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Albumin-Bound Paclitaxel
In Metastatic Breast Cancer

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Contents

Abstract

▲ A new formulation of paclitaxel, 130-nanometre albumin-bound paclitaxel (*nab*™-paclitaxel), solubilises hydrophobic paclitaxel and may increase paclitaxel delivery to tumour cells.

▲ Intravenous *nab*-paclitaxel 260 mg/m^2 had a higher maximum whole-blood concentration, shorter time to peak concentration, larger distribution volume and greater clearance than a 175 mg/m^2 dose of a conventional polyoxyethylated castor oil (Cremophor® EL) solublised paclitaxel (CrEL-paclitaxel).

▲ The reconciled target-lesion response rate was significantly higher in patients receiving intravenous *nab*-paclitaxel 260 mg/m^2 once every 3 weeks than in those receiving CrEL-paclitaxel 175 mg/m^2 once every 3 weeks (21.5% vs 11.1%) in a randomised, nonblind, phase III trial in 454 patients with metastatic breast cancer.

▲ The objective response rate (ORR) was also significantly greater in *nab*-paclitaxel than in CrEL-paclitaxel recipients (33% vs 19%).

▲ In noncomparative phase II trials, ORRs of 48% and 51% were observed in patients receiving *nab*-paclitaxel 175 or 300 mg/m^2 once every 3 weeks.

▲ *nab*-Paclitaxel 260 mg/m^2 caused less grade 4 neutropenia than CrEL-paclitaxel 175 mg/m^2. The incidence of grade 3 sensory neuropathy was higher in *nab*-paclitaxel recipients, reflecting the higher dosage of *nab*-paclitaxel, and improved with treatment interruption. Despite the absence of corticosteroid and antihistamine premedication, no severe hypersensitivity reactions were reported.

Features and properties of 130nm albumin-bound paclitaxel (*nab*™-paclitaxel) [ABRAXANE®]	
Indication	
Metastatic breast cancer after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy	
Mechanism of action	
Inhibits reorganisation of microtubular networks required for interphase and mitotic functions	
Dosage and administration	
Initial dose	260 mg/m^2
Route of administration	Intravenous infusion over 30 minutes
Frequency of administration	Once every 3 weeks
Pharmacokinetic profile of *nab*-paclitaxel 260 mg/m^2 in patients with advanced solid tumours (mean values)	
Peak whole-blood concentration	23.0 μg/mL
Time to peak whole-blood concentration	0.36h
Area under the whole-blood concentration-time curve	14.8 μg • h/mL
Clearance	21.1 L • h/m^2
Terminal elimination half-life	21.6h
Volume of distribution	664 L/m^2
Adverse events	
Most common (>30%)	Alopecia, sensory neuropathy, fatigue, neutropenia and arthralgia

Invasive breast cancer is the most frequently diagnosed cancer among women in the US, accounting for an estimated 32% of all new cancer cases and 15% of all cancer-related deaths in women in 2005.[1] While surgical resection is the preferred option in the treatment of early localised breast cancer, in the US only 64% of patients with breast cancer are diagnosed at this stage and patients with regional or distant metastases have poorer prognoses (5-year survival rates of 81% and 26%).[2]

The taxanes are among the more effective first- and second-line chemotherapeutic single-agents for the treatment of metastatic breast cancer, and the taxane paclitaxel has a response rate of 29–63% as a first-line agent and 19–57% as second-line therapy.[3]

Paclitaxel is a hydrophobic agent that requires a vehicle for intravenous use, and some of the adverse events associated with taxane therapy may be related to the use of polyoxyethylated castor oil (Cremophor® EL)[1] and ethanol as the vehicle in conventional paclitaxel formulations (CrEL-paclitaxel).[4] These agents are thought to be involved in taxane-associated hypersensitivity reactions (necessitating premedication with corticosteroids and antihistamines[5]) and neurotoxicity.[4] This formulation of paclitaxel also requires long infusion times (3 hours) and the use of special infusion sets to minimise exposure to di(2-ethylhexyl)phthalate, which may be leached from standard polyvinyl chloride (PVC) sets.[6]

Increases in CrEL-paclitaxel dose from 175 to 210 or 250 mg/m^2 did not increase efficacy in patients with metastatic breast cancer,[7] and it has been suggested that the use of polyoxyethylated castor oil may limit tumour penetration through the formation of large paclitaxel-entrapping micelles.[8]

In order to minimise the toxicities associated with polyoxyethylated castor oil and to increase the ease, and reduce the cost, of drug administration, 130-nanometre albumin-bound paclitaxel (*nab*™-paclitaxel) [ABRAXANE®] was developed for use as a colloidal suspension for intravenous infusion.[9] This profile reviews the use of *nab*-paclitaxel in the treatment of metastatic breast cancer after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy.

