if some positive data can be drawn from real life and clinical studies, the strength of evidence is too weak to support a recommendation in this specific population.

Few data are available at the moment regarding specific analyses in pre-treated TNBC with symptomatic and/or visceral metastatic disease.

Forero-Torres et al. [13] conducted a randomized phase II trial evaluating the activity Nab-P w/o tigatuzumab (TIG), an agonistic anti-DR5 antibody, in patients with metastatic TNBC who had already been exposed to taxanes; only 17 patients out of 64 have received taxanes in the advanced setting. ORR was 22% in pre-treated patients, without any separate report between the two treatment arms. In this group of patients, median PFS was 2.5 (95% CI 1.9–3.7). No results have been reported according to the site of relapse.

Few trials have analysed the duration of treatment in TNBC patients: Kassam et al. [14] reported that patients with TNBC disease relapse quickly on palliative CHT,

Table 4 Nab-P efficacy results in TNBC patients

Author, year	Phase	Nab-P regimen and dose	Schedule	Combination therapy	Line of treatment	Pts with TNBC N/n total	ORR (%)	CBR (%)	PFS (months)	OS (months)
Lobo, 2010	II	150 mg/m^2	q2w	Yes	First line	13/29	69	84.6	NR	NR
Hamilton, 2010	II	100 mg/m^2	qw 3/4	Yes	First line	34/34	85	94	9.2	NR
Blum, 2007	II	100–125 mg/m^2	qw 3/4	No	Second and further	28/181	14	24 (100 mg/m^2) 14 (125 mg/m^2)	NR	NR
Palumbo, 2015	II	260 mg/m^2	q3w	No	Second line	16/52	68.8	NR	NR	NR
Fabi, 2015	II	260 mg/m^2 125 mg/m^2	q3w qw 3/4	No	Second and further	8/42	25	NR	5.7	NR
Forero-Torres, 2015	II	100 mg/m^2	qw 3/4	Yes	Second and further	64/64	28–38*	41–52*	2.8–3.7	NR84.6

TNBC triple-negative breast cancer, *ORR* overall response rate, *CBR* clinical benefit rate, *PFS* progression-free survival, *OS* overall survival, *q2w* every 2 weeks, *qw* once weekly, *qw 3/4* first 3 weeks of 4 weeks, *q3w* every 3 weeks, *NR* not reported

*According to the combination with tigatuzumab

with median durations of treatment in the first, second, and third lines of only 11.9 weeks, 9 weeks, and 4 weeks, respectively.

No firm conclusion could be drawn for the role of Nab-P as second or further line of treatment in advanced TNBC patients previously exposed to taxanes with symptomatic or visceral disease. Further evaluations, even in the real-life setting, are strongly encouraged.

1.5 Nab-P has a specific efficacy and activity in advanced TNBC—consensus not reached: totally + partially agree 60%; totally + partially disagree 30%; neutral 10%

More than half of the experts recognized that Nab-P has some activity against TNBC cell; however, consensus to agree on the specific statement has not been reached.

Main reasons of disagreement expressed by the experts regarding a specific activity of Nab-P in advanced TNBC patients were as follows:

- Absence of prospective trials addressing the specific question of Nab-P efficacy in TNBC, better if derived from a direct comparison with efficacy in luminal cancers.
- Even if Nab-P has demonstrated a specific activity in TN LABC in the neo-adjuvant setting, this issue should not be translated into the metastatic setting without a prospective validation study.

The activity of Nab-P in the TNBC subset has been well investigated in the neo-adjuvant GeparSepto trial [15]: this prospectively randomized phase III trial showed a significant increase in the proportion of patients achieving a pathological complete response (pCR—ypT0 ypN0) from 29 to 38% ($p = 0.00065$) with weekly Nab-P versus weekly solvent-based (sb) paclitaxel followed by epirubicin plus cyclophosphamide in patients with primary high-risk early breast cancer.

This result (pCR) was consistent irrespective of the pathological complete response definition and patient subgroup. The study detected a significant interaction between the CHT effect and the hormone receptor status, resulting in a more pronounced effect in patients with triple-negative breast cancer (OR 2.61; 95% CI 1.57–4.33; $p = 0{\cdot}00020$).

Table 4 summarizes results in the TNBC setting.

2. Hormone receptor (HR+)-positive setting

General statements in HR+ tumours

2.1 The first-line therapy is usually an endocrine treatment alone

The experts strongly agree (100%) that an endocrine treatment should be considered for all HR + MBC patients without visceral crisis, as recommended by all guidelines.

Hormone receptor positive (HR+) is the most common breast cancer phenotype worldwide. Therefore, access to accurate and reliable ER/PgR testing and established and affordable endocrine therapies could have a profound impact on breast cancer outcomes in high- and low-/middle-income countries around the globe. Testing, for the presence of hormone receptors as part of breast cancer diagnosis, is the standard of care and is used to guide therapy decisions. ER/PgR overexpression is associated with clinical outcomes and is an important predictive and prognostic factor. The relationship between target expression (ER/PgR) and efficacy of endocrine therapy is well established. Accurate assessment of ER/PgR status permits informed treatment decisions for targeted therapy, thereby identifying those patients, who most likely would benefit from an endocrine therapy [16].

