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# Weekly *nab*-Paclitaxel in Metastatic Breast Cancer – Summary and Results of an Expert Panel Discussion

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**Keywords**
First-line therapy · Metastatic breast cancer · Chemotherapy · Weekly · *nab*-Paclitaxel · Paclitaxel · Docetaxel

**Summary**
Taxanes are regarded as the most effective single agents in the treatment of metastatic breast cancer (MBC). For conventional taxanes, crucial toxicities and impairments in clinical efficacy are related to solvents necessary because of the agents' hydrophobicity. The mandatory premedication with corticosteroids causes additional side effects. *Nab*-paclitaxel is a solvent-free colloidal suspension of paclitaxel and human serum albumin that exploits the physiological transport properties of albumin. It is registered as monotherapy with a recommended dose of 260 mg/m$^2$ every 3 weeks for the treatment of patients with MBC, who have failed a first-line treatment of metastatic disease and for whom a standard anthracycline treatment is not indicated. Clinical evidence is available for the registered 3-weekly administration and for alternative weekly schedules in first and further lines of therapy of patients with MBC. During an advisory board meeting, a group of 8 German breast cancer experts reviewed the clinical data of *nab*-paclitaxel in MBC and discussed how *nab*-paclitaxel could be used in clinical practice on the basis of the current data.

**Schlüsselwörter**
Erstlinientherapie · Metastasiertes Mammakarzinom · Chemotherapie · Wöchentlich · *nab*-Paclitaxel · Paclitaxel · Docetaxel

**Zusammenfassung**
Taxane gelten als die wirksamsten Substanzen in der Therapie des metastasierten Mammakarzinoms. Relevante Nebenwirkungen der konventionellen Taxane und Einschränkungen ihrer klinischen Wirksamkeit werden wesentlich durch die aufgrund ihrer hydrophoben Eigenschaften notwendigen Lösungsmittel verursacht. Die obligate Prämedikation mit Kortikosteroiden bedingt weitere Nebenwirkungen. *Nab*-Paclitaxel ist eine lösungsmittelfreie, kolloidale Suspension von Paclitaxel und humanem Serumalbumin. Es nutzt die natürlichen Transporteigenschaften von Albumin. *Nab*-Paclitaxel ist als Monotherapie mit einer empfohlenen Dosierung von 260 mg/m$^2$ alle 3 Wochen für die Behandlung des metastasierten Mammakarzinoms bei erwachsenen Patientinnen zugelassen, bei denen die Erstlinientherapie der metastasierten Erkrankung fehlgeschlagen ist und für die eine standardmäßige Anthrazyklin-enthaltende Therapie nicht angezeigt ist. Daten aus klinischen Studien liegen für das zugelassene 3-wöchentliche Schema und für alternative wöchentliche Dosierungen in der Erstlinien- und Mehrlinientherapie von Patientinnen mit metastasiertem Mammakarzinom vor. Eine Gruppe von 8 deutschen Brustkrebsexperten begutachtete und diskutierte im Rahmen eines Advisory Boards die klinischen Daten zu *nab*-Paclitaxel in der Therapie des metastasierten Mammakarzinoms und diskutierte wie *nab*-Paclitaxel in der klinischen Praxis auf Grund der aktuellen Daten optimal eingesetzt werden sollte.

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## Introduction

There is growing evidence from clinical trials suggesting that the use of chemotherapy is improving survival even in metastatic breast cancer (MBC). Retrospective analyses of clinical trials have shown chemotherapy to result in prolongation of median overall survival of patients with MBC over time. The current guidelines of the German AGO (Arbeitsgemeinschaft für Gynäkologische Onkologie; Working Group on Breast Cancer) breast group recommend chemotherapy with a single cytotoxic agent if patients progress slowly and do not suffer from considerable symptoms or life-threatening disease, and restrict polychemotherapy to the treatment of patients with considerable symptoms and acute life-threatening metastases [1]. The choice of cytotoxic agent to be used depends on the aggressiveness of the disease and the site of metastasis, tumor biology, combination with biologicals, prior exposure to other cytotoxic agents, patient's age and performance status, and last but not least the patient's expectations and reservations especially regarding specific toxicities.