1. Pharmacodynamic Profile

nab-Paclitaxel was designed to exploit the properties of the natural carrier of lipophilic molecules in humans, albumin, removing the necessity for lipophilic vehicles and utilising albumin transport mechanisms to increase delivery of paclitaxel to tumour cells.[10] Paclitaxel acts by inhibiting reorganisation of microtubular networks required for interphase and mitotic functions, through the assembly and stabilisation of microtubules.[11]

- *In vitro*, endothelial binding of *nab*-paclitaxel was 9.9-fold higher, and transport across an endothelial cell monolayer 4.2-fold higher, than that of CrEL-paclitaxel (both $p < 0.0001$).[10] Methyl β-cyclodextrin completely inhibited endothelial transcytosis of *nab*-paclitaxel, indicating active transport via gp60 (albondin)-mediated caveolar-albumin transport. In addition, this transport pathway was found to be inhibited by polyoxyethylated castor oil.[10]
- *In vivo* in nude mice, *nab*-paclitaxel caused human breast tumour (MX-1) xenograft regression and prolonged survival.[10] More animals were tumour free 103 days after implant with *nab*-paclitaxel 30 mg/kg/day (10 of 10) than with CrEL-paclitaxel when administered at equal (30 mg/kg/day; 2 of 4) or equitoxic (13.4 mg/kg/day; 1 of 5) doses.
- A significantly longer median time to MX-1 xenograft tumour recurrence (>103 vs 22 days; $p = 0.004$) and tumour doubling time (>95 vs 31 days; $p = 0.0015$), and a significantly smaller tumour volume ($p = 0.009$) were observed in animals receiving *nab*-paclitaxel 30 mg/kg/day than in those receiving CrEL-paclitaxel 13.4 mg/kg/day.[10] Differences in the time to tumour recurrence and tumour-volume doubling time between groups receiving equal doses (30 mg/kg/day) of *nab*-paclitax-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

el or CrEL-paclitaxel were not significant (>103 vs 47 days and >95 vs 49 days).

- In 19 patients with advanced solid tumours receiving intravenous *nab*-paclitaxel 135–375 mg/m^2 administered as a 30-minute infusion once every 3 weeks, the maximum tolerated dose (MTD) of *nab*-paclitaxel was 300 mg/m^2.[5] Dose-limiting toxicities occurring at a dose of 375 mg/m^2 included sensory neuropathy, stomatitis and superficial keratopathy.
- In 39 patients with advanced nonhaematological malignancies, the MTD during administration of intravenous *nab*-paclitaxel 80–200 mg/m^2 once per week for 3 weeks followed by a week's rest, was 100 mg/m^2 in heavily pretreated patients and 150 mg/m^2 in lightly pretreated patients; peripheral neuropathy and neutropenia were the dose-limiting toxicities.[12]

2. Pharmacokinetic Profile

The pharmacokinetics of intravenous *nab*-paclitaxel have been examined in 16 patients with advanced solid tumours[5] and in 23 patients with advanced nonhaematological malignancies[12] in the human trials discussed in section 1. In addition, the pharmacokinetics of a 30-minute infusion of *nab*-paclitaxel 260 mg/m^2 once every 3 weeks were compared with those of a 3-hour infusion of CrEL-paclitaxel 175 mg/m^2 in a trial in 27 patients (data available for 26 patients) with advanced solid tumours.[13] Further data have been obtained from the manufacturer's prescribing information[14] and from a nonclinical trial.[10]