Basing on the availability of HR status, patients could receive the most appropriate therapy, thus considering that breast cancer is no longer seen as a single disease, but a multifaceted disease comprised of distinct biological subtypes with a diverse natural history. Onitilo et Al [17] compared clinical–pathological features and survival in the four breast cancer subtypes defined by immunohistochemistry (IHC) expression of oestrogen receptor (ER) or progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2). The subjects with ER/PgR+, HER2− subtype were more likely to be older ($p < 0.001$), have early-stage breast cancer ($p < 0.001$), present with smaller tumour ($p < 0.001$) and have a low/intermediate histological grade ($p < 0.001$). They were less likely to be lymph node positive ($p < 0.001$), have a lobular tumour type ($p < 0.001$), and be treated with CHT ($p < 0.001$). The 5-year overall survival for all subjects was 87.8% (95%CI 85.4–89.9) and the disease-free survival was 83.1% (95% CI 80.5–85.5). In the Cox regression analysis, subjects with the TNBC subtype had the worst overall survival (hazard ratio 1.8; 95% CI 1.0–3.0) and worst disease-free survival (hazard ratio 1.5; 95% CI 0.8–3.0) when compared to subjects with ER/PgR+, HER2− subtype. One of the most important recommendations relates to the preferred treatment for luminal (ER+/PgR+ or ER+/PgR−) MBC, which should be endocrine therapy in the majority of cases, excluding those with visceral crisis and concern or proof of endocrine resistance [18]. All breast cancer guidelines concur with this recommendation but some real-life studies show that most of these patients still receive CHT as their first treatment, despite the lower efficacy [19]. In the above-mentioned study, from the total of 520 patients with HR+/HER2− metastatic breast cancer, 482 patients (93%) received any palliative systemic therapy. Half of the patients treated with endocrine therapy had bone metastases as initial metastatic site, in comparison to 15% of patients treated with initial CHT. When looking at HR + MBC patients categorized by initial metastatic site, patients with visceral and multiple sites of metastases were more likely to receive initial CHT compared to patients with bone metastases only [35% and 37% versus 9% (both $P < 0.0001$)]. Patients that received initial CHT ($n = 116$) were significantly younger, had less co-morbidities, had received more prior adjuvant systemic therapy and were less likely to have bone metastases compared to patients that received initial endocrine therapy ($n = 366$). Median PFS of initial palliative CHT was 5.3 months [95% confidence interval (CI) 4.2–6.2] and of initial endocrine therapy 13.3 months (95% CI 11.3–15.5), with a median OS of 16.1 and 36.9 months, respectively. Initial CHT was also associated with a worse outcome in terms of PFS and OS after adjustment for prognostic factors. The scenario of endocrine treatment for luminal MBC patients has deeply changed over the last 3 years, related to the availability of new data coming from prospective, randomized trials. The FALCON study evaluated the efficacy and safety of high-dose (HD) fulvestrant in comparison to anastrozole in HR+/HER2− recurrent or metastatic de novo breast cancer patients. Median duration of PFS with fulvestrant was 16.6 months (95% CI 13.83–20.99) in the whole population and 22.3 months (95% CI 16.62–32.79) in patients with non-visceral disease [20]. More recently, data regarding the addition of CDK 4/6 inhibitors to single-agent endocrine therapy have been released [21, 22]. The availability of these agents in the clinical practice could further change the strategy of treatment in luminal MBC patients.

2.2 First-line therapy usually includes endocrine therapy in combination with CDK 4/6

The experts only partially agree (50%) that the recently approved CDK 4/6 inhibitors should be offered to all HR + MBC patients as the first line treatment. Main reasons for disagreement are the lack of OS data and the absence of biomarkers useful to identify specific subgroups for treatment even though the PFS is statistically significant and the improvement obtained in terms of PFS and ORR is of great value. These reasons, together with the affordability of these treatments in many countries, should be considered in the selection of treatment.

One of the most important progresses in luminal MBC management, over the last years, has been the introduction of a new class of agents, the CDK4/6 inhibitors, in combination with an endocrine agent. All these agents, in combination with aromatase inhibitors, have demonstrated to improve PFS in endocrine-sensitive patients [21–23]. Beyond the first-line endocrine therapy, Palbociclib combined with fulvestrant resulted in longer progression-free survival than fulvestrant alone {9.2 months [95% confidence interval (CI), 7.5 to not estimable and 3.8 months, 95% CI 3.5 to 5.5]} in

the PALOMA 3 phase III trial [24], as well the addition of abemaciclib to fulvestrant [25]. At the moment of this expert meeting, no data are available regarding the potential impact of these drugs on OS.

2.3 In intermediate-/low-risk patients, endocrine agents + everolimus is the referral second-line treatment

The experts only partially agree (40%) on the use of everolimus + exemestane as the standard second-line treatment in all patients. Main reason for disagreement is related to the toxicity of this combination, especially in elderly patients, and to the complete lack of efficacy and safety data after CDK 4/6 inhibitors.

The choice of the second-line treatment strongly depends upon what has been used in the first-line setting. The BOLERO-2, randomized phase III trial compared everolimus and exemestane versus exemestane and placebo in 724 patients with hormone receptor-positive advanced breast cancer who had recurrence or progression while receiving previous therapy with a non-steroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both) [26]. The primary end point was PFS. Patients included in this trial were postmenopausal women with ER-positive, HER2 non-amplified advanced breast cancer whose disease was refractory to previous letrozole or Anastrozole, defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease. The median duration of exposure to everolimus was 14.6 weeks, as compared to 12.0 weeks of exposure to placebo. Serious adverse events (SAEs) were reported among 23% of patients in the combination-therapy group. This combination has shown a PFS benefit of approximately 6 months, without a significant OS benefit, and with significant toxicities [26]. Based on this evidence, the NCCN panel unanimously agreed that the addition of everolimus to exemestane may be considered for those women who fulfil the entry criteria for BOLERO-2 [27]. In addition, no data are available, at the moment of this Expert Meeting, regarding the efficacy and safety of everolimus + exemestane combination after failure of the first-line CDK 4/6 inhibitors.

