CADTH

CADTH Reimbursement Review

CADTH Review Report

NAB-PACLITAXEL

(Non-Sponsored Review)

Therapeutic area: Patients with Solid Tumours Experiencing Hypersensitivity Reactions to Taxanes

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
CI	confidence interval
HR	hazard ratio
HRQoL	health-related quality of life
HSR	hypersensitivity reaction
ITT	intention-to-treat population
OR	odds ratio
OS	overall survival
mBC	metastatic breast cancer
NSCLC	non-small-cell lung cancer
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation

Executive Summary

An overview of the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Nanoparticle, albumin-bound (nab)-paclitaxel (Abraxane) powder for injectable suspension
Health Canada Indication	The treatment of metastatic breast cancer The first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine
Indication under consideration for reimbursement	Patients with Solid Tumours Experiencing Hypersensitivity Reactions to Taxanes
NOC date	June 7, 2006
Requester	Provincial Advisory Group

NOC = Notice of Compliance

Introduction

Hypersensitivity reactions (HSRs) can occur in patients receiving taxane-based therapies for the treatment of solid organ tumours such as breast cancer, NSCLC, gastroesophageal cancer and gynecological malignancies.[1] The traditional taxanes paclitaxel and docetaxel have been reported to cause HSR.[1] The two commonly used generic taxanes paclitaxel and docetaxel require Cremophor EL and polysorbate80, respectively, for solubility; these carrier agents can cause an immediate HSR in patients. As an albumin-bound formulation of paclitaxel, nab-paclitaxel all but eliminates this hypersensitivity risk.. Hence, the incidence for HSR in patients receiving nab-paclitaxel is reported to be much lower.[2,3]

Mild to moderate HSRs may be managed by increasing the intensity of premedications and lengthening the infusion time.[1,3] For more severe or life threatening HSRs, desensitization protocols may be utilized but are labour intensive for physicians, pharmacy and nursing resources and not always feasible in treatment unit facilities. Given a lower incidence for HSR is expected[3], nab-paclitaxel may be a suitable treatment option in patients who have experienced prior HSRs to traditional taxanes.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups and clinician groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review. No input was received from industry groups.

Patient Input

Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink) submitted patient input. Both patient groups have submitted input highlighting perspectives of patients who experienced side effects to taxanes. These include fatigue, increased infection risk post-surgery, nerve damage, suicidal thoughts, stomach acid issues and PTSD. Some respondents experienced severe blistering on feet hindering mobility, rashes and temporary or lasting numbness in extremities. Hospitalization was necessary for all respondents due to either immediate HSRs or long-term treatment side effects. The cumulative impact of both HSRs and side effects led to medication changes or reduction of taxane doses.

Rethink's submission was based on a single patient with metastatic triple-negative breast cancer with experience with receiving nab-paclitaxel due to HSR from a taxane. The patient recounted that experiencing HSRs with paclitaxel was a severe immediate reaction, followed by nausea and flushing. This compounded the trauma of living with metastatic triple-negative breast cancer. Despite

immediate treatment of HSR, the overall experience left the patient feeling profoundly anxious about subsequent treatments. This patient was able to receive nab-paclitaxel in subsequent treatments and reported manageable and tolerable side effects, contrasting starkly with the HSR experienced with paclitaxel.

Clinician input

Input from clinical experts consulted by CADTH

Two clinical specialists provided input. One clinical specialist has expertise in the diagnosis and management of breast cancer. Another clinical specialist has expertise in the diagnosis and management of gynecological malignancies and gastroesophageal cancers. Both clinical specialists have experience with patients developing taxane-induced HSRs. Both clinical specialists highlighted the broad application of taxanes in the treatment of various solid organ tumours, both in curative and metastatic contexts. While HSRs have been reported, the clinical experts noted that treatment can sometimes be continued with intensified premedication and/or slower infusion rates, which can lower the HSR risk. Multistep serial dilution desensitisation protocols are used in refractory cases and are very resource-intensive and time-consuming. Despite the routine administration of premedication to mitigate hypersensitivity risks, the incidence of hypersensitivity reactions in patients ranges from 5-10% for paclitaxel and approximately 2-4% for docetaxel. The clinical specialists noted that nab-paclitaxel presents as an appealing alternative for patients who would otherwise necessitate desensitization for each dose, or for those who experience reactions despite desensitization, or when re-challenge is not advisable.

Input from clinician groups

Clinician group input was submitted by three advisory committees from Ontario Health: Breast Cancer Drug Advisory Committee, Lung Cancer Drug Advisory Committee, Gynecology Cancer Drug Advisory Committee.

The Breast Cancer Clinician group noted that for patients who experience HSR despite premedications or increasing infusion times, nab-paclitaxel is used. However, there is currently limited access to nab-paclitaxel and this varies across centres and disease sites. Hence, taxanes are often excluded from the treatment regimen after a serious HSR. In addition, switching to docetaxel in cases of serious reactions to paclitaxel is not a standard of practice, as docetaxel and paclitaxel are not always interchangeable in terms of efficacy and for concerns of cross-reactivity.

The Breast Cancer Clinician Group noted that there is evidence supporting the use of nab-paclitaxel as an upfront treatment in early-stage breast cancer. They also suggested that nab-paclitaxel is suitable for patients with any stage of breast cancer and who have a serious HSR to paclitaxel despite optimal treatment and prevention strategies.

The Lung Cancer Clinician group noted that in the setting of lung cancer, there are currently comparable alternative treatment regimens for patients who cannot tolerate taxanes due to HSR. Nab-paclitaxel has limited use in lung cancer and would be directed towards patients with grade 3 or 4 reaction, or in those who experience recurrent infusion reactions despite appropriate premedications.

The Gynecology Cancer Clinician group has echoed similar input in that there are patients who continue to experience HSRs despite premedications or slower infusion rates. For those who have life-threatening reactions or intolerance to steroids (e.g., patients with poorly controlled diabetes), nab-paclitaxel would be considered.

Drug program input

The drug plans have highlighted that a clear definition of patient population suitable for nab-paclitaxel should be established. They also suggested that this review should be approached from a tumour or disease agnostic perspective.

Clinical Evidence

The original objective was to perform a systematic review of the efficacy and safety of nab-paclitaxel for patients with HSRs to taxanes. However, the original literature search screening indicated that no evidence from phase III or IV RCTs was available among patients with previous HSRs to a taxane. In order to inform committee deliberations, the analysis was supplemented with additional studies for patients without previous HSRs.

Protocol Selected Studies

Description of the Studies

The main evidence base for this review was from 6 randomized, open label, phase III trials comparing nab-paclitaxel to paclitaxel in treatment regimens appropriate for the following settings: early breast cancer[4,5], metastatic cancer[6,7], NSCLC[8] and gastric cancer[9].

- Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): A randomised, phase 3 trial. *The Lancet Oncology.* 2016;17(3):345-356. [4]
- Gianni L, Mansutti M, Anton A, et al. Comparing Neoadjuvant Nab-paclitaxel vs Paclitaxel Both Followed by Anthracycline Regimens in Women With ERBB2/HER2-Negative Breast Cancer-The Evaluating Treatment With Neoadjuvant Abraxane (ETNA) Trial: A Randomized Phase 3 Clinical Trial. *JAMA Oncol.* 2018;4(3):302-308. [5]
- Jain MM, Gupte SU, Patil SG, et al. Paclitaxel injection concentrate for nanodispersion versus nab-paclitaxel in women with metastatic breast cancer: a multicenter, randomized, comparative phase II/III study. *Breast Cancer Research and Treatment.* 2016;156(1):125-134. [6]
- Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol.* 2005;23(31):7794-7803. [7]
- Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol.* 2012;30(17):2055-2062. [8]
- Shitara K, Takashima A, Fujitani K, et al. Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE): an open-label, randomised, non-inferiority, phase 3 trial. *The Lancet Gastroenterology and Hepatology.* 2017;2(4):277-287.[9]

The efficacy endpoints included progression-free survival, overall survival and pathological complete response for studies that evaluated treatments in the neoadjuvant setting of breast cancer. HRQoL was also included as an outcome in this review.

Critical Appraisal

The overall risk of bias is that there are at least some concerns for all domains as per RoB2. While all included studies are phase III randomized controlled studies, few studies did not describe methods of concealment. The deviations from intended interventions such as dose modifications are not always clearly and consistently described in the protocols. Some studies have patients who withdrew from studies or loss of follow up without clear explanation. Some measurements of outcome are subjective in nature (e.g., fatigue) which raises some concerns as well. In addition, there is question if the HRQoL tool is validated. Selection of reported results was overall of low risk of bias.

In terms of external validity, the studies' inclusion and exclusion criteria were clinically relevant and the administration of nab-paclitaxel or paclitaxel, along with concurrent treatments also appeared to be consistent with common practice. The efficacy endpoints of progression free survival and overall survival were reasonable in metastatic settings. In the early breast cancer setting, pathological complete response was used as the primary endpoint. However, additional survival data have since been published.[10,11]. It is important to note that the classification of the disease and the standard of practice has evolved since the publication dates of these studies which range from 2005 to 2018. This raises the potential concern for external validity of the evidence since these studies were published beyond the last 5 years.

Efficacy Results

The key summary results of overall survival and progression-free survival are summarized in Table 2.

Table 2: Summary of Key Results on Overall Survival and Progression Free Survival

Outcome	Jain et al. 2016 Metastatic Breast Cancer			Gradishar et al. 2005 Metastatic Breast Cancer		Socinski et al. 2012 NSCLC		Shitara et al. 2017 Gastric Cancer			
	Nab-paclitaxel 260mg/m^2 N =58	Paclitaxel 260mg/m^2 N = 64	Paclitaxel 295mg/m^2 N = 58	Nab-paclitaxel 260mg/m^2 N = 229	Paclitaxel 175mg/m^2 N = 225	Nab-paclitaxel 100mg/m^2 N = 514	Paclitaxel 200mg/m^2 N = 524	Nab-paclitaxel 260mg/m^2 every 3 weeks N =247	Paclitaxel 80mg/m^2 weekly N = 248	Nab-paclitaxel 100mg/m^2 weekly N = 246	Paclitaxel 80mg/m^2 weekly N = 248
Overall Survival											
Number of events, n (%)	-	-	-	NR	NR	360 (69.1%)	384 (72.3%)	NR	NR	NR	NR
Median (95% CI)	-	-	-	65.0 weeks (NR)	55.7 weeks (NR)	12.1 months (10.8 to 12.9)	11.2 months (10.3 to 12.6)	10.3 months (8.7 0 11.4)	10.9 months (9.4 – 11.8)	11.1 months (9.9 – 13.0)	10.9 months (9.4 – 11.8)
HR (95% CI)	-	-	-	NR		0.922 (0.797 to 1.066)		1.06 (0.87 to 1.31)		0.97 (0.76 to 1.23)	
p-value	-	-	-	0.374		0.271		0.062		0.0085	
Progression Free Survival											
Number of events, n (%)	NR	NR	NR	-	-	NR	NR	NR	NR	NR	NR
Median (95% CI), months	34 weeks (25 to not reached)	23 weeks (21 to 21)	35 weeks (27 to not reached)	-	-	6.3 months (5.6 to 7.0)	5.8 months (5.6 to 6.7)	3.8 months (3.5-4.4)	3.8 months (3.7 to 3.9)	5.3 months (4.0-5.6)	3.8 months (3.7 to 3.9)
HR (95% CI)	NR			-	-	0.902 (0.767 to 1.060)		1.03 (0.85 to 1.24)		0.88 (0.73 to 1.06)	
p-value	P=0.1085 (between paclitaxel 260mg/m^2 with nab-paclitaxel) P=0.9240 (between paclitaxel 295mg/m^2 with nab-paclitaxel)			-	-	P=0.214		P=0.778		P=0.176	

CI = confidence interval; HR = hazard ratio; NR = not reported

Overall Survival

The evidence in overall survival was informed by 3 included studies[7-9] (metastatic breast cancer, NSCLC and gastric cancer) with 2 follow-up studies in early breast cancer settings. In NSCLC study by Socinski et al.[8], non-inferiority was demonstrated for overall survival when nab-paclitaxel was compared to paclitaxel (HR =0.922, CI 0.797 to 1.066, p=0.271). This analysis appeared post-hoc without multiplicity adjustment. In gastric cancer by Shitara et al[9], there was non-inferiority for one dose comparison (between nab-paclitaxel weekly and paclitaxel weekly treatment groups, HR =0.97, CI 0.76 to 1.23, p =0.0085). Yet, the non-inferiority hypothesis was not rejected when nab-paclitaxel every 3 week treatment arm was compared to paclitaxel weekly treatment arm (HR = 1.06, CI 0.87 to 1.31, p =0.062). In metastatic breast cancer study by Gradishar et al[7], limited information was provided, with p-value (p=0.374), where the null hypothesis was rejected. Without the confidence interval, it would be difficult to estimate uncertainties.

In the extension study by Untch et al[11] in the early breast cancer, the overall survival was based on hazard ratio (0.82) with wide confidence interval (0.59 to 1.16), which introduces uncertainty about which treatment could have favoured. Gianni et al[10] published an event-free survival with only a p-value (0.245) with no measures of precision.

Progression Free Survival

For progression free survival, the evidence was informed by 3 studies across 3 cancers (metastatic breast cancer[6], NSCLC[8] and gastric cancer[9]). In the study by Jain et al.[6], it tested for superiority. There is limited information provided beyond p values and medians. Refer to Table 2 The null hypothesis was not rejected. However without measures of precisions, there would be uncertainty about how wide the confidence interval might be and if there is potential for either group being favoured. Socinski et al.[8] showed non-inferiority (HR =0.902, CI 0.797 to 1.060, p=0.214). The study appears to be post-hoc without multiplicity adjustment. In gastric cancer, Shitara et al[9] tested for superiority. The null hypotheses were not rejected. For the comparison between weekly nab-paclitaxel and

paclitaxel treatment arms, the confidence interval shows potential for benefit when nab-paclitaxel weekly group was compared to paclitaxel weekly (HR 0.88, CI 0.73 to 1.06, p=0.176) or little-to-no difference when nab-paclitaxel every 3 week group was compared to paclitaxel weekly group (HR 1.03, CI 0.85 to 1.24, p=0.778). Given the evidence, it appears that there is some signal from one study to support non-inferiority with limitations.

Pathological Complete Response in Breast Cancer

When nab-paclitaxel is used in the neoadjuvant setting in the early breast cancer, other relevant surrogate outcomes are reported at earlier time points as survival data is expected to take several years to accrue. In GeparSepto-GBG 69 study (n = 1,206)[4], the authors evaluated pathological complete response as the primary efficacy endpoint and was tested for non-inferiority as well as superiority. In the nab-paclitaxel treatment arm, 233 out of the 606 treated patients (38.4%, 95% CI 34.6 to 42.3) achieved a pathological complete response versus 174 out of 600 treated patients (29.0%, 95% CI 25.4 to 32.6) in the paclitaxel arm. The absolute between-group difference was not reported but favoured nab-paclitaxel (superiority unadjusted X^2 p=0.00065). This corresponded to an OR of 1.53 (95% CI, 1.20 to 1.95; unadjusted superiority Wald p=0.00054) for nab-paclitaxel vs. paclitaxel. In multivariable logistic regression analysis, nab-paclitaxel remained an independent predictor for achieving pathological complete response after adjustment for baseline and minimisation factors (OR 1.59; 95% CI 1.20 to 2.11; p = 0.0013).

In another study, ETNA by Gianni et al. (2018)[5] (n = 695), the pathological complete response was also evaluated as a primary efficacy endpoint between the nab-paclitaxel treatment arm and the paclitaxel treatment arm in the neoadjuvant setting of breast cancer. In the nab-paclitaxel treatment arm, 78 of the 346 patients (22.5%, 95% CI, 18.2 to 27.3) achieved pathological complete response compared to 65 of the 349 patients (18.6%, 95% CI, 14.7 to 23.1) in the paclitaxel arm. No absolute between-group difference was reported. The OR was 0.77 (95% CI, 0.52 to 1.13), for paclitaxel vs. nab-paclitaxel, and the null hypothesis was not rejected (p = 0.19).