Taxanes are regarded as the most effective single agents in the treatment of breast cancer and as the agents of choice in anthracycline-pretreated patients according to the most recent AGO guidelines [1]. Docetaxel and paclitaxel have been registered as 3-weekly regimens. However, for paclitaxel weekly administration is regarded as the gold standard based on clinical evidence in adjuvant [2] and metastatic disease [3]. Despite their clinical activity, the use of conventional taxanes is often limited by significant toxicities that remain a major challenge especially when treating patients with MBC. Crucial toxicities and impairments in clinical efficacy are based on solvents necessary because of the agents' hydrophobicity. Cremophor used as solvent in paclitaxel has been reported to be associated with several major side effects such as neutropenia, hypersensitivity reactions, and neuropathy due to axonal degeneration [4]. Polysorbat 80, the solvent used in docetaxel, has been shown to partially contribute to fluid retention by altering membrane fluidity [5]. Thus, the dose of paclitaxel and docetaxel that can be administered is limited by these toxic effects. Formation of large polar micelles of cremophor-dissolved paclitaxel in the plasma compartment and subsequent entrapment of the drug leads to non-linear pharmacokinetics [6, 7]. Also, docetaxel and paclitaxel are now broadly used in adjuvant chemotherapy regimens. Thus, the majority of patients will have been exposed to either of these 2 taxanes once they develop metastases. For palliative chemotherapy of patients with MBC pretreated with taxanes and anthracyclines, the current AGO guidelines clearly recommend the inclusion into clinical trials (AGO evidence-based recommendations on therapy of primary and advanced breast cancer, grade of recommendation ++) or monotherapy with capecitabine (AGO evidence-based recommendations on therapy of primary and advanced breast cancer, grade of recommendation ++). Monotherapy with pegylated liposomal doxorubicin or with single agent vinorelbine are 2 further options with a weaker grade of recommendation (AGO evidence-based recommendations on therapy of primary and advanced breast cancer, grade of recommendation +) [1].

*Nab*-paclitaxel is a solvent-free colloidal suspension of paclitaxel and human serum albumin that exploits the physiological transport properties of albumin. The nanoparticle drug delivery system eliminates the need for toxic solvents like cremophor through binding of paclitaxel to albumin, thus alleviating the limitations of paclitaxel dosing and affecting overall drug efficacy. Moreover, albumin binding to the glycoprotein receptor gp60 on endothelial cells results in activation of caveolin-1 and the transcytosis of intact nanoparticles across the cell membrane [8], and thus facilitates the passage of paclitaxel from the bloodstream via the blood vessels to the underlying tumor tissue. *Nab*-paclitaxel has shown good clinical results in first- and further line therapy of patients with MBC [9–11]. It has also demonstrated considerable activity in taxane-pretreated patients with MBC [12]. It is registered as monotherapy with a recommended dose of 260 mg/m$^2$ every 3 weeks (q3w) for the treatment of patients with MBC, who have failed a first-line treatment of metastatic disease and for whom a standard anthracycline treatment is not indicated [13]. Clinical evidence is available for the registered 3-weekly administration and for alternative weekly schedules. This paper summarizes the data and the authors' view of how *nab*-paclitaxel could be used in the treatment of patients with MBC in clinical practice based on the review and discussion of available data at a 1-day advisory board meeting.

## Overview of Clinical Trials with *nab*-Paclitaxel in MBC

### *Pivotal Phase III Study: nab-Paclitaxel versus Conventional Paclitaxel*

In the pivotal phase III trial in MBC [9], 460 patients randomly received *nab*-paclitaxel dosed at 260 mg/m$^2$ (no premedication, 30-min infusion) or solvent-based paclitaxel dosed at 175 mg/m$^2$ (standard premedication with antihistamines and dexamethasone) on day 1 q3w. Roughly 40% were first-line patients, and around 80% of patients had been pretreated with anthracyclines. Intention-to-treat (ITT) analyses demonstrated for all patients that the overall response rate for *nab*-paclitaxel was significantly greater than for standard paclitaxel (33 vs. 19%; p = 0.001). This was confirmed for patients who received first-line therapy (42 vs. 27%; p = 0.029), patients who received second-line or greater therapy (27 vs. 13%; p = 0.006), and patients who had received prior anthracycline therapy in the adjuvant or metastatic setting (34 vs. 18%; p = 0.002) or the metastatic setting only (27 vs. 14%; p = 0.01) and further subgroups. Median time to progression was significantly longer with *nab*-paclitaxel than with standard paclitaxel for all patients (23.0 vs. 16.9 weeks, hazard ratio (HR) = 0.75; p = 0.006) and for patients who received second-