Recently, an update of the ESO-ESMO guidelines has been released: they have remarked that the optimal sequence of single endocrine agents and combinations with targeted agents is currently unknown and is a research priority. It is crucial to collect data from clinical trials, beyond progression, to better understand the efficacy of the sequence for each class of agent

2.4 HR + patients are considered at high risk in the presence of visceral and symptomatic disease

Most of the experts (80%) agree on this statement: visceral crisis by itself, as identified in guidelines, is difficult to define in the daily practice and some other clinical situations, for example, a massive bone involvement, could contribute to increase the risk of progression and death.

Current guidelines recommend endocrine therapy for women with HR + advanced breast cancer, with the exception of patients with visceral crisis. Endocrine therapy is an important treatment option for women with hormone receptor-positive (HR+) advanced breast cancer, yet many tumours are either intrinsically resistant or develop resistance to these therapies. Treatment of patients with advanced breast cancer presenting with visceral metastases, which is associated with a poor prognosis, is also problematic. There is an unmet need for effective treatments for this patient population. The 5-year survival rate for breast cancer is only 24% in patients with distant metastases [28] with a higher overall incidence of metastatic disease at diagnosis in older over younger women. First metastasis is reported to occur in the skeletal system in 46%, in the visceral organs in 41%, and in both systems in 13% of patients, with the disease remaining confined to the skeleton or visceral system in nearly 60% of patients and developing into bone and visceral metastases in more than 40% of patients [29]. Prognosis is worse in patients with metastases involving visceral organs than in those without visceral organ involvement. In early clinical trials of the first-line non-steroidal aromatase inhibitors, overall survival was 18–24 months for patients with visceral metastases and approximately 40 months for patients without visceral disease [30]. Although endocrine therapy benefits patients with advanced breast cancer, this clinical benefit and time to disease progression are comparatively less in patients with visceral metastases than in patients with no visceral metastases. CHT is perceived to be more effective than endocrine therapy in patients with visceral metastases, and it is believed that endocrine therapy should be avoided in such cases. However, current guidelines recommend endocrine therapy for postmenopausal women with HR+ advanced breast cancer, with the exception of patients with visceral crisis, defined as the presence of lymphangitic lung metastases, bone marrow replacement, carcinomatous meningitis, or significant liver metastases. However, contrary to current treatment guidelines, a substantial proportion of patients with visceral disease who are not in visceral crisis and, therefore, not in need of immediate symptom control may also benefit from treatment with endocrine therapy and new combinations with CDK4/6 inhibitors or with mTOR inhibitors [31]. In such cases, the need for CHT could be delayed, and an endocrine therapy could be used.

2.5 In high-risk patients without visceral crisis, endocrine agents + CDK4/6 inhibitor is usually the first-line choice

Most of the panelists expressed disagreement in this statement due to the following reasons:

1. CDK 4/6 inhibitors have demonstrated efficacy both in symptomatic and asymptomatic patients, thus there is no reason to define their use specifically in symptomatic patients;
2. CDK 4/6 inhibitors are better tolerated than everolimus and should be preferred to this latter treatment.

In HR+ metastatic breast cancer patients, endocrine therapy + everolimus or CDK 4/6 inhibitors are now considered the standard of treatment. Two key clinical studies have shown that everolimus significantly improved time to progression in patients with HR+ metastatic breast cancer undergoing everolimus plus endocrine therapy for endocrine-resistant HR+ advanced breast cancer [26, 32]. The different pattern of toxicity could be of help in selecting everolimus or CDK 4/6 inhibitors as the partner of endocrine agents in the first-line setting. Recent data have shown that the addition of palbociclib to letrozole is unlikely to be cost effective for the treatment of advanced breast cancer from a Canadian healthcare perspective with its current price. While advanced breast cancer patients derive a meaningful clinical benefit from palbociclib, considerations should be given to increase the willingness-to-pay (WTP) threshold and reduce the drug pricing, to render this strategy more affordable [33].

Specific statements of Nab-P in HR+ tumours

2.6 In high-risk patients, Nab-P is considered one of the possible options of treatment after failure of endocrine agents—consensus not reached: totally + partially agree 70%; neutral 10%; totally + partially disagree 20%

Most of the experts expressed an agreement on the statement, even if consensus was not reached according to the pre-planned cut-off.

Main reasons of disagreement expressed by the experts were as follows:

- Specific efficacy in HR+ patients has not been tested in randomized trials.
- Nab-P is one of the potential options of treatment, but no data are available specifically to address the question, if it is better than other options.
- Other possible options to be considered include anthracyclines and standard taxanes.
- The choice between Nab-P and other agents also depends on the indolence or the site of relapse of the disease and on patient's preference.

There is no compelling evidence that combination regimens are superior to sequential single agents in terms of long-term outcome [27]. Nab-P may be used instead of paclitaxel or docetaxel due to medical necessity (i.e. hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of Nab-P should not exceed 125 mg/m^2.

2.7 Nab-P has a specific efficacy profile in the advanced stage HR + BC—consensus not reached: totally + partially agree 20%; neutral 10%; totally + partially disagree 70%

Main reasons of disagreement expressed by the experts regarding the statement were as follows:

- Specific efficacy in HR + patients has not been tested in randomized trials.
- Most of the available data are an extrapolation from randomized studies in the second-line setting, but lack of details regarding previous endocrine treatments is one of the main issues.