HRQoL

While HRQoL was available from two studies[7,9], the high risk of bias with the evidence (e.g., open label, high missing data) renders it difficult to arrive at any meaningful conclusions.

Harms Results

Harms including AEs, SAEs, WDAEs, and deaths due to AE were evaluated. However, the reporting isn't consistent across studies, rendering it difficult for direct comparisons. In general, serious adverse event involving death was rare. However, withdrawal due to adverse event would be as expected for chemotherapies. Harms of special interest included HSRs, neutropenia, neuropathy and fatigue were evaluated in this review. Based on 5 of the 6 included studies[4-7,9], the HSRs or allergic reactions were reported. Details of incidences related to neutropenia, neuropathy and fatigue were also reported.

Overall, the incidence of HSR was higher in the paclitaxel treatment arms (6 % or less) when compared with the nab-paclitaxel treatment arms (2% or less) in all included studies. Note that 4 of the 6 studies[6-9] have criteria to exclude patients with pre-existing HSR to taxanes, so the true incidences to taxanes could have been higher. These differences may be of clinical relevance when deciding on a regimen for patients with previous hypersensitivity reactions. Also, only one study provided the definition of HSR and other remaining studies did not provide additional details on either the definition(s) of HSR or the severity of the HSRs being noted. Note that hospitalization as a result of HSR was not evaluated or captured in the clinical evidence.

Overall, neutropenia is commonly reported in both nab-paclitaxel and paclitaxel treatment arms. In the study by Gianni et al. (2018)[5], any grade neutropenia was reported in 41.8% (CI 36.5 to 47.3) in the nab-paclitaxel arm compared to 36.4% (CI 31.3 to 41.8) in the paclitaxel treatment arm. Neutropenia may also be influenced by the dose administered, frequency of the regimen as well as other concurrent cytotoxic therapies that can contribute to neutropenia. In 4 studies that have also reported febrile neutropenia which is often associated to worse outcomes, the incidence is overall low (3% or less) and does not appear to be different between groups. One potential outlier is in gastric cancer where 11% experienced grade 3 febrile neutropenia in the nab-paclitaxel every 3 weeks treatment group, when compared to nab-paclitaxel weekly group (2%) and paclitaxel weekly group (1%). In addition, Jain et al.[6] reported that grade 3 and 4 febrile neutropenia with 3% from the nab-paclitaxel 260mg/m^2 group, 2% in the paclitaxel 260mg/m^2 group and 7% in the paclitaxel 295mg/m^2, suggesting this harm may be connected to the dose intensity. Further investigation would be needed.

As reported in the 6 included studies, neuropathy appeared to be more common among the nab-paclitaxel treatment arms, if receiving the same dose. For example in the study by Gianni et al., any grade peripheral neuropathy was reported in 62.9% (CI 57.5 to 68.1) in the nab-paclitaxel treatment arm versus 53.7% (CI 48.2 to 59.2) in the paclitaxel treatment arm. One exception is in Socinski et al. (2012) where taxanes were administered together with carboplatin which could also contribute to neuropathy. In the study by Jain et al.[6], the paclitaxel treatment arm with higher dose appeared to have highest any grade neuropathy (64%) and grade 3 and 4 neuropathy (21%) as compared to other two treatment arms (58 – 60% for any grade neuropathy, 8-17% for grade 3 and 4 neuropathy).

Fatigue was reported in 5 of the 6 included studies. Based on the descriptive statistics, patients in the nab-paclitaxel treatment arms had a higher or similar incidence of fatigue in most studies when compared with the paclitaxel treatment arms. The one exception is with the study by Socinski et al. (2012) in NSCLC where the paclitaxel treatment arm reported higher incidence of grade 3 fatigue with 6% versus 4% in nab-paclitaxel treatment arm. This was, however, informed by few events.

Other Relevant Evidence

The three non-comparative retrospective cohort studies[12-14] included in the review provide additional information about the use of nab-paclitaxel in gynecological malignancies as well as in patients who have prior HSR from the traditional taxanes. Maurer et al.[13] reported on the incidence of nab-paclitaxel HSRs in patients with prior taxane HSR. Wang et al.[12] evaluated the effectiveness and safety of nab-paclitaxel plus platinum as first line chemotherapy for ovarian cancer in a retrospective study. Finally, Parisi et al.[14] described a single-institution experience of using first-line carboplatin-nab-paclitaxel in advanced ovarian cancer patients after experiencing HSR to solvent-based taxanes. Due to the limitations with small sample size, lack of comparison group with retrospective study design and lack of external validity, no causal conclusions can be made.

Cost Information

The economic review included a comparison of the treatment costs of nab-paclitaxel and those of comparators deemed to be appropriate based on clinical expert consultations and drug plan feedback.

Based on wholesale prices and when considering commonly used 21-day regimens, the drug acquisition cost of nab-paclitaxel (average $6,059 per patient per 28-days) is more expensive than that of paclitaxel (average $3,097 per patient per 28-days) and docetaxel (average $835 to $2,081 per patient per 28-days). When considering commonly used weekly regimens (3 weeks on, 1 week off), the drug acquisition cost of nab-paclitaxel (average $5,243 to $7,865 per patient per 28-days) is generally more expensive than that of paclitaxel (average $5,386 per patient per 28-days) and docetaxel (average $1,002 to $2,185 per patient per 28-days). However, as nab-paclitaxel requires less time to infuse than paclitaxel and docetaxel, associated administration costs for nab-paclitaxel are lower. When considering a patient population who have had an HSR to paclitaxel or docetaxel, these administration cost differences are magnified due to the need to slow infusions of the drug causing the reaction (in the case of a mild to moderate HSRs) or use a full desensitization protocol (in the case of severe HSRs).

For patients requiring a slowed infusion due to a mild to moderate HSR when receiving a 21-day regimen of paclitaxel or docetaxel, when drug acquisition, administration and premedication costs are included, the standardized 28-day total cost of nab-paclitaxel (at the typical rate of infusion) is $136 to $404 less per patient than that of the slowed paclitaxel infusion and $2,874 to $4,535 more per patient than that of slowed docetaxel infusion. For weekly regimens, the standardized 28-day total cost for nab-paclitaxel (at the typical rate of infusion) ranged from a savings of $1,076 per patient to increased costs of $1,542 per patient relative to slowed paclitaxel infusion and $2,135 to $5,940 more per patient than slowed docetaxel infusion.

For patients requiring a full desensitization protocol due to a severe HSR when using a 21-day regimen of paclitaxel or docetaxel, when drug acquisition, administration, and premedication costs are included, the standardized 28-day total cost of nab-paclitaxel (at the typical rate of infusion) is $670 less per patient than the desensitization protocol of paclitaxel and $1,803 to $3,464 more per patient than the desensitization protocol of docetaxel. For weekly regimens, the standardized 28-day total cost for nab-paclitaxel (at the typical rate of infusion) is $868 to $3,490 less per patient than that of the desensitization protocol for paclitaxel and ranged from a savings of $275 to increased costs of $3,530 per patient compared to that of the desensitization protocol for docetaxel. These

incremental costs are based on publicly available wholesale prices and may not reflect actual prices paid by Canadian public drug payers.

Conclusions

Based on the evidence included in this review, there is limited and inconsistent evidence to suggest nab-paclitaxel may be comparable to paclitaxel in the treatment of patients in some solid organ tumours. This is based on efficacy outcomes in overall survival and progression free survival in studies evaluating the comparison in early breast cancer, metastatic breast cancer, NSCLC and gastric cancer. The population reviewed includes any patients with solid organ tumours requiring taxanes as their treatments, as opposed to the requested population which is in patients with previous HSRs.

The proportion of patients experiencing adverse event was not consistently reported in all included studies. However, serious adverse event due to death was rare. The incidence of HSR from the nab-paclitaxel group was 6% or less, whereas the incidence from the paclitaxel group was 2% or less. Both nab-paclitaxel and paclitaxel can cause neutropenia, neuropathy and fatigue. Other factors can contribute to these side effects such as dose intensity and regimen.

Results of the cost-comparison demonstrate that while the drug acquisition cost of nab-paclitaxel is more expensive than that of paclitaxel and docetaxel used in similar regimens, administration costs are lower. When considering patients with a mild to moderate HSR to paclitaxel or docetaxel, the total cost per 28 days of using typically administered nab-paclitaxel was within the range of costs for similar regimens of slowed paclitaxel infusion (range: cost savings of $1,076 to increased costs of $1,542 per patient) and more expensive than similar regimens of slowed docetaxel infusion (range: increased costs of $2,135 to $5,940 per patient). For patients with a severe HSR to paclitaxel or docetaxel, the total cost per 28 days of using typically administered nab-paclitaxel was less expensive than the desensitization protocol for similar regimens of paclitaxel (range: cost savings of $868 to $3,490 per patient) but was generally more expensive than the desensitization protocol for similar regimens of docetaxel (range: cost savings of $275 to increased costs of $3,530 per patient). These incremental costs are based on wholesale prices and may not reflect actual prices paid by Canadian public drug payers. A generic version of nab-paclitaxel has marketing authorization from Health Canada; if it is available to public payers at a reduced price, the cost associated with nab-paclitaxel would be less than estimated and the assessment of comparative costs may change. To consider this alongside the healthcare resource implications associated with any differences in comparative clinical benefits, a cost effectiveness analysis of nab-paclitaxel would be required.

Introduction

Disease Background

Antineoplastic medications such as paclitaxel, docetaxel and cabazitaxel are taxanes commonly used to treat cancers. However, they are also known to cause hypersensitivity reactions (HSRs) in about 10% of patients.[1] It is thought that the HSR is often caused by the cremophor EL or polysorbate 80 which are ingredients added in the formulations to increase solubility. There are two main reasons for HSRs: "Reactions are caused by either a histamine release in response to polyoxyl 35 castor oil (Cremophor® EL), or a non-IgE mediated reaction to the taxane moiety."[15]

The clinical presentation of HSR can vary greatly. For immediate HSRs, cutaneous symptoms such as flushing are most common. Chest pain, back pain or abdominal pain can also be observed as well as respiratory symptoms.[1] Most severe reactions may include oxygen desaturation and / or hypotension.[1] Nonimmediate HSRs may consist of a maculopapular skin eruption with or without flushing immediately up to several hours to 15 days after the drug infusion.[1]

A three-point severity grading system is often used to characterize the severity of taxane-induced HSRs as mild (grade 1), moderate (grade 2) and severe (grade 3). Refer to Table 3 for descriptions.

Table 3: Severity Grading of Immediate Hypersensitivity Reactions

Grade	Severity	Description
1	Mild	Symptoms are limited to the skin (e.g., flushing) or involve a single organ or system and are mild (e.g., mild back pain)
2	Moderate	Symptoms involve at least 2 organs or systems (e.g., flushing and dyspnea) but there is no significant drop in blood pressure or in oxygen saturation.
3	Severe	Symptoms typically involve at least 2 organs or systems and there is a significant drop in blood pressure (systolic ≤ 90 mmHg and / or syncope) and/or oxygen saturation (≤ 92%)

Source: Picard, 2017[1]

Note that other criteria exist and there may not be a universally accepted definition.

There is a National Cancer institute Common Terminology Criteria for Adverse Event (NCI CTCAE) grading system for infusion-related reactions.[16] An infusion related reaction is defined as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances".[16] Grade 1 adverse events are mild transient reactions. Grade 2 events are ones where therapy or infusion interruption is indicated but responds promptly to symptomatic treatment. Grade 3 events involve prolonged recurrence of symptoms. Grade 4 events are deemed life-threatening and Grade 5 events refer to complications involving deaths.[16]

Cancer Care Ontario[17] has defined that hypersensitivity reactions (HSRs) are a subset of infusion reactions that occur at doses normally tolerated by patients and are not consistent with a known toxicity of the drug. HSRs can be divided into subtypes as defined by Gell and Coombs, depending on the mechanism of reaction.[17]

In British Columbia, the BC Cancer defines infusion-related reaction[18] as "an adverse sign or symptom occurring during drug infusion or within the first day of drug administration. Infusion-related reactions include hypersensitivity or allergic reactions such as anaphylaxis (antibody mediated), or anaphylactoid reactions (not antibody mediated) such as cytokine-release syndrome Reactions may include urticaria, dyspnea, bronchospasm, angioedema, hypotension, tachycardia and back or abdominal discomfort or pain. Occasionally cardiorespiratory arrest may occur."[18] The BC Protocol has also adapted the NCI CTCAE[16] grading system for infusion-related reactions.

Diagnosis of an immediate HSR to taxane may require testing for serum tryptase level within 4 hours of severe immediate HSR or skin testing to identify patients in whom an IgE-mediated mechanism is present.[1] However it is also noted that most immediate HSRs

may not be IgE-mediated, thus it remains controversial whether taxane skin testing is helpful or not.[1] Consultation with an allergist or immunologist is often required for guidance on diagnosis and management.

Standards of Therapy

The management of HSR can depend on the clinical severity of the reactions. For mild reactions, the drug can be rechallenged in subsequent administration with additional precautions, such as adding more pre-medications (e.g., antihistamines or corticosteroids) and prolonging the taxane infusion times. For more severe reactions, desensitization protocols may be initiated. Desensitization protocols must be repeated each time the drug is administered, and this can be labour intensive and not accessible or feasible in some treatment facilities. In addition, if the patient is thought to have developed delayed reaction (e.g. Type 4 hypersensitivity with delayed reactions mediated by T-cells) to the taxanes, desensitization protocols may not be the appropriate strategy for prevention.

Drug

Nab-paclitaxel is a nanoparticle, albumin-bound formulation containing paclitaxel. Health Canada has approved nab-paclitaxel for the following two indications: 1) the treatment of metastatic breast cancer, and 2) the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

It is a solvent-free formulation which is associated with less infusion related reactions, although HSR related to the active ingredient, paclitaxel, cannot be ruled out. However, for patients who have developed HSRs to traditional taxanes, nab-paclitaxel can be an added option for consideration. Nab-paclitaxel does not contain hyperallergic ingredients. According to the product monograph[19], no premedication to prevent hypersensitivity reaction is required prior to the administration of nab-paclitaxel.

CADTH completed a reimbursement review of nab-paclitaxel in 2014 for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine[20].

The Provincial Advisory Group (PAG) and clinical experts consulted by CADTH for this review indicated that there is an interest in clinical practice to use nab-paclitaxel for patients with solid tumours who have developed taxane-induced HSRs. As taxanes are indicated in various oncology indications, there is an unmet need to identify and fund alternatives for patients who have developed HSRs from the traditional taxanes. The PAG requested that CADTH review nab-paclitaxel for this patient population and provide a reimbursement recommendation.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. wo patient advocacy groups, Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink), submitted patient input for this review.

CBCN shared perspectives from 3 early-stage breast cancer patients who experienced HSRs to taxanes. One patient shared their experience with taxane side effects but not HSRs, and 2 patients shared their experiences with taxane side effects but whether these patients experienced HSRs remained unclear. CBCN also shared findings from past patient survey reports. Respondents undergoing taxane chemotherapies reported a range of debilitating side effects, including fatigue, increased infection risk post-surgery, nerve damage, suicidal thoughts, stomach acid issues, and PTSD. Additionally, respondents experienced severe blistering on feet hindering mobility, rashes, and temporary or lasting numbness in extremities. Hospitalization was necessary for all respondents due to either immediate hypersensitivity reactions (HSRs) or long-term treatment side effects. The cumulative impact of both HSRs and side effects prompted medication switches or reduction of taxane doses.

These challenges extended beyond the patients themselves, affecting their families, work, and overall quality of life (QoL). Respondents with childcare responsibilities were unable to participate fully during treatment, while others faced employment struggles due to lasting anxiety and cognitive decline. Emotional trauma lingered among caregivers, amplifying the toll of treatment. Although some patients found a sense of purpose through breast cancer advocacy, others struggled with altered abilities post-treatment, highlighting the complexity of post-treatment QoL. One respondent, previously ?refused nab-paclitaxel due to cost concerns, now advocates against such barriers, emphasizing the importance of prioritizing patient well-being over financial considerations in treatment decisions.