or further line therapy (20.9 vs. 16.1 weeks, HR = 0.73; p = 0.02). Median overall survival for treatment with *nab*-paclitaxel was absolutely greater than for conventional paclitaxel (65.0 vs. 55.7 weeks) without reaching statistical significance, but was significantly prolonged by *nab*-paclitaxel in second- and further line treatment (56.4 vs. 46.7 weeks, HR = 0.73; p = 0.024). Patients treated with *nab*-paclitaxel received an on average 49% greater dose intensity. There were no differences in quality of life between the 2 treatment groups. *Nab*-paclitaxel was well tolerated with a significantly lower rate of neutropenia as compared to standard paclitaxel. Grade 3 sensory neuropathy was higher for *nab*-paclitaxel as compared to standard paclitaxel (10 vs. 2%), but this could be managed easily with dose reductions and interruptions and improved more rapidly as compared to neuropathy under conventional paclitaxel (median 22 vs. 79 days, respectively). No episodes of motor neuropathy or grade 4 sensory neuropathy were reported.

*Weekly Administration of nab-Paclitaxel as Single Agent in MBC*

In a randomized phase II study, 302 first-line patients randomly received either *nab*-paclitaxel at a dose of 300 mg/m$^2$ on day 1 q3w, 100 mg/m$^2$ or 150 mg/m$^2$ on days 1/8/15 q1w or docetaxel at a dose of 100 mg/m$^2$ on day 1 q3w [10]. *Nab*-paclitaxel at 100/150 mg/m$^2$ weekly showed a higher overall response rate than docetaxel (45/49% vs. 35%, respectively) as assessed by an independent radiologist review, but this did not reach statistical significance. On the basis of investigator assessment, there was a significant increase in overall response rate for *nab*-paclitaxel at 100 mg/m$^2$ ($p < 0.001$) and 150 mg/m$^2$ (p = 0.002) versus docetaxel (63 and 74% vs. 39%, respectively). Furthermore, the independent radiologist assessed the independent disease control rate to be significantly higher for *nab*-paclitaxel at both 100 mg/m$^2$ (p = 0.009) and 150 mg/m$^2$ (p = 0.017) versus docetaxel (75 and 80% vs. 58%, respectively).

Treatment with *nab*-paclitaxel 150 mg/m$^2$ weekly resulted in significantly longer median progression-free survival as compared to docetaxel in both the independent radiologist assessment (12.9 vs. 7.5 months, HR 0.495; p = 0.0065) and the investigator (14.6 vs. 7.8 months, HR 0.568; p = 0.012) assessment. No statistical difference between 300 mg/m$^2$ *nab*-paclitaxel q3w and docetaxel treatment was observed in terms of overall response rate, disease control rate, and progression-free survival.

When results were reported by Gradishar et al. in 2009 [10], survival data were not yet mature. A final analysis of survival was presented very recently at the 2011 ASCO Breast Cancer Symposium [11]. *Nab*-paclitaxel at 150 mg/m$^2$ weekly showed a median overall survival of 33.8 months as compared to 22.2 months for *nab*-paclitaxel 100 mg/m$^2$ weekly, 27.7 months for *nab*-paclitaxel 300 mg/m$^2$ q3w, and 26.6 months for docetaxel 100 mg/m$^2$ q3w. However, statistical significance was only reached for the comparison of *nab*-paclitaxel 150 mg/m$^2$ vs. *nab*-paclitaxel 100 mg/m$^2$ (p = 0.008). For docetaxel, a higher rate of grade 3/4 fatigue, neutropenia, and febrile neutropenia was reported. The incidence of sensory neuropathy was similar in the docetaxel regimen and all 3 *nab*-paclitaxel regimens ($p > 0.1$ for all 3 comparisons). The median time to onset of grade 3 neuropathy was 151 (300 mg/m$^2$), 189 (100 mg/m$^2$), and 162 (150 mg/m$^2$) days for *nab*-paclitaxel, and 176 days for docetaxel. Median time to improvement to $\leq$ grade 2 was shorter for all *nab*-paclitaxel arms with a minimum of 20 days (median) for the 150 mg/m$^2$ weekly schedule, as compared to 41 days (median) for docetaxel [11].

Safety results were also reported for an ongoing phase II study of *nab*-paclitaxel at 100 mg/m$^2$ as first-line therapy in 23 patients with and 58 without prior adjuvant or neoadjuvant taxane exposure. Treatment was well tolerated. Neuropathy grade 1/2 occurred in 17% of patients. There was no grade 3/4 sensory neuropathy [14].