Different randomized trials [3, 4] evaluated the efficacy and safety of Nab-P in MBC patients. Unfortunately, no data in specific subgroups of patients, such as those treated with endocrine agents in the first-line setting, are available. In the updated trial [34] comparing Nab-P, administered at different doses, with docetaxel, no statistical difference was noted in the median OS among the treatment groups for different patient subsets, including age, visceral relapse, number of visceral lesions, and menopausal status. Twenty-eight to 41% of the patients had received previous hormone therapy and the difference was not statistically significant (p value 0.38); however, the authors did not detail the setting in which endocrine therapy has been used. In a trial comparing weekly Nab-P or weekly ixabepilone to weekly paclitaxel as the first-line therapy in association with bevacizumab for patients with advanced breast cancer [34], ixabepilone resulted inferior to paclitaxel. Nab-P was not superior with a trend toward inferiority in terms of PFS. More than 70% of the patients had HR + BC. A multivariable Cox proportional hazards model was used to compare each experimental arm to paclitaxel, adjusting for stratification factors, DFI of 2 years versus more than 2 years, and the presence or not of visceral metastases. Results are concordant with log-rank tests: prior taxane use, hormone receptor negativity, shorter DFI, and visceral metastases all predicted worse PFS. An unplanned, exploratory subset analysis in patients with triple-negative and hormone receptor-positive disease was conducted. For patients with HR+ disease, the median PFS for paclitaxel was 12.4 months. Using a multivariable Cox proportional hazards model for PFS, ixabepilone (median

PFS, 8.0 months; HR 1.62; 95% CI 1.29–2.04; $p = 0.001$) and Nab-P (median PFS, 10.0 months; HR 1.45; 95% CI 1.16–1.81; $p = 0.0012$) treatments were inferior to paclitaxel.

3. Elderly patients

General statements for the use of CHT in elderly patients

3.1 Single-agent CHT is preferred for elderly patients to preserve QoL

Almost all the panelists (90%) recognize that, when chemotherapy is indicated, the sequential use of different CHT agents is the best choice for elderly patients, especially for reducing toxicity and maintaining QoL.

Recommendations for management of breast cancer in older individuals are limited by a lack of level 1 evidence. Treatment is based on limited retrospective subgroup analyses and extrapolation of study results from younger patients. Such extrapolation might not be valid since breast cancer biology differs in older patients, treatment tolerance varies, and there are competing risks of non-breast-cancer mortality [35]. Older women are more likely, than younger women, to present a more advanced breast cancer. There is a delicate balance between overtreatment and under-treatment of advanced disease, in which maintenance of QoL is a priority. CHT is indicated in older patients with ER-negative disease, hormone-refractory disease, or rapidly progressing disease. Elderly patients with MBC are expected to derive similar benefits from CHT as younger patients. Single-agent chemotherapy is generally preferred to combination regimens, which are usually more toxic and provide, at most, a limited survival gain. Preference should be given to CHT agents with better safety profiles (such as weekly taxanes, PEGylated liposomal doxorubicin, capecitabine, and vinorelbine) that have been widely studied in older patients [36].

Specific statements for Nab-P use in elderly patients

3.2 The low impact on daily life and the avoidance of steroids are the key values for Nab-P—consensus reached: totally + partially agree 70%; neutral 10%; totally + partially disagree 20%

The majority of the experts believes that Nab-P could be one of the best options for diabetic patients, when a taxane is indicated, due to the possibility to avoid steroid medication.

In a study comparing a single 1-h infusion of solvent-based paclitaxel at 80 mg/m^2 in MBC patients ≥ 70 years versus 100 mg/m^2 in patients less than 70 years old, the older women had reduced unbound (active) paclitaxel clearance, with concomitantly increased paclitaxel bioavailability of the drug [6]. More extensive data have recently been reported [37] in a combined analysis on 1048 elderly women included in two randomized trials evaluating the efficacy and toxicity of paclitaxel in elderly MBC patients. In this analysis, treatment activity was similar among the age groups (< 55 years, 45%; 55–64 years, 29%; > 65 years, 26%), but an increased incidence of paclitaxel-related toxicities was observed in the elderly population. A subgroup analysis by age of data from the pivotal phase III study [38] indicated that Nab-P showed improved clinical benefit in both younger (< 65 years) and older (> 65 years) patients, compared to solvent-based paclitaxel. ORR was greater for Nab-P, with respect to solvent-based paclitaxel in patients 65 years old or above (27% vs 19%, respectively), but the results did not reach statistical significance because of the small number of patients in this subset. For the elderly population, the incidence of the following adverse events was notably lower in the Nab-P group than in the standard paclitaxel group: neutropenia (23% versus 59%, respectively), leukopenia (10% vs 31%, respectively), nausea (20% vs 38%, respectively), hyperglycemia (0% versus 19%, respectively) and flushing (0% vs 16%, respectively). For patients with a slowly progressing disease, who may benefit from a longer treatment, or for patients whose key objective of therapy is to maintain QoL, the 100–125 mg/m^2/weekly schedule of Nab-P might be the preferred choice, considering that in this setting obtaining prolonged stabilization of disease can provide the same clinical advantage as exhibiting an objective response. Because of its favourable toxicity profile, the weekly schedule also appears to be an attractive option for elderly patients, allowing physicians to closely monitor the treatment and to promptly react to the onset of side effects such as neuropathy [6].

4. Nab-P—efficacy

All the following statements are specific for the purpose of the present consensus on Nab-P

4.1 Nab-P in taxane-pre-treated patients is feasible and well supported by the literature data—consensus reached: totally + partially agree 80%; neutral 10%; totally + partially disagree 10%

Several pivotal trials evaluated the efficacy and safety of Nab-P in the treatment of MBC patients, even in heavily pre-treated patients, both at the dose of 260 mg/m^2 as a 3-weekly regimen and 150 mg/m^2 weekly. These studies showed that Nab-P was superior to the other conventional taxanes in terms of overall response rate (ORR) and progression-free survival (PFS), with a favourable toxicity profile [3, 12, 39].