- Noncompartmental pharmacokinetic analyses of data from phase I trials[5,12] revealed relatively linear increases with dose in mean maximum whole-blood paclitaxel concentration (C_{max}) and area under the concentration-time curve from time zero to infinity (AUC_∞) in patients receiving *nab*-paclitaxel doses up to the MTD (300 mg/m^2; figure 1) [see section 1 for MTD data]. When data from the highest dose (375 mg/m^2) was included in the pharmacokinetic analysis, a nonlinear relationship was observed between dose and mean AUC_∞.[5] Mean time to *nab*-paclitaxel C_{max} (t_{max}) ranged from 0.25 to 0.52 hours.[12]
- Over the dose range of 80–375 mg/m^2, the mean apparent volume of distribution during the terminal phase (V_z) ranged from 236 to 772 L/m^2.[5,12] This relatively large V_z exceeds the volume of total body water and reflects extensive extravascular protein and/or tissue binding.[12]

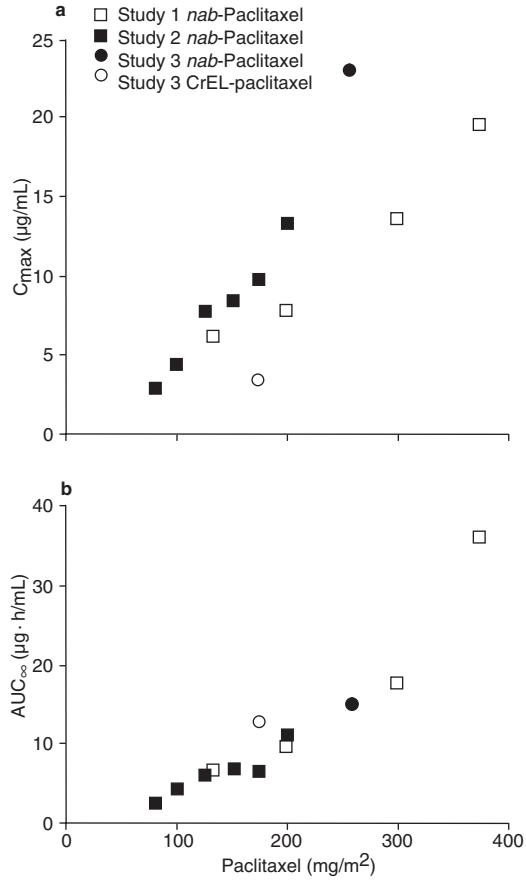

Fig. 1. Pharmacokinetics of 130-nanometre albumin-bound paclitaxel (*nab*-paclitaxel). Increase in (**a**) mean maximum whole-blood paclitaxel concentration (C_{max}) and (**b**) area under the concentration-time curve from time zero to infinity (AUC_∞) in three trials in 16 (study 1),[5] 23 (study 2)[12] or 26 (study 3)[13] patients with advanced solid[5,13] or nonhaematological[12] malignancies receiving a 30-minute intravenous infusion of *nab*-paclitaxel over a range of doses from 80 to 375 mg/m^2[5,12,13] or a 3-hour infusion of a conventional polyoxyethylated castor oil (Cremophor® EL) solubilised paclitaxel (CrEL-paclitaxel) 175 mg/m^2.[13]

• The mean terminal elimination half-life ($t_{½z}$) of *nab*-paclitaxel 80–300 mg/m^2 was 13.4–18.6 hours and mean clearance (CL) was 17.7–30.6 L • h/m^2.[5,12]

• Mean whole-blood pharmacokinetic parameters (mean values) at the approved dosage of *nab*-paclitaxel (260 mg/m^2[14]) differed significantly from those at the recommended dosage of CrEL-paclitaxel (175 mg/m^2[6]), with a higher C_{max} (23.0 vs 3.5 μg/mL; $p < 0.001$) [figure 1], shorter t_{max} (0.36 vs 2.65 hours; $p < 0.001$), larger V_z (664 vs 433 L/m^2; $p = 0.04$) and greater CL (21.1 vs 14.8 L • h/m^2; $p = 0.048$).[13] Values for AUC_∞ (14.8 vs 12.6 μg • h/mL) [figure 1] and $t_{½z}$ (21.6 vs 20.5 hours) did not differ significantly between treatment groups. The differing CL and V_z values but similar $t_{½z}$ values may reflect a difference in the initial drug disposition after administration,[13] with a more rapid distribution of *nab*-paclitaxel out of the vascular compartment.[5]