Another phase II study included patients with MBC, whose disease progressed despite conventional taxane therapy. Taxane failure was defined as metastatic disease progression during taxane therapy or relapse within 12 months of adjuvant taxane therapy. Patients with a median of 3 prior chemotherapies (range 0–14) including paclitaxel, docetaxel, or both were treated with *nab*-paclitaxel at 100 mg/m$^2$ (n = 106) and in a second cohort at 125 mg/m$^2$ (n = 75) on days 1/8/15 q4w [12]. Overall response rate was 14 and 16%, disease control rate 26 and 37%, median progression-free survival 3 and 3.5 months, and median overall survival 9.2 and 9.1 months, respectively. No survival difference was observed between patients who achieved stable disease $\geq$ 16 weeks and those with a confirmed response. Patients received a median of 15.2 doses in the 100 mg/m$^2$ cohort and of 13.1 doses in the 125 mg/m$^2$ cohort corresponding to median cumulative doses of 900.5 and 1,125 mg/m$^2$, respectively. *Nab*-paclitaxel was generally well tolerated. 9 (8%) patients in the 100 mg/m$^2$ cohort and 14 (19%) in the 125 mg/m$^2$ cohort developed grade 3 sensory neuropathy. In both groups, 3 patients had preexisting grade 1 neuropathy. Median onset occurred after 5 and 3 cycles, respectively. No grade 4 sensory neuropathy was reported. Patients who developed treatment-limiting peripheral neuropathy could be restarted on a reduced dose of *nab*-paclitaxel after a delay of 1–2 weeks. A short overview of the trials with weekly single agent *nab*-paclitaxel in MBC described in detail above is given in table 1.

*Weekly nab-Paclitaxel in Combination with Other Cytotoxic and/or Biological Agents*

In a phase II trial, 50 patients received first-line treatment with *nab*-paclitaxel at 125 mg/m$^2$ with no premedication on days 1/8 and capecitabine 825 mg/m$^2$ twice a day on days 1–14 of a 21-day cycle. In 38 patients evaluable for response, overall response was 47.5% and the disease control rate 87%.

**Table 1.** Overview of weekly single agent *nab*-paclitaxel schedules in metastatic breast cancer

| Study [ref.] | n | Treatment line | *nab*-Paclitaxel | Efficacy | Toxicity |
|---|---|---|---|---|---|
| Gradishar et al. [10, 11] | 74 | first-line | 150 mg/m$^2$ days 1/8/15 q28d | ORR 49%, DCR 80%, PFS 12.9 months, OS 33.8 months | 44% grade 3/4 neutropenia, 14% grade 3 sensory neuropathy |
| Gradishar et al. [10, 11] | 76 | first-line | 100 mg/m$^2$ days 1/8/15 q28d | ORR 45%, DCR 75%, PFS 12.8 months, OS 22.2 months | 25% grade 3/4 neutropenia, 8% grade 3 sensory neuropathy |
| Brezden et al. [14] | 81 | first-line | 100 mg/m$^2$ weekly | not reported | 9% grade 3/4 neutropenia, no grade 3 or 4 neuropathy |
| Mirtsching et al. [21] | 50 | first-line | 125 mg/m$^2$ days 1/8/15 q28d | ORR 38.1%, PFS 12.8 months, OS 27.3 months | 11% grade 3 neutropenia, 8% grade 3 sensory neuropathy |
| Blum et al. [12] | 75 | median of 3 prior lines, taxane-refractory | 125 mg/m$^2$ days 1/8/15 q28d | ORR 16%, PFS 3.5 months, OS 9.1 months | 34% grade 3/4 neutropenia, 19% grade 3 sensory neuropathy |
| Blum et al. [12] | 106 | median of 3 prior lines, taxane-refractory | 100 mg/m$^2$ days 1/8/15 q28d | ORR 14%, PFS 3 months, OS 9.2 months | 18% grade 3/4 neutropenia, 8% grade 3 sensory neuropathy |

ORR = Overall response rate; DCR = disease control rate; PFS = progression-free survival; OS = overall survival.

Grade 3/4 non-hematological toxicity occurred in 23.3% of patients. The incidence of grade 1/2 neuropathy was 25%, and there was no grade 3/4 neurotoxicity [15].

First-line combination therapy of weekly *nab*-paclitaxel and gemcitabine was evaluated in a phase II trial enrolling 50 patients. *Nab*-paclitaxel was administered at 125 mg/m$^2$ and gemcitabine at 1,000 mg/m$^2$ on days 1/8 every 21 days. Overall response rate by RECIST was 50%, median progression-free survival 7.9 months, and overall survival at 6 months 92%. The most common toxicity was neutropenia with 42% grade 3 and 12% grade 4. Neutropenia was generally uncomplicated and managed in an outpatient setting. There was only 1 episode of febrile neutropenia. Neuropathy grade 3 occurred in 8% of patients [16].