Rethink's submission was based on an in-depth virtual interview with one patient living with metastatic triple-negative breast cancer (mTNBC) who had had experience with treatment with nab-paclitaxel due to HSR from a taxane. The patient interviewed by Rethink recounts experiencing HSRs with paclitaxel, describing a severe immediate reaction marked by nausea and flushing, which compounded the trauma of living with metastatic triple-negative breast cancer (mTNBC). Despite immediate treatment of HSRs, the overall experience left the patient feeling profoundly anxious about subsequent treatments. Subsequent paclitaxel treatments required desensitization beforehand. However, upon qualifying to switch to nab-paclitaxel, the patient reported manageable and tolerable side effects, contrasting starkly with the HSR experienced with paclitaxel.

Undergoing a total of 18 treatments (4 with paclitaxel and 14 with nab-paclitaxel), the patient disclosed significant tumor shrinkage, complete disappearance of two tumors, and no new growth. They attributed this favorable outcome solely to the switch to nab-paclitaxel, emphasizing that completing all treatments would have been unfeasible if they had to endure the anxiety and stress of desensitization before paclitaxel administration. The patient emphasized that nab-paclitaxel should be an accessible option for all patients in Canada who have experienced a hypersensitivity to taxanes.

Clinician Input

Input from clinical experts consulted by CADTH

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by two clinical specialists with expertise in treatment and management of patients with HSRs to taxanes.

Unmet Needs

The clinical experts highlighted the broad application of taxanes in the treatment of various malignancies, both in curative and metastatic contexts. Paclitaxel and docetaxel, the two commonly used generic taxanes, necessitate the use of Cremophor EL and polysorbate80 respectively, as carrier agents, respectively, for solubility, which may prompt immediate HSRs in patients. Nab-paclitaxel, an albumin-bound formulation of paclitaxel, largely mitigates this hypersensitivity risk. Notwithstanding, taxanes are associated with hypersensitivity reactions, which can pose life-threatening risks. The experts noted that in many cases, treatment can be continued with intensified premedication and/or slower infusion rates, which can be resource-intensive and time-consuming. Despite the administration of premedication to mitigate hypersensitivity risks, the incidence of hypersensitivity reactions in patients ranges from 5-10% for paclitaxel and approximately 2-4% for docetaxel. Nab-paclitaxel presents an appealing alternative for patients who would otherwise necessitate desensitization for each dose, or for those who experience reactions despite desensitization, or when re-challenge is not advisable.

The experts emphasized that the treatment goals for these patients would be improved safety profile and reliability of chemotherapy delivery, as well as disease control, prolonged survival (progression-free survival and overall survival), symptom management, and maintenance or improvement of quality of life.

Place in therapy

The clinical experts suggested that nab-paclitaxel would replace traditional taxane agents following HSRs in various cancer settings. Nab-paclitaxel should be reserved for patients who have developed significant HSRs to taxanes if 1) first reaction was considered clinically severe or 2) after failure of reasonable preventative measures such as intensive premedication and/or slower infusion rates. The clinical experts cited a lack of trials comparing nab-paclitaxel and traditional taxanes and suggested that, as a member of the taxane class, nab-paclitaxel is generally accepted to be equivalent in efficacy to other taxanes across indications.

Patient population

The experts indicated that individuals most likely to benefit from nab-paclitaxel treatment are those with an indication for taxane therapy who have experienced severe HSRs or anaphylaxis to taxanes that cannot be effectively managed despite premedication use. These patients may present across cancer types and clinical scenarios. The experts underscored that the identification of patients suitable for nab-paclitaxel treatment mainly relies on clinician judgment, as routine adoption of severity scales or validation of specific diagnostic tests has not been established.

Assessing response to treatment

The clinical experts indicated that response to treatment would depend largely on the clinical setting. One expert with expertise in breast cancer suggested that in measurable disease settings (e.g., metastatic or locally advanced), response is primarily determined by stable or improving disease status, both on imaging and clinical examination, as well as improvement or stabilization of symptoms. Preoperatively or neoadjuvantly, response can be assessed based on pathologic findings. In the adjuvant setting, response evaluation primarily focuses on preventing disease recurrence. The experts emphasized that evaluating response to nab-paclitaxel treatment follows the same principles as for the taxane being substituted noted to depend largely on the clinical setting.

Discontinuing treatment

The clinical experts suggested aligning discontinuation criteria for nab-paclitaxel with that of the substituted taxane. They further highlighted that nab-paclitaxel treatment discontinuation may occur upon completion of the treatment plan (e.g., in the adjuvant setting), disease recurrence or progression, or due to intolerable side effects.

Prescribing conditions

It was noted that treatment with nab-paclitaxel would take place in settings where intravenous chemotherapy is administered. Nab-paclitaxel would be initiated by a medical oncologist and can also be administered under the supervision of oncology physician extenders, where available. Given the history of HSRs to taxanes, the experts strongly advocated for administering the first dose of nab-paclitaxel in settings with readily available emergency response teams.

Additional considerations

The clinical experts have highlighted the absence of a universally standardized definition for HSRs to taxanes with clinical judgment pivotal in determining suitable candidates for nab-paclitaxel therapy. It was proposed to consider adopting definitions used by reputable organizations such as the British Columbia Cancer Agency and Cancer Care Ontario, or standardized grading systems such as the National Cancer Institute's CTCAE grading system and 3-grade scale based on the number of organ systems involved and the presence of cardiorespiratory instability.

Local desensitization protocols for patients experiencing HSRs) to taxanes are commonly formulated based on existing literature. When patients encounter HSRs to taxanes, the decision to switch to nab-paclitaxel or undergo desensitization hinges on multiple considerations. Given the time-intensive nature of desensitization, which necessitates repetition with each taxane administration, patient preferences and logistical factors are carefully weighed. There is no definitive criterion for choosing between nab-paclitaxel and desensitization, often necessitating consultation with allergy/immunology specialists.

The experts also advised exercising caution during nab-paclitaxel administration due to reported rare instances of patients exhibiting reactions not only to taxanes but also to nab-paclitaxel, indicating a hypersensitivity to the taxane itself rather than its carrier. While HSRs to nab-paclitaxel are infrequent, they have been documented. Otherwise, patients are routinely monitored for common taxane

side effects during nab-paclitaxel administration, which include fatigue, aches/pains, alopecia, nail changes, nausea/vomiting, diarrhea, peripheral neuropathy, fluid retention, pneumonitis, thrombocytopenia, neutropenia, and febrile neutropenic events.
The presence of trained medical staff and a HSR protocol, along with access to requisite medical equipment, medications, and emergency response teams would be necessary for effective management of taxane-related HSRs.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups. Clinician input was submitted by the following three advisory committees from Ontario Health:

- Ontario Health Cancer Care Ontario Breast Cancer Drug Advisory Committee
- Ontario Health (CCO) Lung Cancer Drug Advisory Committee
- Ontario Health (CCO) Gynecology Cancer Drug Advisory Committee

Ontario Health Cancer Care Ontario Breast Cancer Drug Advisory Committee

According to the breast cancer clinician group, paclitaxel is one of the most active drugs in the treatment of breast cancer. The standard practice involves administering premedication (e.g. corticosteroids, antihistamines, H2-receptor antagonists, montelukast) alongside paclitaxel. If a patient experiences HSR despite premedication, there exists a specific protocol for managing HSR despite premedication.

The breast cancer clinician group noted that for patients who still experience HSR despite these measures, especially in advanced disease settings, nab-paclitaxel is used. However, in early-stage breast cancer, due to limited access to nab-paclitaxel, taxanes are generally excluded from the treatment regimen. It is important to note that switching to docetaxel in cases of serious reactions to paclitaxel is not a standard of practice, as docetaxel and paclitaxel are not interchangeable in terms of efficacy. This limitation significantly reduces treatment options for patients experiencing HSR to paclitaxel.

The breast cancer clinician group also noted that there is evidence supporting the use of nab-paclitaxel as an upfront treatment in early-stage breast cancer. The breast cancer clinician group suggested that nab-paclitaxel is suitable for patients with any stage of breast cancer and who have a serious HSR to paclitaxel despite optimal treatment and prevention strategies. The clinician group noted that around 1-3% of patients will have a serious HSR to paclitaxel despite the use of premedication.

The breast cancer clinician group is proposing that nab-paclitaxel can be substituted for paclitaxel in patients who have exhibited HSR to paclitaxel. This includes applying the same criteria for treatment discontinuation as for the patients' original therapy, while also considering factors such as disease stage and treatment objectives. The group also noted that switching to nab-paclitaxel would require less premedication and monitoring for HSRs.

The breast cancer clinician group also forwarded two publications for consideration in this review:

- Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): A randomised, phase 3 trial. *The Lancet Oncology.* 2016;17(3):345-356. [4]
- Gianni L, Mansutti M, Anton A, et al. Comparing Neoadjuvant Nab-paclitaxel vs Paclitaxel Both Followed by Anthracycline Regimens in Women With ERBB2/HER2-Negative Breast Cancer-The Evaluating Treatment With Neoadjuvant Abraxane (ETNA) Trial: A Randomized Phase 3 Clinical Trial. *JAMA Oncol.* 2018;4(3):302-308. [5]

Ontario Health (CCO) Lung Cancer Drug Advisory Committee

In lung cancer, paclitaxel is used in the following settings:
(a) weekly carboplatin and paclitaxel concurrent with radiation in stage III NSCLC,
(b) carboplatin and paclitaxel plus nivolumab in neoadjuvant therapy - primarily in patients with squamous cancer, and
(c) carboplatin and paclitaxel plus pembrolizumab in stage IV squamous NSCLC.

The lung cancer clinician group highlighted that, unlike other tumour settings (e.g., ovarian cancer) where treatment with taxanes has no comparable alternatives, the lung cancer treatment landscape allows different options if taxanes are contraindicated or not tolerated.

In the neoadjuvant or adjuvant setting, the clinician may choose to treat with cisplatin-gemcitabine or carboplatin-gemcitabine (with or without immunotherapy), or cisplatin-vinorelbine or other platinum-based regimens if the patient has developed HSR to paclitaxel.

In the metastatic first line setting, cisplatin-gemcitabine-pembrolizumab or cisplatin-vinorelbine-pembrolizumab are options, although prior approval is required for funding. In the concurrent setting, patients can receive carboplatin-etoposide, vinorelbine, vinblastine, and other options. In the second line setting (post-platinum doublet with immunotherapy if appropriate), taxanes may be used as monotherapy. So, in rare instances of a HSR, nab-paclitaxel would be preferred.

The clinician group has noted that infusion reactions occur in 10-15% of patients receiving paclitaxel. Most cases are mild to moderate and can be managed with premedication or treatment. Severe reactions precluding the repeat dosing with paclitaxel are uncommon, estimated to be approximately 1% or 2%. While there are alternatives such as with regimens containing gemcitabine, some physicians have concerns about gemcitabine and immunotherapy due to increased risk of lymphopenia. They emphasized the importance of having an alternative to paclitaxel that offers similar efficacy but without the risk of infusion reactions.

The lung cancer clinician group noted that nab-paclitaxel would have limited use in lung cancer. The use of nab-paclitaxel would be directed towards patients with a grade 3/4 reaction, or in those who experience recurrent infusion reactions despite appropriate premedication.

Finally, the lung cancer clinician group shared a publication for consideration in this review:

Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol.* 2012;30(17):2055-2062.

Ontario Health (CCO) Gynecology Cancer Drug Advisory Committee

This gynecology cancer clinician group made note that the current options for preventing HSR to taxanes include premedication with corticosteroids, diphenhydramine, famotidine, and administering the taxane at a slower infusion rate. Despite these measures, there are still patients who cannot receive paclitaxel, such as patients who experience HSR even after premedication or a slower infusion rate, those who have life-threatening reactions, and those who are intolerant to steroids (e.g. patients with poorly controlled diabetes). The gynecology cancer clinician group expressed that nab-paclitaxel would be considered in these situations.

The gynecology cancer clinician group also forwarded two publications for consideration in this review:

Maurer K, Michener C, Mahdi H, Rose PG. Universal tolerance of nab-paclitaxel for gynecologic malignancies in patients with prior taxane hypersensitivity reactions. *Journal of Gynecologic Oncology.* 2017;28(4):e38.
Parisi A, Palluzzi E, Cortellini A, et al. First-line carboplatin/nab-paclitaxel in advanced ovarian cancer patients, after hypersensitivity reaction to solvent-based taxanes: a single-institution experience. *Clin Transl Oncol.* 2020;22(1):158-162.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's non-sponsored reimbursement review processes by identifying issues that may impact their ability to implement a recommendation.

The drug plans highlighted that a clear definition of patient population suitable for nab-paclitaxel should be established. They also suggest that this review should be approached from a tumour or disease agnostic perspective.

The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in the Responses to Questions from Drug Programs to be posted in Nab-paclitaxel | CADTH.

Industry Input

No input was provided to CADTH from the industry.

Clinical Evidence

The clinical evidence included in the review of nab-paclitaxel is presented in three sections. The first section, the Systematic Review, includes studies that were selected according to an a priori protocol.

The second section would include indirect evidence selected from the literature that met the selection criteria specified in the review. However, no indirect comparisons were identified.

The third section includes additional relevant studies to address important evidence gaps in the systematic review such as the clinical evidence of nab-paclitaxel use in patients with gynecological malignancies.

Systematic Review

Objectives

The original objective was to perform a systematic review of the efficacy and safety of nab-paclitaxel for patients with HSRs to taxanes. However, the original literature search screening indicated that no evidence from phase III or IV RCTs was available among patients with previous HSRs to a taxane. In order to inform committee deliberations, the analysis was supplemented with additional studies for patients without previous HSRs..

Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 4. The population of primary interest was patients with solid tumours (cancers) who had a previous HSR to a taxane. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 4: Inclusion criteria for the systematic review

Patient Population	Cancer patients with solid tumours with previous HSR to taxanes [a]
Intervention	Nab-paclitaxel (any doses)
Comparators	Traditional taxanes (docetaxel, paclitaxel) (any doses)
Outcomes	***Efficacy outcomes:*** Overall survival (OS) Progression free survival (PFS) Other Relevant Surrogate Outcomes HRQoL ***Harms outcomes:*** AEs, SAEs, WDAEs, Mortality Hypersensitivity Reaction Neutropenia Neuropathy Fatigue
Study Design	Phase III and IV RCTs

AE=adverse events; HRQoL=quality of life; HSR = hypersensitivity reaction; RCT=randomized controlled trial; SAE=serious adverse events; WDAE=withdrawal due to adverse events

[a] Though the original objective was constrained to patients who had experienced a HSR to traditional taxanes, however initial literature search screening indicated that no evidence from phase II and IV RCTs were available in this population. To provide information on the efficacy and safety of nab-paclitaxel to inform committee deliberations, the analysis was supplemented to include information from a wider population. The expanded population includes patients who were eligible for treatment with taxanes, without a previous HSR.

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[21] The search strategy was aligned with the original intention of the systematic review, which was to review the available evidence among patients with previous HSRs. Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were nabpaclitaxel and taxane hypersensitivity. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on December 19, 2023. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee (FMEC) on May 10, 2024.
Two clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Following the amendment to include a wider population, it was not feasible to screen results from a new systematic review search that would include the broadened population. A focused literature search for indirect treatment comparisons (ITCs) dealing with nab-paclitaxel was run in MEDLINE on December 19, 2023. No limits were applied. Additional studies were identified through the screening of these ITC results.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from our Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

Protocol Selected Studies

Characteristics of Included Studies

A total of 201 records were identified in the literature search. Among these, 195 reports were excluded by title and abstract. 45 relevant reports were retrieved for screening with full text. 3 studies have been selected for inclusion in this review. In addition, 3 studies were identified from the ITC search results. Among these 6 studies, 3 studies were also identified by clinician group inputs. Refer to Figure 3: Flow Diagram for Inclusion and Exclusion of Studies in Appendix 1: Literature Search Strategy. These studies evaluated the use of nab-paclitaxel as compared to traditional taxanes in early breast cancer (2 studies[4,5]), metastatic breast cancer (2 studies[6,7]), non-small cell lung cancer (1 study[8]) and gastric cancer (1 study[9]).