• *nab*-Paclitaxel plasma concentrations declined in a biphasic manner,[5] with an initial rapid decline as a result of distribution to the peripheral compartment, and a slower phase due to drug elimination.[14]

• Mean cumulative urinary recovery of unchanged drug and metabolites was <5%, indicating extensive nonrenal clearance; ≈20% of the total dose administered was excreted in faeces.[14]

• *In vitro* studies have shown that paclitaxel is primarily metabolised to 6α-hydroxypaclitaxel by the cytochrome P450 (CYP) 2C8 isoform.[14] Minor metabolites, 3′-*p*-hydroxypaclitaxel and 6α, 3′-*p*-dihydroxypaclitaxel, were produced by CYP3A4. *In vitro* data also suggest the potential for interactions with ketoconazole, verapamil, diazepam, quinidine, dexamethasone, ciclosporin, teniposide, etoposide, vincristine, testosterone, ethinylestradiol, tretinoin and quercetin.

• Intratumour paclitaxel accumulation was greater in mice with MX-1 xenografts receiving tritiated *nab*-paclitaxel 20 mg/kg than in those receiving tritiated CrEL-paclitaxel 20 mg/kg ($p < 0.0001$).[10] Partitioning into tumour tissue was rapid, with a 3.3-fold greater absorption constant (0.43 vs 0.13 h^{-1}) in animals receiving *nab*-paclitaxel than in CrEL-paclitaxel recipients, and a greater intratumoural area under the concentration-time curve (3632 vs 2739 nCi • h/g) in *nab*-paclitaxel recipients (statistical analyses not reported).

3. Therapeutic Efficacy

The efficacy of *nab*-paclitaxel in the treatment of metastatic breast cancer has been examined in a randomised, nonblind, multicentre phase III trial in 229 female patients receiving intravenous *nab*-paclitaxel 260 mg/m^2 and 225 patients receiving intravenous CrEL-paclitaxel 175 mg/m^2 once every 3 weeks.[9] Additional data from this trial were obtained from the manufacturer's prescribing information[14] and a US FDA report.[15] Data are also available from two noncomparative, phase II trials in 43[16] or 63[17] women with breast cancer receiving *nab*-paclitaxel 175[16] or 300[17] mg/m^2 once every 3 weeks. Both phase II trials used identical inclusion criteria and designs; the lower-dose study was reported in an abstract.[16] Comparisons of *nab*-paclitaxel with other first-line agents have not been published.

Nonpregnant,[9,17] nonlactating[9] women aged ≥18 years[9,17] with histologically or cytologically confirmed metastatic breast cancer[9,17] were eligible for inclusion in these trials.

Patients were excluded if they had an Eastern Cooperative Oncology Group or Southwest Oncology Group performance status ≥2,[9,17] had received previous taxane treatment for metastatic carcinoma,[9] had received a taxane within the previous 6 months[17] or had relapsed within 1 year of adjuvant taxane treatment.[9]

nab-Paclitaxel was administered intravenously over 30 minutes without premedication or special infusion sets,[9,17] whereas CrEL-paclitaxel was administered intravenously over 3 hours with corticosteroid or antihistamine premedication and special infusion sets.[9]

Tumour lesion responses were based on Response Evaluation Criteria in Solid Tumour (RECIST)[9,18] or WHO[17] criteria, which require the disappearance of all clinical evidence of visible tumour for a complete response,[17,18] and a ≥30%

decrease in the sum of the longest diameter of target lesions,[18] or a ≥50% reduction in the product of the largest perpendicular diameters of measurable lesions[17] for a partial response. In phase II trials, the primary endpoint was the percentage of patients in the intent-to-treat (ITT) population who achieved a confirmed (≥4 weeks after initial staging) objective response.

In the phase III trial, imaging (modality and specific protocol not defined) was performed at baseline, at 5, 9 and 15 weeks, and at the end of treatment.[9] Tumour lesion responses were assessed using RECIST guidelines in the treated patient population.