A phase II study by the US Oncology Research Network enrolled patients with HER2-negative MBC to receive first-line therapy with *nab*-paclitaxel 125 mg/m$^2$ on days 1/8/15 and bevacizumab 10 mg/kg on days 1/15 of a 28-day cycle. Patients had received prior anthracyclines (41%), docetaxel (12%), and paclitaxel (12%) as part of their adjuvant treatment. The confirmed overall response rate was 30% and the disease control rate 52% for the 45 patients evaluable for response. The median progression-free survival was 9.4 months. 46% of patients experienced > grade 3 neutropenia, and 12% grade 3/4 sensory neuropathy [17].

In a randomized phase II study, 208 patients with HER2-negative MBC were randomly assigned to first-line therapy with 260 mg/m$^2$ *nab*-paclitaxel and 15 mg/kg bevacizumab q3w, 260 mg/m$^2$ *nab*-paclitaxel and 10 mg/kg bevacizumab and filgrastim q2w, or 130 mg/m$^2$ *nab*-paclitaxel weekly and 10 mg/kg bevacizumab q2w. For the 202 evaluable patients, there was no difference in overall response rate between the 3 regimens (arm A: 42%, arm B: 42%, arm C: 41%). Median time to progression with weekly *nab*-paclitaxel was 9.2 months and significantly longer than time to progression when *nab*-paclitaxel was given every 3 weeks or every 2 weeks (7.7 and 6.4 months, respectively; p = 0.028). The study arm with biweekly *nab*-paclitaxel had to be closed early due to an unacceptable toxicity profile as per the protocol-specified stopping rules. The incidence of neurotoxicity > grade 2 was 50% for all 3 regimens [18].

Another phase II study evaluated the combination of weekly *nab*-paclitaxel, gemcitabine, and bevacizumab as first-line treatment of MBC. 30 patients received *nab*-paclitaxel 150 mg/m$^2$ and gemcitabine 1,500 mg/m$^2$ and bevacizumab 10/mg/kg on days 1/15 of a 28-day cycle. Overall response rate was 75.9%, median progression-free survival 10.4 months, and 18-months survival rate 77.2%. 8 (27.6%) patients had grade 3/4 toxicity. Only 1 of these patients experienced peripheral neuropathy [19].

Recently, another phase II study reported on the combination of weekly *nab*-paclitaxel, gemcitabine, and bevacizumab as first-line treatment in 48 evaluable patients with MBC. Patients received *nab*-paclitaxel at 125 mg/m$^2$, and gemcitabine at 1,000 mg/m$^2$ on days 1/8 and bevacizumab 15 mg/kg on day 1 of a 21-day cycle. Overall response rate was 69%, median progression-free survival 11.7 months, and median 1-year survival rate 84%. The most common grade 3/4 adverse event was neutropenia with 71%. Neuropathy grade 3 occurred in 4 (8%) patients [20].

The combination of weekly *nab*-paclitaxel and trastuzumab as first-line treatment was evaluated in a phase II study with 72 patients (50 HER2-negative and 22 HER2-positive) with locally advanced breast cancer or MBC. *Nab*-paclitaxel was administered at 125 mg/m$^2$ on days 1/8/15 of a 28-day cycle plus concurrent trastuzumab (loading dose 4 mg/kg, then 2 mg/kg weekly) for HER2-positive patients. The objective response rate was 38.1% in HER2-negative patients and 52.4% in HER2-positive patients. Median progression-free survival was 12.8 and 18.7 months and median overall survival 27.3 and 36.8 months, respectively. The majority of adverse events was grade 1/2 with only 3 episodes of grade 4 toxicity (neither hematologic nor neurotoxicity). Sensory neuropathy grade 3 occurred in 6 (8%) patients [21].