Details of included studies in breast cancer are summarized in Table 5, whereas details of included studies in lung and gastric cancers are summarized in Table 6

Study Design

All 6 included studies are multi-centre, open-label, phase III randomized controlled trials assessing the efficacy and safety of nab-paclitaxel as compared to solvent-based paclitaxel in different cancers. GeparSepto GBG69[4] and Gianni et al. 2018[5] evaluated the efficacy and safety of nab-paclitaxel as compared to solvent-based paclitaxel in patients with early breast cancer. GeparSepto GBG69 was conducted primarily in Germany including 1229 randomized patients. The Gianni et al trial was a multi-center study that enrolled and randomized 695 patients from Italy, Spain, Russia, Germain, Australia, Austria and Singapore.

Jain et al. (2016)[6] and Gradishar et al. (2005)[7] compared nab-paclitaxel to solvent-based paclitaxel in patients with metastatic breast cancer. The study conducted by Jain et al. (2016) [6] involved 20 sites in India and randomized 180 patients. Gradishar et al. (2005) was an international, randomised phase III trial conducted through 70 sites located in Russia, Ukraine, United States, Canada, and United Kingdom. 460 patients were randomized into the study.

The study conducted by Socinski et al. (2012)[8] evaluated weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first line therapy in patients with advanced non-small-cell-lung cancer (NSCLC). These included 1052 untreated patients with stage IIIB to IV NSCLC from the following regions: North America, Russia, Ukraine, Japan and Australia.

Finally, Shitara et al. (2017)[9] evaluated nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer in 72 sites in Japan with a total of 741 patients.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for all 6 studies are detailed in Table 5 and Table 6.

In GeparSepto-GBG 69 study,[4] the inclusion criteria included adult (18 years and older) women with previously untreated unilateral or bilateral primary invasive breast cancer. Gianni et al. (2018)[5] included previously untreated, unilateral invasive HER2 (or ERBB2)-negative breast cancer population.

In the metastatic breast cancer setting, Jain et al. (2016) [6] included women between age 18 and 70 years, with measurable histologically or cytologically confirmed metastatic breast cancer.

The study conducted in metastatic breast cancer by Gradishar et al. (2005) [7] included nonpregnant, nonlactating females at least 18 years of age, with histologically or cytologically confirmed, measurable metastatic breast cancer with expected survival of more than 12 weeks.

In the NSCLC study conducted by Socinski et al. (2012)[8], the inclusion criteria included adults with histologically or cytologically confirmed nonresectable stage IIIB (with or without pleural effusion) or stage IV NSCLC as classified by AJCC 6th edition measurable by Response Evaluation Criteria in Solid Tumour (RECIST), and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and a life expectancy of more than 12 weeks.

The ABSOLUTE Trial in gastric cancer by Shitara et al. (2017)[9] included eligible patients who were 20 years or older with histologically or cytologically confirmed gastric adenocarcinoma, measurable or non-measurable disease, who were refractory to fluoropyrimidine-containing first-line chemotherapy and with progressive disease or relapse fewer than 24 weeks after the final dose of adjuvant chemotherapy.

Interventions, Concomitant Medications and Subsequent Therapy

All 6 included studies compared nab-paclitaxel with solvent-based paclitaxel, with some studies evaluating different dosing regimens as well as inclusion of premedication and varying infusion times. Refer to Table 5 and Table 6 for the dosing and regimen of the intervention (nab-paclitaxel) and comparator (solvent-based paclitaxel). In addition, patients in different studies also received other concomitant or subsequent therapies.

For GeparSepto-GBG 69 study in early breast cancer setting [4], patients received epirubicin and cyclophosphamide following taxane treatments. Patients with HER2-positive tumours also received trastuzumab and pertuzumab.

In Gianni et al. (2018)[5], all patients also received anthracycline regimen as per the investigator's choice among doxorubicin and cyclophosphamide, epirubicin and cyclophosphamide and fluorouracil, epirubicin. and cyclophosphamide

In the metastatic breast cancer setting, in the study by Jain et al. (2016)[6] routine premedication to prevent hypersensitivity reactions with paclitaxel was not required. Dose adjustments were allowed for toxicities.

In the metastatic breast cancer setting, Gradishar et al. (2005) [7] assigned patients to either nab-paclitaxel treatment arm or solvent-based paclitaxel treatment arm. Some patients also had exposure to anthracycline. The authors ensured there was within-country balance for anthracycline exposure. Dose reductions were allowed for toxicities.

In the NSCLC study by Socinski et al. (2012)[8], patients were assigned to either nab-paclitaxel treatment arm or solvent-based paclitaxel treatment arm. In this study, treatment of at least six cycles were recommended. However, patients could continue in the absence of progressive disease and unacceptable toxicity.

In the study on gastric cancer by Shitara et al. (2017)[9], patients were randomly assigned to one of the three arms: nab-paclitaxel 260mg/m^2, nab-paclitaxel 100mg/m^2 or solvent-based paclitaxel. Treatment was continued without limitation of maximum treatment cycles until disease progression, occurrence of unacceptable severe toxicity, or at patient's request.

Outcomes

Both studies [4,5] evaluating nab-paclitaxel versus solvent-based paclitaxel in the early breast cancer setting have included relevant surrogate outcome as pathological complete response as the primary efficacy outcomes in their studies. The GeparSepto-GBG 69 study by Untch et al. (2016)[4] reported on safety outcomes including neutropenia, fatigue, allergic reactions, anaphylaxis and peripheral sensory neuropathy. Gianni et al. (2018)[5] reported adverse events of grade 3 or higher, serious adverse event as well as notable safety outcomes including peripheral sensory neuropathy and neutropenia.

In the study by Jain et al. (2016)[6], the authors have evaluated progression-free survival as a secondary outcome. Neutropenia and peripheral neuropathy were reported for any grade adverse events as well as grade3/4 adverse events.

Gradishar et al. (2005) [7] included overall survival as a secondary outcome. Quality of Life assessment data were collected. Safety outcomes including neutropenia, sensory neuropathy and fatigue were all reported in this study.

In NSCLC study by Socinski et al. (2012)[8], progression-free survival and overall survival were reported as secondary efficacy endpoints. Incidence of treatment-related adverse events were reported. Neutropenia was reported as a hematological adverse event and fatigue and sensory neuropathy were reported as nonhematological adverse events.

Shitara et al. (2017) [9] reported overall survival as the primary endpoint and progression-free survival as the secondary endpoint. Safety outcomes including peripheral sensory neuropathy, fatigue and neutropenia were reported. HRQoL data were collected using EQ-5D-utility index scores.

Table 5: Details of the Included Studies in Breast Cancer

Detail	GeparSepto-GBG 69	Gianni et al. 2018	Jain et al. 2016	Gradishar et al. 2005
Study Design	Multicenter, open-label, phase 3 randomised trial	Multicenter, open-label, phase 3 randomised trial	Multicenter, open-label, randomised, phase 2/3 trial	International, Phase III randomized, open-label trial
Locations	Germany	Italy, Spain, Russia, Germany, Australia, Austria, Singapore	20 sites in India	70 sites (from Russia/Ukraine, United States, Canada, United Kingdom)
Patient enrolment dates	July 30, 2012 to December 23, 2013	May 2013 to March 2015	July 2010 to April 2013	November 2001 to November 2002
Randomized (N)	1229 patients were randomized with 1206 patients started treatment (nab-paclitaxel: 606; solvent-based paclitaxel: 600)	695 randomized (nab-paclitaxel: 346; paclitaxel: 349)	180 randomized (nab-paclitaxel: 58; paclitaxel 260mg/m^2: 64; paclitaxel 295mg/m^2: 58)	460 patients were randomized; 454 patients received treatment (nab-paclitaxel: 229; paclitaxel 225)
Inclusion Criteria	• Women with previously untreated unilateral or bilateral primary invasive breast cancer • Have central histology assessment of core biopsies for hormone receptor and HER2 (also known as ERBB2) status and determination of Ki67 and secreted protein acidic and rich in cysteine (SPARC) expression and the presence of tumour-infiltrating lymphocytes • Had to be 18 years or older with Karnofsky performance status index of at least 80% • The tumour had to be larger than 2cm (cT2 to CT4a-d) without additional risk factors, or between 1 cm and 2cm (cT1c) with one of the following additional criteria: ○ Either clinical or pathological nodal involvement or hormone receptor-negative, or HER2-positive, or Ki67 greater than 20%. Tumours of 1cm or smaller were not accepted.	• Patients with previously untreated, unilateral invasive, ERBB2/HER2-negative breast cancer • Have a central histologic assessment of core biopsy specimens for hormone receptor and ERBB2/HER2 status and determination of Ki67 values • Had to be 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. • The tumour had to be classified as cT2 or CT4a-d.	• Women between 18 and 70 years with measurable histologically or cytologically confirmed metastatic breast cancer (MBC) were eligible to participate in the study if they were candidates for single agent paclitaxel therapy in accordance with current standards of care • Eastern Cooperative Oncology Group (ECOG) performance status score 2 or less; • Life expectancy 12 weeks or greater • Prior use of chemotherapy as adjuvant or for metastatic disease • Use of chemotherapy (apart from palliative bisphosphonate therapy), major surgery or radiotherapy greater than 4 weeks before enrollment (6 weeks for mitomycin C or nitrosoureas)	• Nonpregnant, nonlactating females at least 18 years of age with histologically or cytologically confirmed, measurable metastatic breast cancer and an expected • survival of more than 12 weeks were eligible for participation. • Patients were included if they were candidates for single-agent paclitaxel therapy; had not received paclitaxel or docetaxel for metastatic carcinoma; had not relapsed with metastatic disease within 1 year or adjuvant paclitaxel or docetaxel treatment; had no other malignancy within the previous 5 years except non-melanoma skin cancer, cervical intraepithelial neoplasia, or in situ cervical cancer; and had acceptable clinical laboratory test results at baseline

Detail	GeparSepto-GBG 69	Gianni et al. 2018	Jain et al. 2016	Gradishar et al. 2005
Exclusion Criteria	• Left ventricular ejection fraction less than 55% • Metastases • Known or suspected cardiac disease • Previous thromboembolic event • Pre-existing peripheral sensory neuropathy or event of grade 2 or higher • Clinically significant gastrointestinal disease • Concurrent treatment with other anticancer or investigational agents	• Metastatic disease (stage IV) • Bilateral breast cancer • Other malignant neoplasms • Inadequate bone marrow, renal function, impaired liver or cardiac function and refusal to use contraception.	• Relapse within 48 weeks after completion of adjuvant taxane therapy • Any other malignancy in the previous 5 years except for non-melanoma skin cancer, cervical intraepithelial neoplasia, or in situ cervical cancer • Only evidence of metastasis as lytic or blastic bone lesions or pleural effusion or ascites • Known hypersensitivity to study drugs or their excipients • Treatment with any investigational agent within 30 days of study entry • Clinically evident active central nervous system metastases, including leptomeningeal involvement, requiring corticosteroid or radiation therapy • Pre-existing peripheral neuropathy grade 1 or greater • Any severe concurrent disease that would make the patient inappropriate for study entry in the judgement of the investigator • Prior taxane use for metastatic breast cancer • The presence of pleural or ascitic fluid (if present, fluid was tapped before dosing)	• Had clinical evidence of active brain metastasis or a clinically serious concurrent illness, • An Eastern Cooperative Oncology Group (ECOG) performance status of more than 2 • Received hormone therapy for 2 weeks or chemotherapy, immunotherapy, or another investigational drug for 4 weeks before administration of the first study dose • Pre-existing peripheral neuropathy of grade 1 according to National Cancer Institute Common Toxicity Criteria; or • A history of allergic or hypersensitivity reactions to the study drug or any of its excipients
Intervention	Nab-paclitaxel given intravenously on days 1, 8, and 15 for four 3-week cycles initially at 150mg/m^2. The dose was later reduced to 125mg/m^2 based on recommendation of the independent data monitoring committee after recruitment of 464 patients.	Nab-paclitaxel 125mg/m^2 intravenously over 30 minutes on weeks 1, 2 and 3, followed by a 1-week rest, for 4 cycles.	Nab-paclitaxel 260mg/m^2 intravenously every 3 weeks	Nab-paclitaxel 260mg/m^2 intravenously over 30 minutes every 3 weeks

Detail	GeparSepto-GBG 69	Gianni et al. 2018	Jain et al. 2016	Gradishar et al. 2005
Comparator(s)	Solvent-based paclitaxel 80mg/m^2 intravenously on days 1, 8, and 15 for four 3-week cycles.	Paclitaxel 90mg/m^2 intravenously over 1-hr on weeks 1, 2 and 3, followed by a 1-week rest, for 4 cycles.	Paclitaxel 260mg/m^2 intravenously every 3 weeks or Paclitaxel 295mg/m^2 intravenously every 3 weeks	Paclitaxel 175mg/m^2 intravenously over 3 hours with premedication and special infusion sets every 3 weeks
Follow-up for Primary end point	12 weeks	12 weeks	Not clearly described in the publication; after a minimum of 2 cycles of therapy	Not clearly described in the publication
Primary end point	Pathological complete response – defined as no invasive or non-invasive tumour residuals in breast and axillar lymph nodes (ypT0 ypN0) after neoadjuvant therapy.	Pathological complete response – defined as the absence of invasive cells in the breast and axilliary notes (ie., ypT0/ ypN0) at the time of surgery.	Overall response rate (ORR) – defined as the percentage of patients who achieved complete or partial response for target or nontarget lesions according to RECIST version 1.1, was determined every 2 cycles after a minimum of 2 cycles of therapy in the intention-to-treat (ITT) population assessed by imaging (computed tomography or magnetic resonance imaging).	Overall response rate (ORR). Responses were assessed according to Response Evaluation Criteria in Solid Tumour guidelines. Complete and partial responses required subsequent confirmation of response at least 4 weeks later. The primary efficacy analysis consisted of three nested tests, conducted sequentially and contingent on the prior test(s) being successful.
Secondary end points	Response assessment by other definitions for pathological complete response: • no invasive tumour residuals in breast and axillary lympho nodes) [ypT0/is ypN0], • no invasive tumour residuals in breast [ypt0/is ypN0/+0], and • no invasive tumour residuals in axillary lymph nodes [ypN0] and • by clinical and imaging assessment after neoadjuvant therapy • the proportion of patients requiring breast-conserving surgery and axillary surgery	Compare pCR rates in luminal B-like and triple-negative tumours separately, the rates of clinical overall response after taxane treatment and before surgery, and the tolerability of both neoadjuvant regimens.	Progression Free survival; definition not reported.	Overall survival, time to progression (TTP); definition not reported.

Detail	GeparSepto-GBG 69	Gianni et al. 2018	Jain et al. 2016	Gradishar et al. 2005
Additional endpoints	Invasive disease-free survival, distant-disease-free survival, and overall survival All time-to-event end points were defined as time in months from the date of random assignment. Events for invasive disease-free survival were any invasive locoregional recurrence of diseae, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignancy, or death as a result of any cause.	Clinical response was defined by modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Adverse events were categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Other endpoints were event-free survival and overall survival. Event-free survival was defined as the time from randomization to the first date of disease progression while on primary therapy or disease recurrence after surgery or death due to any cause.	Safety (adverse events): Adverse events were classified with respect to relationship to treatment (unrelated, unlikely, possibly, probably) and intensity, and were derived from changes in vital signs and laboratory parameters, as well as by indirect unbiased questioning, spontaneous patient reports, and observation.	Adverse events related to discontinuations, dose reductions and dose delays.
Publications included	Lancet Oncol 2016;17(3) :345-56 J Clin Oncol. 2019;37(25) :2226-2234	JAMA Oncol. 2018; 4(3):302-308 J Clin Oncol. 2019;37(15 suppl.515)	Breast Cancer Research and Treatment 2016;156 (1):125-134	J Clin Oncol 2005; 23(31) :7794-8703
Sources of support	Celgene, Roche	Celgene	Sun Pharma Advanced Research Co. Ltd.	American Bioscience Inc.