However, prospective studies addressing the question of specific Nab-P activity in taxane-treated ones are few. Fabi et Al [7] conducted a pivotal study with the aim of

analysing the efficacy and toxicity of Nab-P in this particular population, trying to define at the same time its activity according to clinical characteristics and biological features. A total of 42 patients (median age 48 years, median ECOG PS 0, triple-negative MBC 19%, all pretreated with a taxane-based therapy, mainly in advanced disease) were enrolled in the study. The ORR was 23.8%, including one complete response (2.4%) and nine partial responses (21.4%); the DCR was 50%. The median duration of response was 7.2 months. After a median follow-up of 9 months, the median PFS was 4.6 months. ORR and PFS were similar irrespective of the previous chemotherapy lines, metastatic sites, and bio-molecular expression. Nab-P was well tolerated, and the most frequent treatment-related toxicities were mild to moderate (grades 1–2). The authors concluded that Nab-P has a significant antitumour activity and a manageable safety profile in patients pretreated with taxanes and experiencing a treatment failure after at least one line of CHT. In the study performed by Palumbo et al. [6], 52 women with HER2-negative MBC who were candidates for a second-line CHT for advanced disease were enrolled and treated at three centres in Northern Italy. All patients had previously received taxane-based CHT in the adjuvant or first-line metastatic setting. Single-agent Nab-P was administered at the dose of 260 mg/m^2 every 3 weeks. No steroid or antihistamine premedication was provided. The objective response rate was 48% (95% CI, 31.5–61.3%) and included complete responses from 13.5%. Disease stabilization was obtained in 19 patients and lasted ≥ 6 months in 15 of them; the CBR was 77%. The median time to response was 70 days (range 52–86 days). The median PFS was 8.9 months (95% CI 8.0–11.6 months, range 5–21+ months). The median OS point has not been reached. Toxicities were as expected and manageable with a good patient compliance and preserved quality of life, even in those who received long-term treatment. The authors concluded that single-agent Nab-P 260 mg/m^2 every 3 weeks is an effective and well-tolerated regimen as the second-line CHT in HER2-negative, taxane-treated MBC patients, and that it produced interesting values of ORR and PFS without the concern of significant toxicities.

4.2 Meaningful disease control (DC = CR + PR + SD) rate and duration of DC are the key values of Nab-P—consensus not reached: totally + partially agree 50%; neutral 40%; totally + partially disagree 10%

Most of the experts convened that DCR and its duration are of great value for most patients, but they are not specific key values for Nab-P, having different aspects to be considered, such as tolerability and infusion duration, which could be of greater value.

Main reasons of disagreement expressed by the experts regarding the statement were as follows:

- Results similar to those obtained by different agents.
- No data regarding DCR specifically related to particular subgroups of patients and disease control duration.
- Most data are from real-world studies.

DCR is one of the efficacy parameters used to evaluate the performance of a drug. For MBC, for which estimation of OS in the evaluation of new treatment regimens is limited by the prolonged time for patient follow-up and by the potential effect of subsequent therapies, the identification of a surrogate marker to predict OS might help the design of future trials.

In the first-line setting studies [4], DCRs associated with the 3-weekly schedule of Nab-P was 68% and 75%-80% with the weekly regimens (100 mg/m^2 and 150 mg/m^2, respectively). DCR was significantly higher for patients receiving weekly Nab-P compared to docetaxel. The independent central radiology review confirmed superior DCRs for both the 150 mg/m^2 (80%, $p = 0.017$) and 100 mg/m^2 (75%, $p = 0.009$) of Nab-P weekly compared to docetaxel (58%).

Different real-world studies evaluated the CBR of Nab-P even in heavily pre-treated patients [5–7], substantially confirming DCR in approximately 60% of the patients, without any difference according to the schedule (54.3% vs. 59.9% for weekly and every 3 weeks Nab-P, respectively) [5].

4.3 Improved progression-free survival over docetaxel is the key factor for choosing Nab-P—consensus not reached: totally + partially agree 50%; neutral 20%; totally + partially disagree 30%

The experts underline the positive results obtained by Nab-P 150 mg/m^2 over docetaxel; however, considering that docetaxel shows a high rate of hematologic toxicity and for this reason it is not the preferred choice in the metastatic setting, they believe that key factors for choosing Nab-P do not lie only on the results of this comparison.

Main reasons of disagreement expressed by the experts regarding the statement were as follows:

- The main study evaluating a direct comparison between Nab-P and docetaxel is a randomized phase II trial.
- No confirmatory phase III studies are available.

The main study investigating the role of Nab-P in comparison to docetaxel was conducted in 2009 [4] as the first-line therapy in metastatic breast cancer patients. In previous studies comparing weekly, and every 3 weeks solvent-based taxane schedules, a 3-weekly dosing regimen resulted to have a better efficacy for docetaxel, whereas the weekly

regimen proved more advantageous for sb paclitaxel. However, the best dosing regimen for Nab-P remained unexplored at that time. This phase II study was conducted to evaluate the safety and efficacy of three different Nab-P dosing regimens and to investigate differences in safety and efficacy between these Nab-P dosing regimens and docetaxel administered at the highest standard dose. Three-hundred and two patients with previously untreated MBC received Nab-P 300 mg/m^2 every 3 weeks, 100 mg/m^2 weekly, or 150 mg/m^2 weekly or docetaxel 100 mg/m^2 every 3 weeks. Nab-P 150 mg/m^2 weekly demonstrated significantly longer PFS than docetaxel by both independent radiologist assessment (12.9 v 7.5 months, respectively; $p = 0.0065$) and investigator assessment (14.6 vs 7.8 months, respectively; $p = 0.012$). On the basis of the independent radiologist's review, both 150 mg/m^2 (49%) and 100 mg/m^2 (45%) weekly of Nab-P demonstrated a higher overall response rate (ORR) than docetaxel (35%), but this did not reach statistical significance. This trend was supported by statistically significantly assessed ORR for both weekly Nab-P doses, versus docetaxel. Nab-P every 3 weeks versus docetaxel gave the same results in terms of PFS or ORR. The authors concluded that Nab-P was superior to docetaxel, with a statistically and clinically significant prolongation of PFS (≥ 5 months) in patients receiving Nab-P 150 mg/m^2 weekly, compared to docetaxel 100 mg/m^2 every 3 weeks. Most of the experts believe that Nab-P was quite a new drug at the time of the study conduct, with some concerns about the potential toxicity, thus leading in dose reduction.