**Table 2.** Overview of weekly *nab*-paclitaxel combination schedules in metastatic breast cancer

| Study [ref.] | n | Treatment line | *nab*-Paclitaxel | Biological agent | Cytotoxic agent | Efficacy | Toxicity |
|---|---|---|---|---|---|---|---|
| Somer et al. [15] | 50 | first-line | 125 mg/m$^2$ days 1/8 q21d | none | capecitabine 825 mg/m$^2$ BID days 1–14 q21d | ORR 47.5%, DCR 87% | 23.3% grade 3/4 non-hematologic toxicity, no neurotoxicity grade 3 /4 |
| Roy et al. [16] | 50 | first-line | 125 mg/m$^2$ days 1/8 q21d | none | gemcitabine 1,000 mg/m$^2$ days 1/8 q21d | ORR 50%, PFS 7.9 months, OS at 6 months 92% | 54% grade 3/4 neutropenia, 8% grade 3 neuropathy |
| Danso et al. [17] | 45 | first-line | 125 mg/m$^2$ days 1/8/15 q28d | bevacizumab 10 mg/kg, days 1/15 q28d | none | ORR 30%, DCR 52%, PFS 9.4 months | 46% grade 3/4 neutropenia, 12% grade 3/4 neuropathy |
| Conlin et al. [18] | 76 | first-line | 130 mg/m$^2$ weekly | bevacizumab 10 mg/kg biweekly | none | ORR 41%, TTP 9.2 months | 50% ≥ grade 2 neurotoxicity |
| Lobo et al. [19] | 30 | first-line | 150 mg/m$^2$ days 1/15 q28d | bevacizumab 10 mg/kg days 1/15 q28d | gemcitabine 1,500 mg/m$^2$ days 1/15 q28d | ORR 75.9%, PFS 10.4 months | 27.6% grade3/4 toxicity, 3% grade 3 neuropathy |
| Northfelt et al. [20] | 48 | first-line | 125 mg/m$^2$ days 1/8 q21d | bevacizumab 15 mg/kg day 1 q21d | gemcitabine 1,000 mg/m$^2$ days 1/8 q21d | ORR 69%, PFS 11.7 months, 1-year survival 84% | 71% grade 3/4 neutropenia, 8% grade 3 neuropathy |
| Mirtsching et al. [21] | 22 | first-line | 125 mg/m$^2$ days 1/8/15 q28d | trastuzumab weekly | none | ORR 52.4%, PFS 18.7 months, OS 36.8 months | 11% grade 3 neutropenia, 8% grade 3 sensory neuropathy |
| Conlin et al. [22] | 32 | first-line | 100 mg/m$^2$ days 1/8/15 q28d | trastuzumab weekly | carboplatin AUC = 2 days 1/8/15 or AUC = 6, day 1 q28d | ORR 62.5%, DCR 81%, PFS 16.6 months | 9% grade 4 neutropenia, 3% grade 3 peripheral neuropathy |

ORR = Overall response rate; DCR = disease control rate; PFS = progression-free survival; OS = overall survival; AUC= area under the curve.

A multicenter phase II study in 33 patients with HER2-positive MBC evaluated the efficacy and safety of weekly *nab*-paclitaxel in combination with carboplatin and weekly trastuzumab as first-line therapy. Patients received 100 mg/m$^2$ *nab*-paclitaxel on days 1/8/15 in combination with carboplatin at area under the curve (AUC) = 2 on days 1/8/15 (in the first set of 13 patients) or at AUC = 6 on day 1 (in the latter set of 19 patients) of a 28-day cycle. Trastuzumab was administered at 2 mg/kg weekly after a loading dose of 4 mg/kg. The overall response rate was 62.5%, clinical benefit rate 81%, and median progression-free survival 16.6 months. Hematologic toxicities were the only grade 4 toxicities reported with 9% grade 4 neutropenia and 1 case of febrile neutropenia. The frequency of peripheral neuropathy was 13% for grade 2 and 3% for grade 3 toxicity [22]. A short overview of the trials with weekly single agent *nab*-paclitaxel in combination in MBC described in detail above is given in table 2.