Source: Untch et al. (2016)[4], Gianni et al. (2018)[5], Jain et al. (2016)[6], Gradishar et al. (2005)[7]

Table 6: Details of the Included Studies in Lung and Gastric Cancer

Detail	Socinski et al. 2012	ABSOLUTE Trial
Study Design	Multicenter, randomised, open-label, phase 3 study	Multicenter, randomised, open-label, non-inferiority, phase 3 study
Locations	Russia/Ukraine, United States and Canada	72 institutes in Japan
Patient enrolment dates	November 2007 to August 2009	March 13, 2013 to May 14, 2015
Randomized (N)	1052 patients randomized, 1038 patients received treatment (nab-paclitaxel: 514; paclitaxel: 524)	741 patients enrolled and randomized (nab-paclitaxel every 3 weeks: 247; nab-paclitaxel weekly: 246; paclitaxel weekly: 248)
Inclusion Criteria	• Histological/cytologically confirmed nonresectable stage IIIB (with or without pleural effusion) or stage IV NSCLC	• Patients 20 years or older with histologically or cytologically confirmed gastric adenocarcinoma, measurable, or non-measurable disease

Detail	Socinski et al. 2012	ABSOLUTE Trial
	measurable by Response Evaluation Criteria in Solid Tumour (RECIST) • An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 • "*A life static disease*" • Had no radiotherapy within 4 weeks of enrollment *Prior adjuvant chemotherapy was permitted if completed 12 months before study enrollment	• Refractory to a fluropyrimidine-containing first-line chemotherapy regimen, with progressive disease or relapse fewer than 24 weeks after the final dose of adjuvant chemotherapy • Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 • Had adequate bone marrow (neutrophil count ≥ 1,500 cells per uL, platelet count ≥ 100,000 platelets per uL) • Had adequate hepatic and renal function
Exclusion Criteria	Had untreated or symptomatic brain metastasis or if they had greater than grade 1 neuropathy (per National Cancer Institute Common Terminology Criteria for Adverse Events[NCI-CTCAE] v3.0) History of allergy or hypersensitivity to the study drugs	• History of serious hypersensitivity or paclitaxel-based chemotherapy, • Pleural effusion or ascites that required drainage within 2 weeks before registration • Peripheral sensory neuropathy of grade 2 or worse • Severe comorbidities
Intervention	Nab-paclitaxel 100mg/m^2 30-minute intravenous infusion on days 1, 8, and 15 followed by carboplatin AUC 6mg/ml/min on day 1 every 3 weeks	Nab-paclitaxel 260mg/m^2 IV over 30 minutes on day 1 of a 21-day cycle. Dose reductions (220mg/m^2, 180mg/m^2, 150mg/m^2) were permitted in patients with severe hematological or non-hematological toxicity. Nab-paclitaxel 100mg/m^2 IV over 30 minutes on day 1, 8, 15 of each 28-day cycle
Comparator(s)	Paclitaxel 200mg/m^2 3-hour intravenous infusion on day 1, 8 and 15 plus carboplatin at AUC 6mg/ml/min on day 1 every 3 weeks	Pre-medicate with steroid and histamine H2 receptor blockers Paclitaxel 80mg/m^2 IV over 60 minutes on days 1, 8, 15 of a 28-day cycle. Dose reduction (80mg/m^2, 60mg/m^2) were permitted for patients with severe toxicity.
Follow-up	The planned final analyses of PFS and OS was when at least 70% of patients had an event. Survival was followed for 18 months post-treatment	A minimum follow-up period of 12 months
Primary end point	Overall Response Rate (ORR), as confirmed complete response (CR) and / or partial response (PR) rate, based on blinded, centralized, independent radiologic analysis, which was agreed on with the US food and Drug Administration (FDA).	Overall survival, estimated from the date of trial entry to the date of death from any cause or censored at the date of last follow-up.
Secondary end points	Progression-free survival (PFS) and OS. Survival was followed for 18 months post-treatment.	Progression-free survival = time from randomisation to progression or death from any cause Time to treatment failure = time from randomisation to progression, discontinuation of study drug, or death from any cause Overall response = complete or partial response by RECIST Disease control = complete response, partial response or stable disease by RECIST Duration of response = the period of time from the time at which the criteria for complete response or partial response are first satisfied (whichever is recorded first) until the time at which recurrence or disease progression is objectively confirmed

Detail	Socinski et al. 2012	ABSOLUTE Trial
		Dose intensity Safety Quality of Life
Additional endpoints	Other efficacy end points were investigator-determined ORR and stable disease at > 16 weeks. Safety endpoints (incidence of treatment-related adverse events – TRAEs)	-
Publications included	J Clin Oncol 2012; 30(17):2055-2062	The Lancet Gastroenterology and Hepatology 2017;2(4):277-87
Sources of support	Celgene	Taiho Pharmaceutical

Sources: Socinski et al. (2012)[8], Shitara et al (2017).[9]

Statistical analysis

GeparSepto-GBG 69[4]

Planned sample size

The sample size calculation was based on the following assumption, where the overall pathological complete response for weekly solvent-based paclitaxel plus epirubicin and cyclophosphamide to occur in about 33% of patients, for nab-paclitaxel plus epirubicin and cyclophosphamide group was expected to occur in about 41%. This corresponds to an odds ratio (OR) of 1.41. With 596 patients enrolled in each group, a X^2 test calculated would have 80% power for the two-sided significance level (α) of 0.05 to show superiority of nab-paclitaxel.

Non-inferiority margin

A closed test procedure was used to test for non-inferiority in the primary end point (pathological complete response), with the nab-paclitaxel group calculated as non-inferior to the solvent-based paclitaxel if the lower 95% CI for the OR was above 0.858 (OR equivalent to pathological complete response (33%) minus a 10% non-inferiority margin (3.3%); 29.7%).

The authors planned to test for superiority only in case of a positive non-inferiority test, using an α of 0.05.The study was designed as a superiority trial but would present results for the non-inferiority test if the superiority test fails.

Analysis

The between-group difference in pathological complete response was summarized using the OR and 95% CI and tested using continuity-corrected X^2 tests. A secondary logistic regression adjusting for the minimisation factors (breast cancer subtype, Ki67 at baseline, and SPARC) was conducted for the primary endpoint. Univariate and multivariate logistic regression were performed for pathological complete response to adjust additionally for age, tumour size, nodal status, grade, histological type and tumour-infiltrating lymphocytes.

Gianni et al. (2018)[5]

Planned sample size

The sample size calculation for the primary end point was based on an estimated pCR rate to paclitaxel of 20% (32% in triple negative tumours and 15% in luminal B-like cancers) and targeting 10% absolute improvement in favour of nab-paclitaxel. A minimum of 632 patients (316 per treatment arm) were required to reject the OR set by the null hypothesis, with 80% power and a false-positive rate of 5%.

Analysis

The between-group comparison of pathological complete response was summarized using the OR and 95% CI and tested using a 2-sided Cochran-Mantel Haenszel test, stratified by tumor subgroup and disease stage. The absolute between-group difference was also presented with Wald 95% CIs.

Jain et al. (2016)[6]

Planned sample size

This study was designed to allow for direct comparisons of ORR between the 3 treatment arms. The underlying assumptions for the sample size calculation were based on an ITT population with an ORR of 21.51% for the nab-paclitaxel group and an ORR of 16.5% for the solvent-based paclitaxel group at the end of 6 cycles. 45 patients per treatment arm were required to yield at least 80% power at an α level of 0.05 to conclude that the ORR of solvent-based paclitaxel was within 14% of the ORR of nab-paclitaxel (1-sided). With an estimated dropout rate of 25%, the projected sample size required was 180 (60 patients per treatment arm).

Analysis

The Kaplan-Meier method was used to summarize PFS, with the difference between groups compared using the long-rank test. Medians and 95% CIs for each group were also reported.

Gradishar et al. (2005)[7]

Planned sample size.

The statistical power was based on a noninferiority design, intending to demonstrate that nab-paclitaxel was at least 75% as active as solvent-based paclitaxel. There is an assumption of ORR 20% greater than the ORR of solvent-based paclitaxel. The design had 80% power, with a one-sided type I error of 0.025 (two-sided α = 0.050).

Non-inferiority margin

The primary efficacy analysis consisted of three nested tests, conducted sequentially and contingent on the prior test(s) being successful.

These tests were noninferiority with all patients, superiority with all patients and superiority with patients receiving study drug as first-line therapy.

Analysis

Treatment differences in TTP and overall survival were analysed using the Kaplan-Meier method. The statistical test for between-group difference was not reported for TTP. The log-rank test was used to test for differences between groups in overall survival.

QoL measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, was analysed as change from baseline at each cycle. The between-group difference was not reported.

Socinski et al. (2012)[8]

Planned sample size

All patients randomly assigned were evaluated for efficacy (intent-to-treat population). The authors assumed that nab-paclitaxel would have a 40% improvement in response rate verse solvent-based paclitaxel in advanced NSCLC. Hence, 1050 patients provided 80% power to test the superiority of nab-paclitaxel over solvent-based paclitaxel. For the response rate, interim analysis α =0.001 and final analysis α =0.049. The planned final analyses of PFS and OS was when at least 70% of patients had an event, which provided 85% power to detect superiority of a hazard ratio (HR) of 0.80.

Analysis

PFS and OS were analysed using Kaplan-Meier methods. Further, a noninferiority analysis of PFS and OS was conducted on the basis of the European Medical Agency methodologic considerations with a 15% margin (upper bound of the HR 95% CI less than 1.176.

Shitara et al. (2017)[9]

Planned sample size

To test the hypothesis with 80% power and an alpha of 0.05 with a registration period of 18 months and a minimum follow-up period of 12 months, a sample size of 230 patients per group (total 690 patients) would be required. The authors expected median overall survival of 10.0 months for the primary endpoint for both nab-paclitaxel groups and 9.0 months for the solvent-based paclitaxel. The authors assumed 5% of enrolled patients would be excluded from the analysis, and thus planned for an enrollment of at least 730 patients.

Non-inferiority margin

The non-inferiority margin of the hazard ratio was defined as 1.25. This margin was chosen to be 70% of the effect of solvent-based paclitaxel compared with the best supportive care alone. The overall significance level was determined set at 0.05. The primary analysis was conducted using Holm's method for multiple comparisons.

Analysis

Overall survival, progression-free survival and time to treatment failure were analysed in the full analysis set, which included all randomly assigned patients who received at least one dose of the allocated drug and who met the eligibility criteria. Quality of life data were assessed in the full analysis set. The Kaplan-Meier method was used to determine median overall survival and progression-free survival. Fisher's exact test was used to compare the proportion of patients who achieved an overall response. Safety variables were analysed descriptively based on the number of patients with adverse drug reactions.

Critical Appraisal

Outcome-level risk of bias of included randomized controlled trials (RCTs), based on the effect of assignment to the intervention (i.e., intention-to-treat effect), was assessed using the Cochrane Risk of Bias tool, version 2 (RoB 2).19

This assessment tool facilitates the evaluation of potential biases across 5 domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. A judgment of low risk of bias, some concerns regarding the risk of bias, or high risk of bias was assigned for each domain.

The overall risk of bias is that there are at least some concerns for all domains. While all included studies are phase III randomized controlled studies, few studies did not describe methods of concealment. The deviations from intended interventions such as dose modifications are not clearly described in the protocols. Some studies have patients who withdrew from studies or loss of follow up without clear explanation. Some measurements of outcome are subjective in nature (e.g., fatigue) which raises some concerns as well. In addition, there is question if the tool is validated (e.g. for HRQoL). Selection of reported results was overall of low risk of bias. For details, please refer to Table 28 in Appendix 3: Risk of Bias Assessment.

Table 7: Risk of Bias Assessment Per Outcome Within Each RCT Using RoB2

gastri	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Overall Survival						
Gradishar et. al.[7]	Some concerns	Low	Some concerns	Low	Low	Some concerns
Shitara et al. 2017[9]	Some concerns	Low	Low	Some concerns	Some Concerns	Some Concerns
Socinski et al. 2012[8]	Low	Some concerns	Low	Low	Low	Some concerns
Progression Free Survival						
Jain et al. 2016[6]	Some concerns	Low	Some concerns	Low	Low	Some concerns
Shitara et al. 2017[9]	Some concerns	Low	Low	Some concerns	Some Concerns	Some Concerns
Socinski et al. 2012[8]	Low	Some concerns	Low	Low	Low	Some concerns
Other Relevant Surrogate Outcomes (Pathological Complete Response)						
Gianni et al. 2018 [5]	Low	Low	Some concerns	Some concerns	Low	Some concerns
Untch et al. 2016 (GeparSepto GBG 69)[4]	Low	Low	Some concerns	Low	Low	Some concerns
HRQoL						

gastri	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Gradishar et al. 2005[7]	Some concerns	Some concerns	Some concerns	High	Low	High
Shitara et al. 2017[9]	Some concerns	Some concerns	High	High	Low	High
Harms						
Gianni et al. 2018 [5]	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Gradishar et. al.[7]	Some concerns	Low	Low	Some concerns	Low	Some concerns
Jain et al. 2016[6]	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
Shitara et al. 2017[9]	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
Socinski et al. 2012[8]	Low	Some concerns	Low	Some concerns	Low	Some concerns
Untch et al. 2016 (GeparSepto GBG 69)[4]	Low	Low	Low	Some concerns	Low	Some concerns

Note: assessed using the Cochrane Risk of Bias Tool, version 2.*19*
HRQoL = health-related quality of life;

External Validity

Patient Selection

The inclusion and exclusion criteria of all included studies were deemed clinically relevant for the tumour settings, early breast cancer, metastatic breast cancer, NSCLC and gastric cancer. It is important to note that since the publication dates of these studies range from 2005 to 2018, the staging and classification of the disease has evolved or changed from the time of the study as well as the standard of practice.

Treatment Regimen and Length of Follow-Up

The administration of nab-paclitaxel in the various tumour settings appears to be consistent with common practice at the time of these studies, where a traditional taxane (e.g., paclitaxel) is part of a treatment regimen. Length of follow up for early breast cancer setting is appropriate for the neoadjuvant setting. However, longer follow up would be required for overall survival data which have been subsequently published in other publications[10,11]. In metastatic NSCLC and gastric cancer, the follow up period of 18 months and 12 months respectively, would be reasonable for the survival outcome.

Outcome Measures

In early breast cancer setting, the primary efficacy outcome was pathological complete response, which is often used as an early surrogate end point in the neoadjuvant setting according to clinical experts. Additional overall survival data are also available in subsequent publication[11] or abstract[10]. In metastatic breast cancer, NSCLC and gastric cancer, overall survival or progression free

survival were either primary efficacy endpoint or secondary efficacy endpoint. In addition, progression-free survival is a surrogate outcome for overall survival. Other endpoints of importance such as HRQoL were not evaluated in all studies. In addition, nab-paclitaxel may have broader uses in clinical practice setting for various solid organ tumours as an alternative to traditional taxanes. Yet, the findings from this review are limited to breast cancer, NSCLC and gastric cancer. There is also a concern with the population indirectness. Our original question aimed to evaluate patients with HSR, yet the evidence reflects a broader patient population.

Results of the Included Studies

Baseline characteristics

Baseline demographic and disease characteristics were generally balanced between treatment arms. provides a high-level summary of the baseline characteristics. For additional details, please refer to the original publications.

GeparSepto-GBG 69[4] - Early Breast Cancer

The median (range) age was 49 (43 to 57) years in the nab-paclitaxel arm and 48 (41 to 56) years in the paclitaxel arm. The majority of patients presented with clinical T2 tumours, 286 (56%) in the nab-paclitaxel arm and 277 (53%) in the paclitaxel arm. The majority of patients had ductal or ductal-lobular invasive tumour, 517 (85%) in the nab-paclitaxel arm and 519 (87%) in the paclitaxel arm.

Gianni et al. 2018[5] – Early Breast Cancer

The median (range) age was 50 (25 to 79) years. 72% of patients presented with clinical T2 tumours and 50% had positive axillary nodes. The disease stage was locally advanced in 170 (24%) of the patients, triple-negative tumours accounted for 219 (32%), and hormonal receptor (HRs) either ER and / or PgR, were positive in 476 (68%) of the tumours.

Jain et al. (2016)[6] – Metastatic Breast Cancer

The mean (range) age was 50 (32 to 68) years in the paclitaxel 260mg/m^2 arm, 49 (27 to 70) years in the paclitaxel 295mg/m^2 arm and 51 (35 to 69) years in the nab-paclitaxel 260mg/m^2 arm.100% of patients were reported as Asian in all three treatment arms. The majority of patients had ECOG performance status of 0 or 1: 62 (97%) patients in the paclitaxel 260mg/m^2 arm, 57 (98%) in the paclitaxel 295mg/m^2 arm and 56 (97%) in the nab-paclitaxel arm. The majority of patients had received prior chemotherapy (79-98%) and surgery (72-80%). The median number of lesions was 5 (2-9) for the paclitaxel 260mg/m^2 arm, 5 for the paclitaxel 295mg/m^2 (2-12) arm and 4.5 (2-13) for the nab-paclitaxel arm.