According to the FDA report[15] and the manufacturer's prescribing information,[14] the primary endpoint in the phase III trial was the reconciled target-lesion response rate (rTLRR), reconciling (by a predefined algorithm) disagreements between the blinded assessments of a central image reader and investigator assessments of target-tumour responses (which could include clinical data). The efficacy analysis comprised three sequential nested tests, assessing noninferiority (retention of at least 75% of the activity of CrEL-paclitaxel) and superiority in all patients (ITT), and superiority in patients receiving *nab*-paclitaxel as first-line therapy.[9,15] Other efficacy measures were investigator-determined overall response rate (ORR), time to tumour progression (TTP) and overall survival (OS).[9]

Delivered paclitaxel dose intensity was 49% higher in *nab*-paclitaxel (85 mg/m^2/week) than in CrEL-paclitaxel recipients (57 mg/m^2/week) in the phase III trial, and six or more cycles were administered to 129 *nab*-paclitaxel and 112 CrEL-paclitaxel recipients.[9] In the phase II trials, patients received a median of six cycles of treatment,[16,17] with a median dose intensity of 118 mg/m^2/week in the higher-dose trial.[17]

Where reported, average age was 48[17] or 53[9] years; 22%[17] or 97%[9] of patients were Caucasian; 83%[9] were postmenopausal;[17] and in 79%[9] or 83%[17] of patients, the dominant lesion site was visceral. The proportion of patients receiving *nab*-paclitaxel as first-line therapy for metastatic disease was 42%[9] or 62%,[17] while 40%[9] of CrEL-paclitaxel recipients were receiving first-line therapy.

- The rTLRR was significantly higher in patients receiving *nab*-paclitaxel than in those receiving CrEL-paclitaxel (21.5% vs 11.1%; p = 0.003) in the phase III trial.[14,15]
- The ORR was also significantly greater in *nab*-paclitaxel than CrEL-paclitaxel recipients (33% vs 19%; p = 0.001) [figure 2].[9] The between-group difference was significant in predefined subgroups who were receiving first-line therapy (n = 186) [42% vs 27%; p = 0.029] or second-line or greater therapy (n = 268) [27% vs 13%; p = 0.006] for metastatic disease.
- Exploratory analyses of other subgroups indicated significant between-group ORR effects in those who had received prior anthracycline therapy (34% with *nab*-paclitaxel vs 18% with CrEL-paclitaxel; p = 0.002), anthracycline therapy for metastatic disease (27% vs 14%; p = 0.01), visceral dominant lesions (34% vs 19%; p = 0.002) and age <65 years (34% vs 19%; p < 0.001).[9]
- Median TTP was significantly longer with *nab*-paclitaxel than with CrEL-paclitaxel (23.0 vs

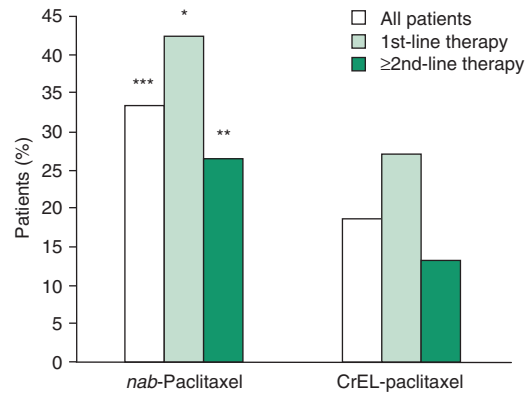

Fig. 2. Efficacy of 130-nanometre albumin-bound paclitaxel (*nab*-paclitaxel) in metastatic breast cancer. Overall response rate in women with metastatic breast cancer receiving intravenous *nab*-paclitaxel 260 mg/m^2 (n = 229) or conventional polyoxyethylated castor oil (Cremophor® EL) solubilised paclitaxel (CrEL-paclitaxel) 175 mg/m^2 (n = 225) once every 3 weeks.[9] Data for all patients and for subgroups receiving first-line therapy (n = 97 or 89) or second-line or greater therapy (n = 132 or 136) for metastatic disease. * p < 0.05, ** p < 0.01, *** p = 0.001 vs CrEL-paclitaxel.