Feasibility of weekly paclitaxel in combination with carboplatin and trastuzumab or bevacizumab was demonstrated in a cohort of 106 patients with large and inflammatory breast cancer resistant or sensitive to the combination of doxorubicin and cyclophosphamide (AC) [23]. Patients were treated with growth factor-supported dose dense AC for 2 cycles if resistant or 4 cycles if sensitive to AC. Patients then received 9–12 doses of weekly conventional paclitaxel or albumin-bound paclitaxel in combination with carboplatin plus bevacizumab in the case of HER2-negative tumors or weekly trastuzumab in the case of HER2-positive disease. This treatment resulted in pathological complete response (pCR) in 38 of 84 assessable tumors with pCR being independent of AC-resistance and sensitivity. More detailed information on the feasibility and toxicity of weekly *nab*-paclitaxel in combination with trastuzumab can also be derived from a phase II neoadjuvant study in 66 patients with locally advanced breast cancer. *Nab*-paclitaxel was administered at a dose of 100 mg/m$^2$ weekly for 12 weeks and then followed by chemotherapy with 4 cycles of FEC (5-fluorouracil 500 mg/m$^2$, epirubicin 100 mg/m$^2$ or 75 mg/m$^2$ in the case of HER2-positivity, cyclophosphamide 500 mg/m$^2$ on day 1 of a 21-day cycle). HER2-positive patients received trastuzumab (4 mg/kg loading dose and 2 mg/kg weekly subsequently) starting with the first dose of *nab*-paclitaxel. pCR was seen in 29% of all patients, and in 58% of the HER2-positive, 17% of the HER2-negative and 28% of the triple-negative subgroup. Estimated progression-free survival at 2 years was 81% and median overall survival at 2 years 95%. Toxicity was reported for all patients regardless of HER2-status. No grade 4 toxicity was reported during *nab*-paclitaxel therapy. For treatment with *nab*-paclitaxel, the frequency of neutropenia grade 3 was 3%; febrile neutropenia was recorded for 2% of cases. The incidence of neuropathy grade 3 was 5%, and 11% for neuropathy grade 2. The authors state that co-administration of trastuzumab did not appear to alter the toxicity profile of *nab*-paclitaxel [24].

## Discussion

*Nab*-paclitaxel has been registered as monotherapy with a recommended dose of 260 mg/m$^2$ q3w for the treatment of patients with MBC, who have failed a first-line treatment of metastatic disease and for whom a standard anthracycline treatment is not indicated. However, data from clinical studies on the use of *nab*-paclitaxel in first-line and in weekly schedules as a single agent and in combination with biologicals, other cytotoxic agents, or both offer the basis for a more flexible scheduling and dosing dependent on the specific situation of the individual patient.

Data of the pivotal clinical study demonstrated that *nab*-paclitaxel at 260 mg/m$^2$ q3w provides a superior overall response rate, time to progression and progression-free survival, and a better safety profile compared to solvent-based paclitaxel. Of note, the study was positive regarding its primary endpoint for all patients and subgroups, i.e. also for the approximately 40% of first-line patients [9]. The exceptional survival benefit in second-line chemotherapy is of particular interest in light of the evidence of other standards for second-line chemotherapy such as capecitabine, vinorelbine, and pegylated doxorubicin.

The weekly administration of single agent *nab*-paclitaxel has shown considerable efficacy as first-line treatment of MBC with an impressive median overall survival of 33.8 months for the 150 mg/m$^2$ dose [11], while overall survival was 26.6 months for first-line therapy with docetaxel 100 mg/m$^2$ q3w and 27.7 months for first-line therapy with *nab*-paclitaxel 300 mg/m$^2$ q3w. In the independent radiologist assessment, both the 150 mg/m$^2$ and the 100 mg/m$^2$ weekly schedule of *nab*-paclitaxel revealed a superior progression-free survival as compared to docetaxel 100 mg/m$^2$ q3w [10, 11]. In heavily pretreated taxane-refractory patients, weekly *nab*-paclitaxel exerted a good efficacy profile at a dose of 125 mg/m$^2$ and at 100 mg/m$^2$ [12]. Weekly *nab*-paclitaxel at 125 mg/m$^2$ could be safely combined with either bevacizumab or trastuzumab. Both combinations showed considerable activity as first-line regimens [17, 18, 21]. *Nab*-paclitaxel combinations at a dose of 125 mg/m$^2$ with capecitabine and gemcitabine were feasible, safe and active [15, 16]. Triple combinations of a biological and 2 cytotoxic agents as first-line treatment were tested with the 125 mg/m$^2$ dose plus gemcitabine and the 100 mg/m$^2$ dose with carboplatin, and proved active and manageable [19, 20, 22].

For most physicians involved in the care of patients with pretreated MBC, a weekly schedule of *nab*-paclitaxel might be the preferred choice because it allows them to monitor treatment closely and to react promptly to the onset of side effects such as neuropathy. The challenge to pick the adequate dose for the individual patient will depend on the therapeutic ratio of the respective regimen. For *nab*-paclitaxel this is linked to the probability of sensory neuropathy. Grade 4 sensory neuropathy did not occur with any of the studied *nab*-paclitaxel regimens. The incidence of grade 3 neuropathy ranges from 10% for the 3-weekly schedule up to 14% for the weekly 150 mg/m$^2$, 6–12% for the weekly 125 mg/m$^2$, and 0–8% for the weekly 100 mg/m$^2$ regimen in first line. In heavily taxane-pretreated patients, the incidence was 19% for the 125 mg/m$^2$ and 8% for the 100 mg/m$^2$ weekly schedule. Sensory neuropathy occurs relatively late in the course of treatment. Gradishar et al. [11] reported the time to onset of grade 3 neuropathy to be 189 days for the 100 mg/m$^2$ q1w, 162 days for the 150 mg/m$^2$ q1w, and 151 days for the 300 mg/m$^2$ q3w dose. They also reported that neuropathy could be adequately managed with interruptions and dose reductions. Time to im-