Gradishar et al. (2005)[7] – Metastatic Breast Cancer

The mean (range) age was 53.1 (26 to 79) years in the nab-paclitaxel arm and 53.3 (30 to 83) years in the paclitaxel arm. 97% were of white ethnicity in both treatment arms. The majority of patients had a ECOG performance status of 1, 134 (59%) patients in the nab-paclitaxel arm and 138 (61%) in the paclitaxel arm. The majority of patients had prior chemotherapy, 201 (88%) in the nab-paclitaxel arm and 191 (85%) in the paclitaxel arm. The majority of patients had more than 3 lesions, 180 (79%) in the nab-paclitaxel arm and 163 (72%) in the paclitaxel arm.

Socinski et al. (2012)[8] – NSCLC

The median (range) age was 60 (28 to 81) years in the nab-paclitaxel arm and 60 (24 to 84) years in the paclitaxel arm. The distribution of sex is about 75% male (n =789) and 25% female (n=263). Patients were predominantly white by race as reported, 416 (80%) in the nab-paclitaxel arm and 433 (82%) in the paclitaxel arm. The majority of patients had a ECOG performance status of 1, 385 (74%) in the nab-paclitaxel arm and 416 (78%) in the paclitaxel arm. The most common reported histologies were adenocarcinoma (254 [49%] in the nab-paclitaxel arm and 264 [50%] in the paclitaxel arm) and squamous cell carcinoma (229 [44%] in the nab-paclitaxel arm and 221 [42%] in the paclitaxel arm. Most patients had stage IV disease, 413 (79%) in the nab-paclitaxel arm and 421 (79%) in the paclitaxel arm. 448 (43%) of all patients smoked and still smoked at the time of the trial, 316 (30%) patients smoked and quit and 281 (27%) patients never smoked.

Shitara et al. (2017)[9]- Gastric Cancer

The median (range) age was 66 (60 to 72) years in the nab-paclitaxel every three weeks treatment arm, 67 (60 to 72) years in the nab-paclitaxel weekly treatment arm and 65 (59 to 71) years in the paclitaxel weekly treatment arm. The majority of patients had a ECOG performance status of 0, 167 (69%) in the nab-paclitaxel every three weeks treatment arm, 168 (70%) in the nab-paclitaxel weekly treatment arm and 168 (69%) in the weekly paclitaxel treatment arm. The majority of patients had indicated no ascites on imaging, 123 (50%) in the nab-paclitaxel every three weeks treatment arm, 127 (53%) in the nab-paclitaxel weekly treatment arm and 139 (57%) in the paclitaxel weekly treatment arm. The most common previous chemotherapy regimens were fluoropyrimidine monotherapy (69 [28%] in the nab-paclitaxel every three weeks treatment arm, 97 [40%] in the nab-paclitaxel weekly treatment arm and 86 [35%] in the paclitaxel weekly treatment arm) or doublet chemotherapy (157 [65%] in the nab-paclitaxel every three weeks treatment arm, 126 [53%] in the nab-paclitaxel weekly treatment arm and 139 [57%] in the paclitaxel weekly treatment arm).

Patient Disposition- refer to

Table *30* in Appendix 4: Other Relevant Information from Included Studies

Efficacy Results

Only those efficacy outcomes identified as relevant in the review protocol are reported below.

Overall Survival

Metastatic Breast Cancer[7]

Among 2 trials that included patients with metastatic breast cancer, only the trial by Gradishar et al. (2005) (n = 454) provided information on overall survival, as a secondary end point, for treatment with nab-paclitaxel versus paclitaxel with pre-medication. Gradishar et al. (2005)[7] completed the analysis in October 200. The length of follow-up was reported as a median censoring time; this was 103 weeks for the nab-paclitaxel treatment arm and 101 weeks for the standard paclitaxel treatment arm. No measure of variation (e.g., range) was reported.. The number of deaths was not reported. The K-M plot showed only a small separation after about 48 months. The median survival for patients in the nab-paclitaxel treatment arm was 65.0 weeks versus for patients in the paclitaxel treatment arm was 55.7 weeks (p = 0.374). No confidence intervals nor relative or absolute between-group differences at relevant timepoints were provided.

Early Breast Cancer[10,11]

In these two studies (Untch et al.2016[4] and Gianni et al. 2018[5]) that evaluated nab-paclitaxel versus paclitaxel in the neoadjuvant setting (refer to section for **Relevant Surrogate Outcomes**), additional evidence on survival has since been published. Untch et al. published additional findings in 2019[11]. At 4 years, overall patients treated with nab-paclitaxel had an invasive disease free survival of 84.0% versus 76.3% for patients treated with paclitaxel. This represents a HR of 0.66 (95% CI, 0.51 to 0.86, p=0.002). The overall survival was 89.7% for the nab-paclitaxel treatment arm and 87.2% for the paclitaxel treatment arm with HR of 0.82 (95% CI, 0.59 to 1.16; p=0.260).

Likewise, Gianni et al (2019)[10] has also published an abstract, including the event-free survival analysis of a subgroup of patients with HER2 negative high-risk breast cancer randomized to receive neoadjuvant nab-paclitaxel versus paclitaxel. Overall 5-year survival was 84.8% after paclitaxel and 87.3% for nab-paclitaxel (unadjusted p=0.245).

NSCLC[8]

In the NSCLC setting, Socinski et al. (2012) (n = 1,052) also evaluated the overall survival as a secondary end point. The analyses were event-driven and the length of follow-up was not reported. At the time of the data-cutoff for the planned final analysis, 36 (69.1%) of patients in the nab-paclitaxel group and 384 (72.3%) of patients in the paclitaxel group had died. The K-M plot did not show clear separation at any time point. Median OS was 12.1 months (95% CI, 10.8 to 12.9 months) in the nab-paclitaxel treatment arm compared with 11.2 months (95% CI, 10.3 to 12.6 months) in the paclitaxel treatment arm. The HR for overall survival was 0.922 (95% CI, 0.797 to 1.066; superiority p = 0.271); neither group was favoured. Absolute differences in OS probability at relevant timepoints as estimated from the K-M curves were not presented. Based on recommendations of the EMA, the authors noted that nab-paclitaxel was deemed

noninferior to paclitaxel because the upper bound of the 95% CI was below 1.176, however this was not formally tested (no multiplicity adjustment) and appears to be a post-hoc determination. No further information on how the non-inferiority margin was selected was provided in the publication.

Gastric Cancer[9]

In the gastric cancer setting by Shitara et al. (2017) (n = 726), OS was the primary outcome and was tested for both non-inferiority and superiority. The median follow-up was 9.99 (IQR, 6.05 to 15.05) months. At the time of data-cutoff, the total number of deaths was not reported. The K-M plot did not show clear separation at any time point. Median OS was 10.3 months (95% CI 8.7 to 11.4) in the nab-paclitaxel every 3 weeks treatment arm, 11.1 (9.9 to 13.0) months in the nab-paclitaxel weekly treatment arm and 10.9 (9.4 to 11.8) months in the paclitaxel weekly treatment arm. The HR for overall survival was 0.97 (95% CI 0.76 to 1.23; inferiority one-sided p = 0.0085) for nab-paclitaxel weekly treatment arm versus paclitaxel weekly treatment arm, demonstrating non-inferiority. Nab-paclitaxel was not superior to paclitaxel. The superiority p value was not reported. When nab-paclitaxel every 3 weeks treatment arm was compared to paclitaxel weekly treatment arm, the HR was 1.06 (95% CI 0.87 to 1.31; non-inferiority one-sided p = 0.062); the inferiority hypothesis was not rejected.

Progression Free Survival

Early Breast Cancer

Progression-free survival is not a relevant end point in this setting.

Metastatic Breast Cancer[6]

In the study conducted by Jain et al. (2016) (n = 180), PFS was reported as an additional end point. The length of follow-up was not reported. The number of PFS events in each treatment group was also not reported.The K-M plot appeared to separate at about 20 months and remained separated thereafter in the comparison of nab-paclitaxel 260 mg/m^2 to paclitaxel 260 mg/m^2. The K-M curve comparing nab-paclitaxel 260 mg/m^2 to paclitaxel 296 mg/m^2 did not show clear separation at any time point. Median PFS was 34 weeks (95% CI, 25 to not reached weeks), 23 weeks (95% CI, 21 to 21 weeks; as reported in the study, but appears to be an error) and 35 weeks (95% CI, 27 to not reached weeks) in the nab-paclitaxel treatment arm, paclitaxel 260mg/m^2 treatment arm and paclitaxel 295mg/m^2 treatment arm respectively. The HR and CI were not presented in the study. The authors reported that there was no significant difference in PFS between the two doses (260mg/m^2 and 295mg/m^2) of paclitaxel treatment arms (p=0.1085, 0.9340 respectively) compared with the nab-paclitaxel 260mg/m^2 treatment arm. No absolute between-group differences were reported.

NSCLC[8]

The progression free survival was also evaluated by Socinski et al. (2012)[8] (n = 1,052) as a secondary end point. The length of follow-up was not reported. At the time of the data cut-off, there were 297 (57.0%) PFS events in the nab-paclitaxel group and 312 (58.8%) in the paclitaxel group. The K-M plot did not show clear separation at any time point. The median PFS was 6.3 months (95% CI, 5.6 to 7.0 months) in the nab-paclitaxel treatment arm versus 5.8 months in the paclitaxel treatment arm (95% CI, 5.6 to 6.7 months). The HR for PFS was 0.902 (95% CI 0.767 to 1.060; superiority p=0.214). Absolute differences in PFS probability at relevant timepoints were not reported. Based on recommendations of the EMA, the authors noted that nab-paclitaxel was deemed noninferior to paclitaxel because the upper bound of the 95% CI was below 1.176, however this was not formally tested (no multiplicity adjustment) and appears to be a post-hoc determination. No further information on how the non-inferiority margin was selected was provided in the publication.

Gastric Cancer[9]

Shitara et al. (2017) (n = 726) also evaluated the progression-free survival as a secondary end point between the nab-paclitaxel every 3 week treatment arm with nab-paclitaxel weekly treatment arm and paclitaxel weekly treatment arm. The median follow-up was 9.99 (IQR, 6.05 to 15.05) months. At the time of the data cut-off, the number of PFS events was not reported. The K-M curves did not show clear separation at any time point. The median progression-free survival was 3.8 months (95% CI 3.5 to 4.4) in the nab-paclitaxel every 3 weeks treatment arm, 5.3 months (4.0 to 5.6) in the nab-paclitaxel weekly treatment arm, and 3.8 months (3.7 to 3.9) in the paclitaxel weekly treatment arm. The HRs for PFS with nab-paclitaxel every 3 weeks treatment arm and nab-paclitaxel weekly

treatment arm compared with paclitaxel weekly treatment arm were 1.03 (95% CI, 0.85 to 1.24; p=0.778) and 0.88 (95% CI, 0.73 to 1.06; p=0.176), respectively. Absolute differences in PFS probability at relevant timepoints were not reported.

Other Relevant Surrogate Outcomes

Early Breast Cancer[4,5]

When nab-paclitaxel is used in the neoadjuvant setting in the early breast cancer, other relevant surrogate outcomes are reported at earlier time points as survival data is expected to take several years to accrue. In GeparSepto-GBG 69 study (n = 1,206)[4], the authors evaluated pathological complete response as the primary efficacy endpoint and was tested for non-inferiority as well as superiority using a closed testing procedure to maintain an alpha of 0.05 (non-inferiority tests only presented if the superiority test failed). In the nab-paclitaxel treatment arm, 233 out of the 606 treated patients (38.4%, 95% CI 34.6 to 42.3) achieved a pathological complete response versus 174 out of 600 treated patients (29.0%, 95% CI 25.4 to 32.6) in the paclitaxel arm. The absolute between-group difference was not reported but favoured nab-paclitaxel (superiority unadjusted X^2 p=0.00065). This corresponded to an OR of 1.53 (95% CI, 1.20 to 1.95; unadjusted superiority Wald p=0.00054) for nab-paclitaxel vs. paclitaxel. In multivariable logistic regression analysis, nab-paclitaxel remained an independent predictor for achieving pathological complete response after adjustment for baseline and minimisation factors (OR 1.59; 95% CI 1.20 to 2.11; p = 0.0013).

In another study, ETNA by Gianni et al. (2018)[5] (n = 695), the pathological complete response was also evaluated as a primary efficacy endpoint between the nab-paclitaxel treatment arm and the paclitaxel treatment arm in the neoadjuvant setting of breast cancer. In the nab-paclitaxel treatment arm, 78 of the 346 patients (22.5%, 95% CI, 18.2 to 27.3) achieved pathological complete response compared to 65 of the 349 patients (18.6%, 95% CI, 14.7 to 23.1) in the paclitaxel arm. No absolute between-group difference was reported. The OR was 0.77 (95% CI, 0.52 to 1.13), for paclitaxel vs. nab-paclitaxel, and the null hypothesis was not rejected (p = 0.19).

HRQoL

Among all the included studies, two publications reported on outcomes for HRQoL.

Metastatic Breast Cancer[7]

Gradishar et al. (2005) (n = 454) measured HRQOL using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire C30, which was analyzed as change from baseline at each cycle (weeks 6, 9, 15, final evaluation, and at follow-up). The authors reported no differences in the HRQOL between the two treatment groups. However,between-group differences and confidence intervals were not provided and no formal statistical testing was performed. While the mean scores are reported in Figure 1, other important details (e.g. total number of patients who completed the questionnaire at each time point) were not available.

Figure 1 : Quality-of-life measurements for patients receiving nab-paclitaxel or paclitaxel therapy

Alt text: The quality-of-life measurements using European Organization for research and treatment of cancer quality of life questionnaire C30 for patients who have received nab-paclitaxel or paclitaxel in metastatic breast cancer. The mean scores with standard deviations were displayed but not explicitly reported for both treatment groups.

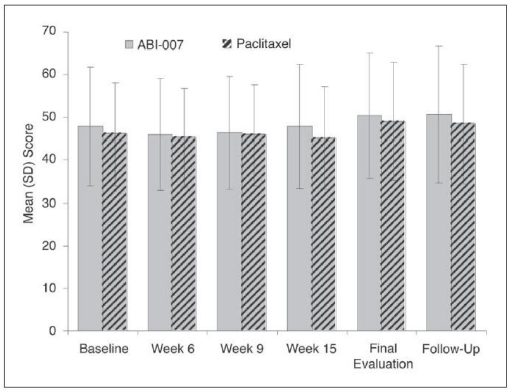

Fig 3. Quality-of-life measurements (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) for patients receiving ABI-007 or standard paclitaxel. SD, standard deviation.

Source: Fig 3., "Quality-of-life measurements [European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) for patients receiving ABI-007 or standard paclitaxel, SD, standard deviation.". Reprinted with permission from: William J. Gradishar, Sergei Tjulandin, Neville Davidson, Heather Shaw, et al., Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil–Based Paclitaxel in Women With Breast Cancer, Journal of Clinical Oncology (An American Society of Clinical Oncology Journal), Vol. 23, Iss. 32, https://ascopubs.org/doi/10.1200/JCO.2005.04.937 [7]

Gastric Cancer[9]

Shitara et al. (2017) evaluated HRQOL using the validated Japanese version of the EQ-5D at baseline and every 8 weeks during the first 24 weeks, and every 24 weeks thereafter. In the nab-paclitaxel every 3 weeks treatment arm, the mean EQ-5D index scores at baseline and at 48 weeks were 0.8548 (SD 0.1526; n = 243) and 0.7044 (SD 0.2214; n = 77) respectively. In the nab-paclitaxel weekly treatment arm, the mean EQ-5D index scores at baseline and at 48 weeks were 0.8686 (SD 0.1471; n = 240) and 0.7733 (SD 0.2140; n = 88) respectively. In the paclitaxel weekly treatment arm, the mean EQ-5D scores at baseline and at 48 weeks were 0.8681 (SD 0.1468; n = 243) and 0.7597 (SD 0.2430; n = 89) respectively. Data for other timepoints were not reported. The between-group differences in change from baseline has not been reported nor formally tested.