4.4 Increase in overall survival is determinant for Nab-P choice over other options—consensus not reached: totally + partially agree 10%; neutral 30%; totally + partially disagree 60%

The experts recognize the importance of these results, even if the limitations observed in some studies do not sufficiently support the consensus; for this reason, the experts strongly suggest evaluating in larger, real-life studies long-term results.

Main reasons of disagreement expressed by the experts regarding the statement were as follows:

- OS advantage not supported by strong data.
- The only data available have been obtained in a small subgroup of patients.

In the study by Gradishar et al. [3], the median censoring time for OS was 103 weeks for the Nab-P group and 101 weeks for the sb-P group. There was a trend for greater median OS for all patients treated with Nab-P compared to sb-P (65.0 vs 55.7 weeks, respectively; $p = 0.374$). Although no difference in survival was observed in the first-line setting, the difference was statistically significant in patients who received Nab-P as the second-line or later subsequent therapies (56.4 vs 46.7 weeks, respectively; HR 0.73; $p = 0.024$). The authors particularly highlighted this latter finding, because for those patients, whose clinical course would be less affected by subsequent therapies, survival had been significantly prolonged, and the death risk reduced by 28%.

In the second trial comparing Nab-P with docetaxel [4], treatment with Nab-P 150 mg/m^2 weekly resulted in a median OS of 33.8 months compared to 22.2, 27.7, and 26.6 months for w Nab-P 100 mg/m^2, Nab-P 300 mg/m^2 every 3 weeks, and docetaxel, respectively (overall $p = 0.047$). Patients receiving 150 mg/m^2 Nab-P had prolonged median OS compared to those in the 100 mg/m^2 Nab-P arm (hazard ratio 0.575; $p = 0.008$). A trend towards prolonged median OS was observed among patients who received 150 mg/m^2 weekly Nab-P, compared to those in every 3 weeks docetaxel arm (26.6 months; HR 0.688). Consistent with the OS results, a greater number of patients were alive and progression free at the completion of the protocol, which specified a 2-year survival follow-up period in the 150 mg/m^2 weekly Nab-P arm (42%), compared to the 100 mg/m^2 weekly Nab-P arm (22%) and docetaxel arm (35%). No statistical difference was noted in the median OS among the treatment groups, even for different patient subsets, including age (< 65 years vs ≥ 65 years), visceral versus non-visceral, number of visceral lesions (<5 vs ≥ 5), and premenopausal versus postmenopausal. Median OS trended in favour of the 150 mg/m^2 weekly arm in each patient subset: age younger than 65 years versus 65 years or older, visceral disease versus non-visceral disease, and number of visceral lesions (< 5 vs ≥ 5).

In a recently published real-world study [5], which collected data of 209 metastatic breast cancer patients, the median OS was 18 months (95% CI 16.0–20.9) in the whole population, 16.9 months (95% CI 14.9–21) in the weekly Nab-P group, and 18 months (95% CI 16–21) in the every 3-week Nab-P group. Most patients (76.1%) received further anticancer treatments after failure of Nab-P treatment, mainly CHT (64.1%). In a large real-life data collection [40], patients who received first-line Nab-P-based therapy appeared to have longer median survival versus second- and third-line or subsequent therapy 22.7, 17.4, and 15.1 months, respectively. In the subgroup of patients aged ≤ 50 years or who had ≥ 3 metastases ($n = 400$), the median OS was 15.6 months (95% CI, 12.9–17.4 months), and the median TNTD (time to next therapy or death) was 5.7 months (95% CI 4.9–6.4 months). Patients who received Nab-P combination therapy had a median survival time of 18.7 months compared to 16.8 months of those who received Nab-P monotherapy. Table 5 summarizes the evidence available for Nab-P for all efficacy end-points.

Table 5 Summary of the evidence available for Nab-P for all efficacy end points

Outcome	No. of patients		Effect		Quality
	nab_Paclitaxel 260 mg/m^2 q3w	Paclitaxel 175 mg/m^2 q3w	Relative (95% CI)	Absolute (95% CI)	
Overall response rate all pts (assessed with: RECIST)	76/229 (33.2%)	42/225 (18.7%)	RR 1.78 (1.28–2.47)	15 more per 100 (from 5 more to 27 more)	⊕⊕⊕◯ MODERATE[a]
Overall response rate first line pts (assessed with: RECIST)	41/97 (42.3%)	24/89 (27.0%)	RR 1.57 (1.04–2.37)	15 more per 100 (from 1 more to 37 more)	⊕⊕◯◯ LOW[a,b]
Overall response rate second or more line pts (assessed with: RECIST)	35/132 (26.5%)	18/136 (13.2%)	RR 2.00 (1.20–3.35)	13 more per 100 (from 3 more to 31 more)	⊕⊕◯◯ LOW[a,b]
Time to progression all pts (follow up: median 2 years; assessed with: RECIST)			HR 0.75 (0.61–0.92)	10 fewer per 100 (from 3 fewer to 17 fewer)[c]	⊕⊕⊕◯ MODERATE[a]
Time to progression second or more line pts (follow up: median 2; assessed with: RECIST)			HR 0.73 (0.56–0.95)	11 fewer per 100 (from 2 fewer to 21 fewer)[c]	⊕⊕◯◯ LOW[a,d]
Overall survival second or more line pts (follow up: median 2 years)			HR 0.73 (0.55–0.96)	11 fewer per 100 (from 1 fewer to 21 fewer)[e]	⊕⊕⊕◯ MODERATE[d]
AE related discontinuation (follow up: median 2 years)	7/229 (3.1%)	16/225 (7.1%)	RR 0.43 (0.18–1.02)	4 fewer per 100 (from 0 fewer to 6 fewer)	⊕⊕⊕⊕ HIGH