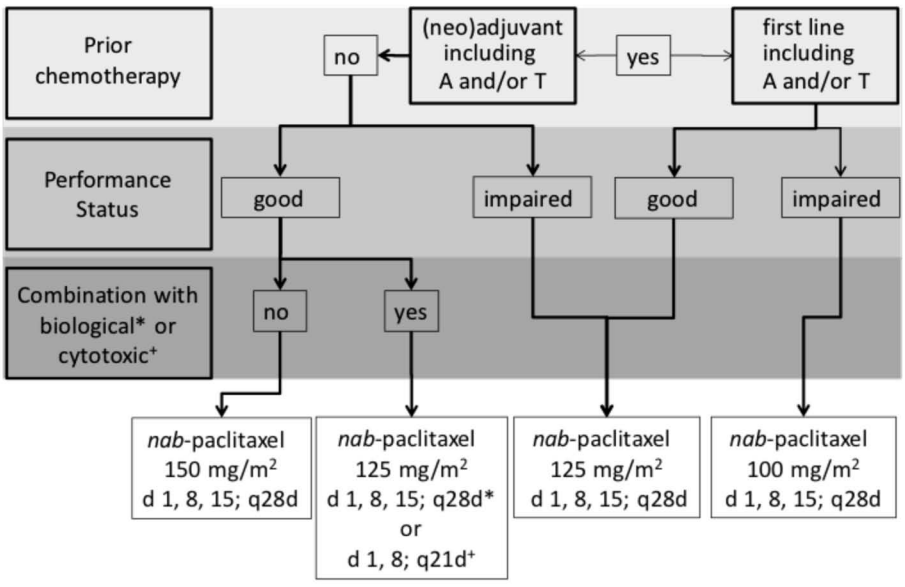


**Fig. 1.** Algorithm for use of weekly *nab*-paclitaxel in metastatic breast cancer (*bevacizumab 10 mg/kg days 1/15, trastuzumab 4 mg loading dose and 2 mg/kg weekly; + data with capecitabine and gemcitabine from phase II trials).

provement to grade 2 or less was consistent for the 3-weekly and the weekly regimens and occurred after only 22, 20 and 22 days, respectively.

In summary, *Nab*-paclitaxel can be used as a 3-weekly schedule, but it is also justifiable to administer it in various weekly schedules in metastatic MBC. Moreover, combinability with biological and cytotoxic agents has been primarily evaluated with weekly schedules. Sensory neuropathy occurs late in the course of treatment, can be managed by interruptions and dose reductions and improves or resolves rapidly. In some cases, logistic considerations may determine the choice of schedule, e.g. a long distance to the treating clinic may trigger the decision for a 3-weekly administration. If a physician decides to use *nab*-paclitaxel to treat a patient with MBC and would prefer a weekly regimen, the algorithm in figure 1 may be a useful guidance regarding schedule and dose based on the evidence discussed. Overall, in first and further lines of therapy of MBC, *nab*-paclitaxel proved to be an effective therapy. It is also a valid chemotherapy option for patients pretreated with both anthracycline and taxane. *Nab*-paclitaxel offers flexible scheduling. The choice of the appropriate *nab*-paclitaxel regimen is guided by prior cytotoxic therapy for metastatic disease, by the patient's condition, or by the combination with a biological or a second cytotoxic agent. In addition, the growing evidence regarding efficacy and safety of combining *nab*-paclitaxel with antibodies opens new options in the systemic treatment of MBC. *Nab*-paclitaxel is also expected to have only limited cross-resistance to solvent-based taxanes and might therefore be indicated in a setting of relapse occurring within < 12 months after a taxane-containing (neo)-adjuvant therapy. This will be evaluated in the ongoing multicenter single arm phase II study TIFFANY in which patients with MBC failing a (neo)-adjuvant treatment with a solvent-based taxane receive first-line weekly *nab*-paclitaxel.

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