Figure 2: Time-course of mean EQ-5D utility index scores in gastric cancer

Alt text : The figure provides the time-course mean EQ-5D utility index score for three treatment arms in gastric cancer. The EQ-5D index scores in the weekly nab-paclitaxel group and the weekly solvent-based paclitaxel group were similar; scores were lower in the group that received nab-paclitaxel every 3 weeks than in the other groups throughout the study period.

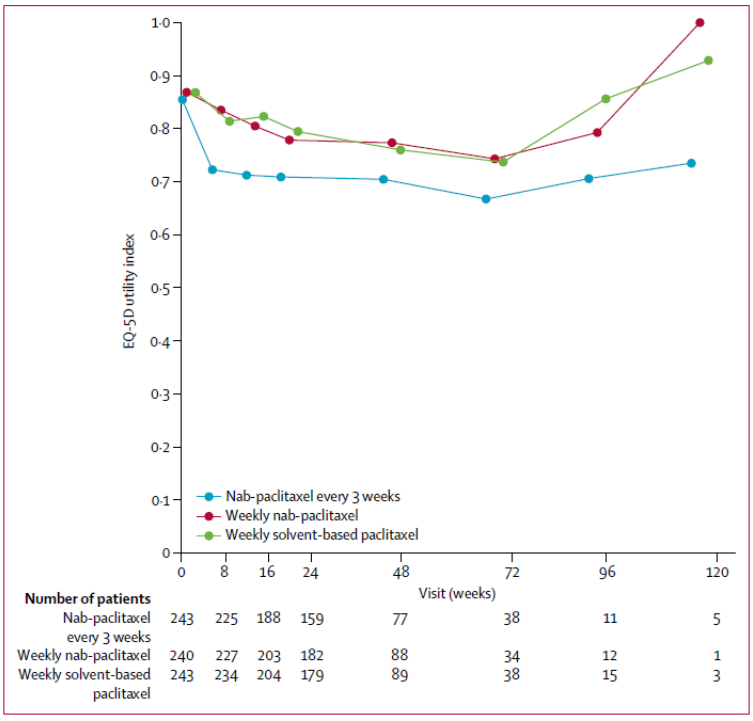

Figure 4: **Time-course of mean EQ-5D utility index scores**
EQ-5D=EuroQol 5 Dimension questionnaire.

Source: Figure 4: "Time-course mean EQ-5D utility index scores". Reprinted from The Lancet Gastroenterology & Hepatology, Vol. 2, Iss. 4, Kohei Shitara,Atsuo Takashima,Kazumasa Fujitani,Keisuke Koeda,Hiroki Hara,Norisuke Nakayama,Shuichi Hironaka,Kazuhiro Nishikawa,Yoichi Makari,Kenji Amagai,Shinya Ueda,Kazuhiro Yoshida,Hideki Shimodaira,Tomohiro Nishina,Masahiro Tsuda et al., Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE): an open label, randomized, non-inferiority, phase 3 trial, Pages 277-287, Copyright (2017), with permission from Elsevier. [9]

Harms Results

Only those harms identified in the review protocol are reported below.

Adverse Events

GeparSepto-GBG 69[4] – Early Breast Cancer

The proportion of patients with any AE was not reported. Instead, a listing of relevant AEs were presented by grade, with the study authors noting that AEs and AEs of grade 3 and higher were more frequent with nab-paclitaxel treatment arm.

Gianni et al. (2018)[5] – Early Breast Cancer

The proportion of patients with any AE was not reported. Instead, the authors reported on AEs that they judged to be related the treatments. During taxane treatment, 94.9% of patients treated with paclitaxel had at least 1 drug-related adverse event compared with 95.5% of those treated with nab-paclitaxel. Drug-related adverse events of grade 3 or higher were 17.3% and 22.3%, respectively.

Jain et al. (2016)[6] – Metastatic Breast Cancer

The proportion of patients with any AE was not reported, however the authors judged that adverse events of any grade were generally reported in similar proportions of patients across the three treatment arms. Similarly, the proportion of patients with grade 3/4 adverse events were not reported but the authors judged that a lower proportion of patients in the paclitaxel 260mg/m^2 treatment arm compared with those in the paclitaxel 295mg/m^2 treatment arm and nab-paclitaxel 260mg/m^2 treatment arms experienced grade 3 or 4 AEs.

Gradishar et al. (2005)[7] – Metastatic Breast Cancer

The proportion of patients with any AE was not reported. The authors reported that the most frequently reported adverse events (all grades) are alopecia, sensory neuropathy, fatigue, neutropenia, arthralgia, myalgia, nausea, infection with unknown ANC and diarrhea. However, no numerical values nor between-group differences were presented. The most common grade 3 or 4 adverse events are neutropenia, elevated GGT, leukopenia, sensory neuropathy, fatigue, arthralgia and myalgia. Similarly, numerical values and between-group differences were not reported.

Socinski et al. (2012)[8] – NSCLC

The proportion of patients with any AE was not reported. The authors reported on common AEs of grade 3 or higher that they judged to be treatment-related. Common nonhematologic grade ≥ 3 TRAEs with nab-paclitaxel and paclitaxel include fatigue (5% and 6%, respectively) and sensory neuropathy (3% and 12%). Common hematologic grade ≥ 3 TRAEs with nab-paclitaxel and paclitaxel include neutropenia (47% and 58%).

Shitara et al. (2017)[9] – Gastric Cancer

243 (100%) of 244 patients in the group that received nab-paclitaxel every 3 weeks, 238 (99%) of the 241 patients in the nab-paclitaxel weekly treatment arm and 243 (100%) of the 243 patients in the paclitaxel weekly treatment arm reported at least 1 adverse drug reaction. The most frequent drug reactions of grade 3 or worse (in ≥ 5% of patients in any group) include neutropenia, sensory neuropathy, febrile neutropenia. Grade 1 peripheral sensory neuropathy was observed in 76 (31%)and grade 2 peripheral sensory neuropathy was observed in 82 (34%).

Serious adverse events

GeparSepto-GBG 69[4] – Early Breast Cancer

Overall, 156 (26%) patients in the nab-paclitaxel treatment arm and 127 (21%) in the paclitaxel treatment arm experienced at least one SAE.

Gianni et al. (2018)[5] – Early Breast Cancer

Serious adverse events classified as taxane-related, based on the judgment of the authors were 2.7% and 2.1% respectively for paclitaxel and nab-paclitaxel.

Jain et al. (2016)[6] – Metastatic Breast Cancer

46, 64 and 28 serious adverse events were reported for all cycles in the paclitaxel 260mg/m^2 arm, paclitaxel 295mg/m^2 arm and nab-paclitaxel 260mg/m^2 arm, respectively. The proportions of patients with at least 1 SAE were not reported.

Gradishar et al. (2005)[7] – Metastatic Breast Cancer

The authors have not provided details related to serious adverse events in the publication except for deaths due to AE which is reported separately under *Death due to AE*.

Socinski et al. (2012)[8] – NSCLC

The authors have not provided details related to serious adverse events in the publication except for deaths due to AE which is reported separately under *Death due to AE*.

Shitara et al. (2017)[9] – Gastric Cancer

The authors have not provided details related to serious adverse events in the publication except for deaths due to AE which is reported separately under *Death due to AE*.

Withdrawals due to adverse events

GeparSepto-GBG 69[4] – Early Breast Cancer

99 (16%) of 605 patients treated with nab-paclitaxel had taxane discontinued due to adverse events. 36 (6%) of 601 patients treated with paclitaxel had taxane discontinued due to adverse event. It is notable that following a pre-planned safety analysis that occurred after 60 patients had completed taxane therapy, the nab-paclitaxel dose used in the study was reduced. The reason for the reduction was that the independent data monitoring committee observed unacceptable increases in treatment discontinuation and peripheral neuropathy in the nab-paclitaxel group.

Gianni et al. (2018)[5] – Early Breast Cancer

12 (3.5%) of 337 patients treated with nab-paclitaxel had discontinued taxanes due to adverse event. 12 (3.4%) of 335 patients treated with paclitaxel had discontinued taxanes due to adverse events.

Jain et al. (2016)[6] – Metastatic Breast Cancer

Unacceptable toxicity resulting in treatment discontinuation occurred in 8 (12%), 11 (20%) and 9 (16%) patients in the paclitaxel 260mg/m^2 arm, paclitaxel 295mg/m^2 arm and nab-paclitaxel 260mg/m^2 arm, respectively.

Gradishar et al. (2005)[7] – Metastatic Breast Cancer

The authors reported that any AE-related discontinuations, dose reduction and dose delays were infrequent (3% to 7%) in both treatment arms. The authors did not report for which groups the proportions apply.

Socinski et al. (2012)[8] – NSCLC

Both treatment arms had 12% (n = 61 for nab-paclitaxel treatment arm, n = 62 for paclitaxel treatment arm) of patients who discontinued due to unacceptable toxicities. Discontinuation due to adverse events were reported as 4% (n = 20) in the nab-paclitaxel treatment arm and 5% (n=24) in the paclitaxel treatment arm.

Shitara et al. (2017)[9] – Gastric Cancer

Adverse drug reactions leading to treatment discontinuation were more common in the group that received nab-paclitaxel every 3 weeks (41 [17%] of 244) than in the weekly nab-paclitaxel (17 [7%] of 241) and paclitaxel weekly treatment arm (12 [5%] of 243). The most common adverse drug reaction leading to treatment discontinuation was peripheral sensory neuropathy (21 [9%] patients in the group who received nab-paclitaxel every 3 weeks, 6 [2%] patients in the weekly nab-paclitaxel weekly treatment arm and three [1%] patients in the paclitaxel weekly treatment arm).

Death due to AE

GeparSepto-GBG 69[4] – Early Breast Cancer

Three deaths occurred in the nab-paclitaxel treatment arm during epirubicin and cyclophosphamide treatment (sepsis, diarrhea, an accident not related to the trial). One death occurred in the paclitaxel treatment arm during trastuzumab and pertruzumab treatment (cardiac failure).

Gianni et al. (2018)[5] – Early Breast Cancer

One patient in the paclitaxel treatment arm was reported to have died from hepatic failure associated with liver metastases. No death was reported in the nab-paclitaxel treatment arm.

Jain et al. (2016)[6] – Metastatic Breast Cancer

5 (8%), 7 (12%), 5 (9%) deaths occurred in the paclitaxel 260mg/m^2 arm, paclitaxel 295mg/m^2 arm and nab-paclitaxel 260mg/m^2 arm, respectively. It was not clear from the publication whether these were deaths due to Aes.

Gradishar et al. (2005)[7] – Metastatic Breast Cancer

No treatment related death occurred in the nab-paclitaxel treatment arm. One patient in the paclitaxel treatment arm died of multiorgan failure, considered to be likely related to treatment, sepsis and or progressive disease.

Socinski et al. (2012)[8] – NSCLC

Two treatment-related deaths occurred, one in each arm of nab-paclitaxel and paclitaxel.

Shitara et al. (2017)[9] – Gastric Cancer

Four treatment-related deaths were reported (one with pneumonia in the nab-paclitaxel every 3 weeks treatment arm, one with febrile neutropenia and pneumonia in the nab-paclitaxel weekly treatment arm and one with respiratory disease or interstitial lung disease in the paclitaxel weekly treatment arm).

Harms of Special Interest

The harms of special interest include hypersensitivity reactions, neutropenia, neuropathy and fatigue.

- *Hypersensitivity Reaction*

GeparSepto-GBG 69[4] – Early Breast Cancer

Specific hypersensitivity reaction was not reported. However, grade 1-2 allergic reactions were reported in 98 (16%) patients for the nab-paclitaxel treatment arm and 120 (20%) patients for the paclitaxel treatment arm. Grade 3 allergic reactions were reported in 3(<1%) patients in the nab-paclitaxel treatment arm and 5 (1%) patients in the paclitaxel treatment arm.

In the nab-paclitaxel treatment arm, one (<1%) patient experienced grade 3 anaphylaxis and none had grade 4 anaphylaxis. In the paclitaxel treatment arm, one (<1%) patient experienced grade 3 anaphylaxis and one (<1%) patient experienced grade 4 anaphylaxis.

Gianni et al. (2018)[5] – Early Breast Cancer

Any grade hypersensitivity was reported in 6% (95% CI, 3.7 to 9.1) in the paclitaxel treatment arm and 1.8% (95% CI, 0.7 to 3.8) in the nab-paclitaxel treatment arm. Grade 3 and higher hypersensitivity was reported in 0.6% (95% CI, 0.1 to 2.1) in the paclitaxel treatment arm and 0.3% (95% CI, 0.0 to 1.6) in the paclitaxel treatment arm.

Jain et al. (2016)[6] – Metastatic Breast Cancer

Hypersensitivity reactions were reported in 3.13% for paclitaxel 260mg/m^2 treatment arm, 0.0% in the paclitaxel 295mg/m^2 treatment arm and 1.72% for nab-paclitaxel 260mg/m^2 treatment arm.

Gradishar et al. (2005)[7] – Metastatic Breast Cancer

The incidence of hypersensitivity reactions (any grade) was reported to be low for both arms (< 1% for nab-paclitaxel treatment arm versus 2% for the paclitaxel treatment arm). No severe (grade 3 or 4) treatment-related hypersensitivity reactions occurred in the nab-paclitaxel treatment arm. However, grade 3 hypersensitivity reactions occurred in the paclitaxel treatment arm despite standard premedications. These include chest pain in two patients and allergic reactions in three patients.

Socinski et al. (2012)[8] – NSCLC

This harm was not reported in the publication.

Shitara et al. (2017)[9] – Gastric Cancer

Hypersensitivity reactions were defined based on MedDRA (version 18.1) terms face edema, injection site reaction, infusion related reaction, hypersensitivity and anaphylactic reaction. Hypersensitivity reactions occurred in two (1%) of 244 patients in the group that received nab-paclitaxel every 3 weeks, three (1%) of 241 in the weekly nab-paclitaxel group and hypersensitivity reactions occurred in 13 patients (5%) of 243 in the paclitaxel treatment arm despite premedication.

- *Neutropenia*

The incidence of neutropenia, by grade is described in Table 8, Table 9, Table 10, Table 11, Table 12 for all included studies except for Gradishar et al[7], where details were summarized in descriptive text. Due to variation of reporting, standardization of details cannot be done.

In GeparSepto-GBG 69 study[4], most patients with early breast cancer reported to have grade 4 neutropenia (nab-paclitaxel 38% versus paclitaxel 36%). This study also provided the incidence of febrile neutropenia; in the nab-paclitaxel treatment arm, 20 (3%) patients experienced grade 3 febrile neutropenia and 8 (1%) experienced grade 4 febrile neutropenia. In the paclitaxel treatment arm, 19 (3%) patients experienced grade 3 febrile neutropenia and 5 (1%) patients experienced grade 4 febrile neutropenia.

In another study by Gianni et al.[5] on early breast cancer, the incidence of neutropenia was 41.8% (CI 36.5 to 47.3) for the nab-paclitaxel treatment arm and 36.4% (CI 31.3 to 41.8) for the paclitaxel treatment arm.

In the metastatic breast cancer setting, Jain et al.[6] reported any grade neutropenia for the following groups: 19 (33%) patients from nab-paclitaxel 260mg/m^2, 21 (33%) patients from paclitaxel 260mg/m^2 and 24 (41%) from paclitaxel 295mg/m^2.

Gradishar et al.[7] reported that despite higher doses of paclitaxel were administered to patient in the nab-paclitaxel treatment arm, the incidence of treatment-related grade 4 neutropenia was significantly lower in the nab-paclitaxel treatment arm than the paclitaxel treatment arm (20 of 226 patients, 9% vs 48 of 222 patients, 22%, respectively; $p < 0.001$). This analysis was unadjusted for multiplicity and the between-group difference was not reported. Febrile neutropenia was reported as less than 2% in both treatment arms. 8 patients (3%) in the nab-paclitaxel and 14 patients (6%) in the paclitaxel treatment arm received growth factor treatment for neutropenia or leukopenia during the study.