16.9 weeks; hazard ratio [HR] 0.75; p = 0.006), while subgroup analyses indicated significantly longer median TTP in patients receiving second-line or greater therapy (20.9 vs 16.1 weeks; HR 0.73; p = 0.020) but not first-line therapy (24.0 vs 19.7 weeks).

- While OS at a median censoring time of 101–103 weeks did not differ significantly between *nab*-paclitaxel and CrEL-paclitaxel treatment groups in all patients (65.0 vs 55.7 weeks) or in the the first-line therapy subgroup, in patients receiving second-line or greater therapy OS was significantly prolonged (56.4 vs 46.7 weeks; HR = 0.73; p = 0.024).[9]
- Data from the noncomparative phase II trials[16,17] support the phase III trial data. An ORR of 48%, with a response rate of 64% in patients who received *nab*-paclitaxel as first-line therapy, was observed in the higher-dose trial of *nab*-paclitaxel,[17] while in the lower-dose trial the ORR was 51%.[16]

Pharmacoeconomic Considerations

Decision-analytical economic models have been used to analyse the incremental cost effectiveness of *nab*-paclitaxel in comparison with CrEL-paclitaxel[19] and docetaxel[20] in the treatment of metastatic breast cancer from a provider and payer perspective (year of costing 2003[19] or 2004[20]) [data from abstract and poster presentations]. Utilisation costs considered included costs of premedication,[19,20] chemotherapy administration,[19,20] treatment failure[19] and toxicity management.[19,20] In one analysis, drug-acquisition costs were also included,[20] whereas in the other, drug-acquisition costs were not included owing to lack of pricing information for *nab*-paclitaxel at the time of the analysis.[19] Treatment failure costs based on expert opinion were included in the comparison of paclitaxel formulations.[19] Efficacy data (ORR and TTP) were obtained from a preliminary report of the *nab*-paclitaxel phase III trial[21] and a phase III comparison of docetaxel and CrEL-paclitaxel.[22]

- Modelling predicted that *nab*-paclitaxel was dominant over CrEL-paclitaxel, being more effective and less costly per responder ($US30 692 vs $US72 790) and per progression-free month ($US2002 vs $US3718).[19] Sensitivity analyses suggest that the results were robust to primary assumptions.
- Likewise, *nab*-paclitaxel had a marginally higher ORR (33%) than previously reported for docetaxel (32%[22]) and was considerably less costly ($US87 429 vs $US123 601) per responder than docetaxel, and was thus dominant.[20] Previous reports suggest that TTP was longer with docetaxel (5.7 months[22]) than with *nab*-paclitaxel (5.3 months), while costs were higher ($US39 552 vs $US28 852); the incremental cost of an additional month of progression-free survival with docetaxel was estimated to be $US26 750.
- In both analyses, the cost of managing grade 3 and 4 toxicities was the key driver of the cost difference between treatments.[19,20]

4. Tolerability

- Overall tolerability of intravenous *nab*-paclitaxel 260 mg/m^2 was generally similar to that of CrEL-paclitaxel 175 mg/m^2 in the phase III trial.[20] Almost all patients reported at least one adverse event (figure 3), with significantly more *nab*-paclitaxel than CrEL-paclitaxel recipients experiencing sensory neuropathy and gastrointestinal disturbances, and fewer *nab*-paclitaxel recipients experiencing neutropenia and skin flushing.[9,15] Despite the absence of corticosteroid and antihistamine premedication and the shorter administration period (30 minutes with *nab*-paclitaxel vs 3 hours with CrEL-paclitaxel) no severe hypersensitivity reactions were reported in *nab*-paclitaxel recipients.[9]
- Treatment-related grade 3 or 4 adverse events occurring in significantly ($p < 0.05$) more CrEL-paclitaxel than *nab*-paclitaxel recipients included neutropenia (46% vs 30%) and leukopenia (9% vs 6%), with grade 4 neutropenia occurring in 22% of CrEL-paclitaxel and 9% of *nab*-paclitaxel recipients ($p < 0.001$).[9,15] However, grade 3 sensory neuropathy occurred in significantly ($p < 0.001$) more *nab*-paclitaxel than CrEL-paclitaxel recipients (10% vs 2%), reflecting the higher dosage of *nab*-paclitaxel;