CI confidence interval, *RR* risk ratio, *HR* hazard ratio

[a]Randomisation concealment is not defined; the study is open label, no independent assessment of response status was used

[b]Small number of pts

[c]Based on 1 year TTP in the control arm = 20%

[d]Small number of events

[e]Calculated based on 2 years OS in the control arm = 20%

5. Nab-P—safety

   5.1 Rapid recovery from peripheral neuropathy makes the difference in comparison to other taxane-based treatments—consensus reached: totally + partially agree 80%; neutral 10%; totally + partially disagree 10%

The most common adverse events across studies are alopecia, sensory neuropathy, neutropenia, fatigue, and arthralgia [3–7].

Neuropathy is a common, dose-limiting side effect of taxane therapy that is often managed by dose reductions and delays. The severity, time to onset, and improvement in neuropathy are important considerations for patients' management and vary among currently approved taxanes.

The rate of grade ≥ 3 neuropathy with taxanes has been shown to be dose and schedule dependent; however, time to improvement to grade ≤ 1 is typically shorter for Nab-P than for other taxanes in patients with MBC.

One study by Liang et Al [40], designed to characterize treatment patterns, efficacy, and safety of Nab-P for MBC treatment, using health claims data from US health plans associated with Optum, reported that the occurrence of select known Nab-P toxicities (e.g. neutropenia, peripheral neuropathy, anaemia, infections, and nausea and vomiting) ranged from 15 to 26% and was lower, in comparison, to the ones noted in clinical trials. Approximately 15% of claims were related to peripheral neuropathy. These events were more frequently recorded in patients undergoing a first-line therapy (15.5 weeks) compared to patients receiving Nab-P in later lines of therapy (12.3 weeks). In particular, the frequency of reported neuropathy was relatively low (< 15%) compared to the one reported in clinical trials for Nab-P, indicating that this adverse event may have been underrepresented in the claims' database. This is partially easily explained by the more robust patient monitoring, and collection of safety data in the clinical trial setting, even if claims data for analysis, tend to bias towards underreporting in comparison to the prospective National Cancer Institute Common Terminology Criteria for Adverse Events documentation.

When Nab-P is used in the first- or second-line therapy [3], grade 3–4 neuropathy was 10% for Nab-P versus 2% for sb-P, resolved to grade 1–2 in 22 days, without any difference between two arms after day 28. Peripheral neuropathy was managed with dose reductions and no grade 4 neurological toxicity was seen, thus allowing to treat the Nab-P group with 49% more drug. Different schedules of weekly

and 3-weekly Nab-P produced the same degree of peripheral neuropathy than docetaxel 100 mg/m^2, but significantly higher ORR [4]. Median time to improvement was 19 days [6]. No correlation between frequency or severity of peripheral neuropathy and previous administration of taxanes was reported [5]. Because peripheral neuropathy associated with Nab-P treatment appears to improve faster, compared to treatments with either paclitaxel or docetaxel, patients previously receiving Nab-P, and who have seen improvement in their peripheral neuropathy, theoretically could be treated with subsequent lines of therapy earlier than those who received solvent-based paclitaxel or docetaxel.

5.2 Haematological toxicity is lower than that observed with other taxanes—consensus reached: totally + partially agree 90%; totally + partially disagree 10%

In the two main randomized studies [3, 4], hematologic toxicity, mainly leukopenia and neutropenia, were observed in less than 10% of the patients. The incidence of grade 4 neutropenia was lower in Nab-P groups compared to sb paclitaxel groups (9% vs. 22%) despite a 49% higher paclitaxel dose in the first Gradishar's study. Febrile neutropenia was uncommon (< 2%), and the incidence did not differ between the two study arms. Similar results were reported from the phase II trial comparing different doses and schedules of Nab-P with docetaxel [4], confirming the results of the preclinical and phase I/II clinical trials, where the use of the Nab-P formulation could result in clinically relevant improvements in the toxicity and the efficacy of solvent-based paclitaxel. In particular, the incidence of any grade 3 and 4 neutropenia was significantly reduced in patients receiving Nab-P compared to those receiving sb paclitaxel, despite an increase in the total dose of paclitaxel.

In the first-line setting, Nab-P doses of 300 mg/m^2 every 3 weeks and 150 mg/m^2 weekly produced more grade 3–4 hematologic toxicity and required 20% dose reduction for 47% and 20% of patients, respectively [4]. In the second-line setting, Nab-P 260/m^2 caused 21.2% neutropenia [6]. Nab-P 260 mg/m^2 every 3 weeks or 125 mg/m^2 weekly in TNBC, taxane-pre-treated patients, led to up to 70% neutropenia and 25% leukopenia [7].