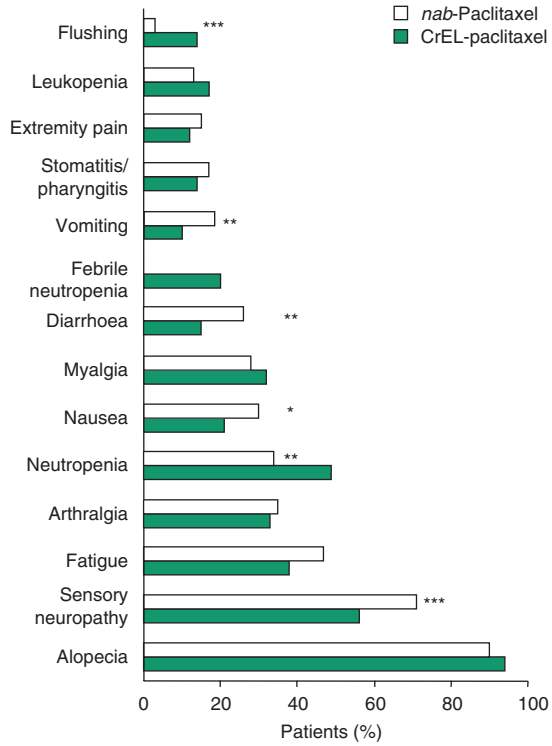

Fig. 3. Tolerability of 130-nanometre albumin-bound paclitaxel (*nab*-paclitaxel). Most commonly reported (≥15% of patients) treatment-emergent adverse events, or events with incidences differing significantly between groups in women with metastatic breast cancer receiving intravenous *nab*-paclitaxel 260 mg/m^2 (n = 229) or conventional polyoxyethylated castor oil (Cremophor® EL) solubilised paclitaxel (CrEL-paclitaxel) 175 mg/m^2 (n = 225) once every 3 weeks.[15] * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs CrEL-paclitaxel.

there were no cases of grade 4 sensory neuropathy.[9,15] Sensory neuropathy was improved to grade 1 or grade 2 after a median 22 days of treatment interruption.

- Other commonly occurring treatment-related grade 3 or 4 adverse events (occurring in ≥5% of patients) included fatigue (≈8% of *nab*-paclitaxel vs ≈3% of CrEL-paclitaxel recipients), arthralgia (7% vs 4%) and myalgia (7% vs 2%).[15] Elevated γ-glutamyltransferase levels occurred in more patients treated with *nab*-paclitaxel than with CrEL-paclitaxel (14% vs 10%) but the relationship to drug administration or underlying metastatic disease was not clear.
- No treatment-related deaths occurred in *nab*-paclitaxel recipients, while one possibly treatment-related death occurred a CrEL-paclitaxel recipient.

5. Dosage and Administration

In patients with metastatic breast cancer, *nab*-paclitaxel is administered at a dosage of 260 mg/m^2 by intravenous infusion for 30 minutes every 3 weeks.[14] *nab*-Paclitaxel should not be administered to patients with baseline neutrophil counts <1500 cell/mm^3.

Local prescribing information should be consulted for dosage reduction guidelines in patients experiencing toxicity, recommendations in special populations, contraindications and precautions.

6. Albumin-Bound Paclitaxel in Metastatic Breast Cancer: Current Status

In the US, *nab*-paclitaxel has been approved for the treatment of metastatic breast cancer after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy.[14] Patients should have received prior therapy with an anthracycline unless contraindicated.

nab-Paclitaxel is currently undergoing clinical trials as adjuvant and neoadjuvant therapy in metastatic breast cancer, in the treatment of a variety of other solid tumours and in combination with other cytotoxic and biological agents.[23]

In a phase III trial in patients with metastatic breast cancer, *nab*-paclitaxel was significantly more effective than CrEL-paclitaxel, with a 94% higher rTLRR and a 74% higher ORR. Delivered *nab*-paclitaxel dose was 49% higher and administration was more rapid than with CrEL-paclitaxel. In addition, while grade 3 peripheral neuropathy occurred more often in *nab*-paclitaxel recipients, reflecting the higher dosage of *nab*-paclitaxel, grade 3 or 4 neutropenia occurred less often than in recipients of CrEL-paclitaxel.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportuni-

ty to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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