Dose adjustment is recommended in patients with hepatic dysfunction, neutropenia and sensory neuropathy. Patients who experience severe neutropenia (neutrophil counts < 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during treatment with Nab-P should reduce dosage to 220 mg/m^2 at subsequent cycles. At the recurrence of severe neutropenia or severe sensory neuropathy, an additional dose reduction to 180 mg/m^2 should be done. Treatment should be withheld until neutrophils return to be > than 1500 cells/mm^3 and platelets recover to a level > than 100,000 cells/mm^3. Although Nab-P is more expensive than solvent-based paclitaxel, its better toxicity profile, its faster infusion time and the non-requirement of premedications are significant cost savings compared to the solvent-based product.

6. Nab-P—schedule and dose

6.1 Optimal schedule and dose have been defined—consensus not reached: totally + partially agree 70%; totally + partially disagree 30%

Main reasons of disagreement expressed by the experts regarding the statement were as follows:

- The 3-week regimen has a better toxicity profile in comparison to the weekly schedules and this finding is important for patient selection.
- No data at this moment are available regarding the comparison between 100 mg/m^2 and 125 mg/m^2 weekly schedules.
- No label available for the weekly schedule.
- Need for more trial data for the weekly regimens.

Among the experts, there was a difference of opinion regarding the standard reference taxane and optimal dosing regimen [41] and this is particular true for of Nab-P. In the phase III trial, Nab-P demonstrated a significantly higher overall response rate (ORR), a significantly longer TTP, and a significantly greater OS in those patients treated with a second-line or further therapies, compared to patients who received 3-weekly Nab-P [3]. Furthermore, weekly Nab-P can be administered at greater doses, compared to the ones typically used for solvent-based paclitaxel [2] and a study in taxane refractory patients confirmed the excellent antitumour activity of weekly Nab-P [12].

Nab-P 150 mg/m^2/weekly demonstrated a significantly longer PFS compared to docetaxel by both independent radiologist assessment (12.9 vs 7.5 months, respectively; $p = 0.0065$) and investigator assessment (14.6 vs 7.8 months, respectively; $p = 0.012$) [4]. On the basis of the independent radiologists' review, both 150 mg/m^2 (49%) and 100 mg/m^2 (45%) weekly of Nab-P demonstrated a higher ORR than docetaxel (35%), but this did not reach statistical significance. This trend was supported by the investigator's assessment of ORR for both weekly Nab-P doses versus docetaxel. Nab-P every 3 weeks versus docetaxel was not different for PFS or ORR. On the basis of both the independent radiologists and investigators review, DCR was significantly longer for patients receiving either dose of weekly Nab-P compared to docetaxel. Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all Nab-P arms. The frequency and grade of peripheral neuropathy were similar in all arms. The authors concluded that weekly Nab-P was superior to docetaxel in terms of both efficacy and safety,

with a statistically and clinically significant prolongation of PFS (> 5 months) in patients receiving Nab-P 150 mg/m^2 weekly compared to docetaxel 100 mg/m^2 every 3 weeks. The dose of 150 mg/m^2 weekly is currently known to be often too high for administration in the clinic, because of limiting toxicity.

A recently published real-world study designed to observe the efficacy and safety of both weekly and 3-weekly regimens of Nab-P [5] in the clinical practice enrolled 209 patients, of whom 92 (39.3%) patients received weekly Nab-P. Median number of cycles was 5.5. ORR was 32.1% in the whole population, without any significant difference according to schedule, previous solvent-based paclitaxel exposure, presence of visceral metastases or line of treatment. Median TTP was 6 months (95% CI 1–34), with no differences according to the schedule of treatment. The authors concluded that although no formal comparison is possible between the two schedules, owing to the observational nature of the study, their findings showed no differences in terms of clinical activity of Nab-P according to the schedule used. This finding is of particular interest for the clinical practice, considering that the choice could be left to the physician, adapting the decision according to the patient's preference, her clinical conditions or the hospital location (geographical accessibility of the centre).

Conclusion

Consensus was reached in 4 out of 13 (30.8%) statements specific to Nab-P, mainly on safety items (2/2), whereas topics regarding efficacy and schedules still remain controversial areas, with no definitive conclusion.

This result could be mainly related to the few number of randomized trials [3, 4], which generally strongly support and reinforce efficacy data. The lack of data in special subgroups of patients (i.e. HR + MBC patients) makes it difficult to place Nab-P in a specific therapeutic sequence.

Furthermore, with the introduction of the new TT in combination with ET into the clinical practice, and their peculiar toxicities, especially the hematologic ones, it will become more complicated to establish the right sequence of CHT agents in the future. Lack of data concerning the potential impact of previous TT toxicities on subsequent CHT treatments still requires more robust data.

For these reasons, we strongly support and encourage the flourishing of both retrospective and mainly prospective real-world studies, which will provide further information regarding the efficacy of Nab-P, especially in TT-treated MBC patients, elderly ones and those with organ function impairment, to better describe the efficacy of this drug.

We all strongly highlighted the importance of avoiding steroids with Nab-P, an aspect particularly important in sensitive subgroups of patients (i.e. diabetic ones), or elderly. Indeed, in contrast to solvent-based paclitaxel, steroid premedication is not required prior to Nab-paclitaxel administration, because this formulation does not require the use of a solvent, this is the main reason for choosing Nab-p in all the clinical situations in which avoidance of steroids is needed.

Even if consensus was not reached regarding the optimal schedule of Nab-P, we endorsed the potential benefit offered by this drug, adapting the schedule to patients' and physicians' preference.

The guidance statements are not absolute recommendations but are intended to be used as a guide for the clinician in their daily clinical practice. The expert panel suggests that the guidance statements emerged in this publication should be used in parallel with existing guidelines to optimize the appropriate use of Nab-P in MBC patients in the clinical practice.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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