In NSCLC, Socinski et al.[8], reported that in the nab-paclitaxel group, 33% of patients experienced grade 3 neutropenia and 14% of patients experienced grade 4 neutropenia. In the paclitaxel group, the numbers of patients who experienced grade 3 and grade 4 neutropenia were 32% and 26%, respectively. The number of patients who experienced febrile neutropenia were 1% or lower.

In gastric cancer, Shitara et al.[9] reported the neutropenia by grade. In the nab-paclitaxel every 3 week treatment arm, the incidence of neutropenia in grade 1-2, grade 3 and grade 4 were 17%, 30%, 34%. In the nab-paclitaxel weekly treatment arm, the incidence of neutropenia in grade 1-2, grade 3 and grade 4 were 24%, 28%, 13%. In the paclitaxel weekly treatment arm, the incidence of neutropenia in grade 1-2, grade 3 and grade 4 were 21%, 24% and 5%. Febrile neutropenia is most common in the nab-paclitaxel every 3 week treatment group with 11% reporting to have hade grade 3 febrile neutropenia.

- *Neuropathy*

In early breast cancer, neuropathy was reported by both studies in early breast cancer setting. In GeparSepto-GBG 69 study[4], grade 1-2 peripheral sensory neuropathy was most common with 451 (75%) patients reported in the nab-paclitaxel treatment arm and 376 (63%) patients reported in the paclitaxel treatment arm. In the study by Gianni et al. [5], the authors reported that 62.9% of patients experienced any grade peripheral neuropathy in the nab-paclitaxel treatment group versus 53.7% of patients experienced any grade peripheral neuropathy in the paclitaxel treatment group.

In metastatic breast cancer, Gradashiar et al.[7] reported that patients in the nab-paclitaxel treatment had more grade 3 sensory neuropathy than patients in the paclitaxel treatment arm with the same dose (24 patients, 10% versus 5 patients2% respectively; p<0.001). This analysis was unadjusted for multiplicity and the between-group difference was not reported. No motor neuropathy or grade 4 sensory neuropathy were reported in both groups. In the study by Jain et al.[6], any grade peripheral neuropathy was reported as follow: 35 (60%) for nab-paclitaxel 260mg/m^2 group, 37 (58%) for paclitaxel 260mg/m^2 group and 37 (64%) for paclitaxel 295mg/m^2 group.

In NSCLC, Socinski et al. reported sensory neuropathy. In the nab-paclitaxel treatment arm, 3% patients experienced grade 3 sensory neuropathy and no patient experienced grade 4 sensory neuropathy. In the paclitaxel treatment arm, 11% patients experienced grade 3 sensory neuropathy and less than 1% experienced grade 4 sensory neuropathy.

In gastric cancer by Shitara et al.[9], the majority of patients reported to have grade 1-2 peripheral sensory neuropathy: 158 (65%) patients from the nab-paclitaxel every 3 weeks group, 153 (63%) from the nab-paclitaxel weekly group and 150 (62%) patients from the paclitaxel weekly group. Refer to Table 13,Table 14,Table 15,Table 16,Table 17.

- *Fatigue*

In early breast cancer, fatigue was reported in the two included studies. In GeparSepto GBG 69[4], 462 patients (76%) experienced grade 1 or 2 fatigue in the nab-paclitaxel treatment arm versus 431 patients (72%) experienced grade 1 or 2 fatigue in the paclitaxel treatment arm. In the study by Gianni et al.[5], any grade fatigue was reported as 36.8% from the nab-paclitaxel treatment arm and 31.3% from the paclitaxel treatment arm.

In metastatic breast cancer, this harm outcome was not reported by Jain et al.[6]. In the study by Gradishar et al.[7], the authors did not explicitly report the number of patients with fatigue in each group, aside from mentioning that more than 20% of patients in either group experienced fatigue and 5% or more experienced grade 3 or 4 fatigue in either group. The proportion of patients in the nab-paclitaxel treatment arm who reported fatigue including grade 3 or 4 fatigue appeared numerically higher when compared to the paclitaxel treatment arm. However, due to limited reporting, the actual magnitude of the difference could not be determined.

In NSCLC, Socinski et al.[8] reported grade 3 and grade 4 fatigue for both treatment arms. For the nab-paclitaxel, the incidence was 4% and less than 1% respectively. For the paclitaxel group, the incidence was 6% and less than 1% respectively.

In gastric cancer, Shitara et al.[9] report fatigue by grade. Most patients experienced grade 1-3 fatigue. For the nab-paclitaxel every 3 weeks treatment arm, the incidences for grade 1-2 and grade 3 were 19% and 4% respectively. For the nab-paclitaxel weekly treatment arm, the incidences were 17% and 2% respectively. For the paclitaxel weekly treatment arm, the incidences were 17% and 2% respectively. Refer to Table 18,Table 19,Table 20,Table 21.

Table 8: Neutropenia, by grade reported by GeparSepto-GBG 69[4]

Adverse Event	Nab-paclitaxel (N=605)		Paclitaxel (N=601)	
	Grade 1-5	Any grade	Grade 1-5	Any grade
Neutropenia n (%)	Grade 1-2: 163 (27%) Grade 3: 139 (23%) Grade 4: 229 (38%) Grade 5: 0	NR	Grade 1-2: 116 (19%) Grade 3: 153 (25%) Grade 4: 36%) Grade 5: 0	NR
Febrile neutropenia n (%)	Grade 3: 20 (3%) Grade 4: 8 (1%) Grade 5: 0	NR	Grade 3: 19 (3%) Grade 4: 5 (1%) Grade 5: 0	NR

Sources: GeparSepto-GBG 69[4] – Early Breast Cancer

Table 9: Neutropenia, by grade reported by Gianni et al (2018)[5]

Adverse Event	Nab-paclitaxel (N=337)		Paclitaxel (N=335)	
	Grade 1 and above	Any grade	Grade 1 and above	Any grade
Neutropenia % (CI)	Grade 1-2: NR Grade 3 and above: 30.6% (25.7-35.8)	41.8% (36.5 to 47.3)	Grade 1-2: NR Grade 3 and above: 19.7% (15.6-24.4)	36.4% (31.3-41.8%)

Sources:, Gianni et al. (2018)[5] – Early Breast Cancer

Table 10: Neutropenia, by grade reported by Jain et al (2016) [6]

Adverse Event	Nab-paclitaxel 260mg/m^2 (N=58)		Paclitaxel 260mg/m^2 (N=64)		Paclitaxel 295mg/m^2 (N=58)	
	Grade 3 and 4	Any grade AE	Grade 3 and 4	Any grade AE	Grade 3 and 4	Any grade AE
Neutropenia n (%)	12 (21%)	19 (33%)	8 (12%)	21 (33%)	14 (24%)	24 (41%)
Febrile neutropenia n (%)	2 (3%)	NR	1 (2%)	NR	4 (7%)	NR

Sources: Jain et al. (2016)[6] – Metastatic Breast Cancer

Table 11: Neutropenia, by grade reported by Socinski et al (2012) [8]

Adverse Event	Nab-paclitaxel (N=514)	Paclitaxel(N=524)
	Grade 3 and 4	Grade 3 and 4
Neutropenia (%)	Grade 3: 33% Grade 4: 14%	Grade 3: 32% Grade 4: 26%
Febrile neutropenia (%)	Grade 3: < 1% Grade 4: < 1%	Grade 3: 1% Grade 4: <1%

Sources:Socinski et al. (2012)[8] – NSCLC

Table 12: Neutropenia, by grade reported by Shitara et al (2017) [9]

Adverse Event	Nab-paclitaxel every 3 weeks(N=244)	Nab-paclitaxel weekly (N=241)	Paclitaxel Weekly(N=243)
	Grade 1-5	Grade 1-5	Grade 1-5
Neutropenia n (%)	Grade 1-2: 41 (17%) Grade 3: 74 (30%) Grade 4: 84 (345) Grade 5: 0	Grade 1-2: 59 (24%) Grade 3: 68 (28%) Grade 4: 31 (13%) Grade 5: 0	Grade 1-2: 50 (21%) Grade 3: 59 (24%) Grade 4: 12 (5%) Grade 5: 0
Febrile neutropenia n (%)	Grade 1-2: 0 Grade 3: 26 (11%) Grade 4: 4 (2%) Grade 5: 0	Grade 1-2: 0 Grade 3: 4 (2%) Grade 4 2 (1%) Grade 5: 1 (<1%)	Grade 1-2: 0 Grade 3: 2 (1%) Grade 4: 0 Grade 5: 0

Sources: Shitara et al. (2017)[9] – Gastric Cancer

Table 13 : Neuropathy, by grade reported by GeparSepto-GBG 69[4]

Adverse Event	Nab-paclitaxel (N=605)				Paclitaxel (N=601)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Peripheral sensory neuropathy	451 (75%)	59 (10%)	4(1%)	0	376 (63%)	16 (3%)	0	0

Sources: GeparSepto-GBG 69[4] – Early Breast Cancer

Table 14: Neuropathy, by grade reported by Gianni et al (2018)[5]

Adverse Event	Nab-paclitaxel (N=337)			Paclitaxel (N=335)		
	Grade 1-2	Grade 3 and above	Any grade	Grade 1-2	Grade 3 and above	Any grade
Peripheral neuropathy	NR	4.5% (2.5-7.2)	62.9% (57.5 to 68.1)	NR	1.8 % (0.7 to 3.9)	53.7% (48.2 to 59.2%)

Sources: Gianni et al. (2018)[5] – Early Breast Cancer

Table 15: Neuropathy, by grade by Jain et al (2016) [6]

Adverse Event	Nab-paclitaxel 260mg/m^2 (N=58)		Paclitaxel 260mg/m^2 (N=64)		Paclitaxel 295mg/m^2 (N=58)	
	Any grade AE	Grade 3 and 4	Any grade AE	Grade 3 and 4	Any grade AE	Grade 3 and 4
Peripheral neuropathy	35 (60%)	10 (17%)	37 (58%)	5 (8%)	37 (64%)	12 (21%)

Sources: Jain et al. (2016)[6] – Metastatic Breast Cancer

Table 16: Neuropathy, by grade reported by Socinski et al. (2012)[8]

Adverse Event	Nab-paclitaxel (N=514)		Paclitaxel (N=524)	
	Grade 3	Grade 4	Grade 3	Grade 4
Sensory neuropathy	3%	0%	11%	<1%

Sources: Socinski et al. (2012)[8] – NSCLC

Table 17: Neuropathy, by grade reported by Shitara et al. (2017)[9]

Adverse Event	Nab-paclitaxel every 3 weeks (N=244)				Nab-paclitaxel weekly (N=241)				Paclitaxel Weekly (N=243)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Peripheral sensory neuropathy	158 (65%)	49 (20%)	0	0	153 (63%)	6 (2%)	0	0	150 (62%)	6 (2%)	0	0

Sources: Shitara et al. (2017)[9] – Gastric Cancer

Table 18 : Fatigue, by grade reported by GeparSepto-GBB[4]

Adverse Event	Nab-paclitaxel (N=605)				Paclitaxel (N=601)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Fatigue	462 (76%)	30 (5%)	-	-	431 (72%)	25 (4%)	-	-

Sources: GeparSepto-GBG 69[4] – Early Breast Cancer

Table 19: Fatigue, by grade reported by Gianni et al. (2018)[5]

Adverse Event	Nab-paclitaxel (N=337)			Paclitaxel (N=335)		
	Grade 1-2	Grade 3 and above	Any grade	Grade 1-2	Grade 3 and above	Any grade
Fatigue	NR	2.4% (1.0-4.6)	36.8% (31.6 to 42.2)	NR	1.2 % (0.3 to 3.0)	31.3% (26.4 to 36.6%)

Sources: Gianni et al. (2018)[5] – Early Breast Cancer

Table 20: Fatigue, by grade reported by Socinski et al. (2012)[8]

Adverse Event	Nab-paclitaxel (N=514)		Paclitaxel (N=524)	
	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	3%	0%	11%	<1%

Sources: Socinski et al. (2012)[8] – NSCLC

Table 21: Fatigue, by grade reported by Shitara et al. (2017)[9]

Adverse Event	Nab-paclitaxel every 3 weeks (N=244)				Nab-paclitaxel weekly (N=241)				Paclitaxel Weekly (N=243)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Fatigue	46 (19%)	9 (4%)	0	0	42 (17%)	4 (2%)	0	0	41 (17%)	4 (2%)	0	0

Sources: Shitara et al. (2017)[9] – Gastric Cancer

Indirect Evidence

Included Indirect Comparisons

No indirect evidence has been included in this review.

Other Relevant Evidence

The use of nab-paclitaxel has been identified by clinical experts that there are unmet needs in patients with gynecological malignancies. If there are no phase III RCTs identified through the literature search, other relevant retrospective studies evaluating nab-paclitaxel in gynecological malignancies will be included in this section.

3 non-comparative retrospective cohort studies[12-14] were included to describe the clinical experience of using nab-paclitaxel in patients who have had prior HSRs in the setting of gynecological malignancies.

Studies Addressing Gaps

The three studies included in Table 22, Table 23 and Table 24 provide additional information about the use of nab-paclitaxel in gynecological malignancies as well as in patients who have prior HSR from the traditional taxanes.

Table 22: Summary of Studies Addressing Gaps – Maurer et al. (2017)[13]

Detail	Description
Evidence gap	No evidence was identified for the efficacy and safety of nab-paclitaxel in patients who have developed HSRs to the traditional taxanes.
Study design	• A retrospective cohort study without a comparison group
Population	• All women over age 18 years with ovarian, primary peritoneal, fallopian tube, cervical, or uterine cancer who had a prior HSR to either paclitaxel and/or docetaxel as the indication for nab-paclitaxel use and received at least one dose of nab-paclitaxel between 2005 and 2015. The patients were identified from a single centre.
Interventions	• Nab-paclitaxel with premedication with dexamethasone 10mg IV

Key findings	• 37 patients with gynecologic malignancies with a history of paclitaxel HSR received nab-paclitaxel were included.
	• Six patients (16.2%) had a prior HSR to both paclitaxel and docetaxel; 31 patients only received paclitaxel and had not received docetaxel.
	• No patients experienced a HSR to nab-paclitaxel.
	• Median number of cycles of nab-paclitaxel was 6 (range 2 to 20).
	• Dosage received:
	  ○ 12 patients received weekly dosing at 60 to 100mg/m^2.
	  ○ The remainder of patients received 135mg/m^2 (n=13), 175mg/m^2 (n=9), or 225mg/m^2 (n=3).
	• Reasons for discontinuation: completion of adjuvant therapy (n=16), progressive disease (n=18), toxicity (n=1), and death (n=1).

Detail	Description
Limitations	• Retrospective cohort study with no comparator which cannot support causal conclusions about the intervention due to high risk of selection bias and confounding. • Small sample size • Lack of external validity due to selection bias

Table 23: Summary of Studies Addressing Gaps – Parisi et al. (2020)[14]

Detail	Description
Evidence gap	No evidence was identified for the efficacy and safety of nab-paclitaxel in patients who have developed HSRs to the traditional taxanes.
Study design	• A retrospective cohort study without comparison group
Population	• Patients with stage IIIc-IV epithelial ovarian cancer (EOC) who were treated with 1st line carboplatin/nab-paclitaxel (with or without bevacizumab), after having an HSR with traditional taxanes (paclitaxel or docetaxel). The patients were identified from a single centre.
Interventions	• Nab-paclitaxel 175mg/m2 on day 1 every 3 weeks in 100mL of sodium chloride, over 30 minutes. • Carboplatin was administered after nab-paclitaxel. • Bevacizumab (standard dose of 15mg/kg) was administered if its combination had been planned for the patient. • In patients unfit for a 3-weekly regimen (age, ECOG-PS and / or comorbidities), weekly regimen was administered with nab-paclitaxel 60mg/m2 • Prophylactic granulocyte-colony-stimulating factor administration was planned for patients who received a 3-weekly schedule.
Key findings	• Between April 2012 and December 2018, 10 patients (20.85) received carboplatin-nab-paclitaxel (with or without bevacizumab) after the having an HSR to traditional taxanes. • ORR = 100% (95% CI 66.4 to 100; 8 partial responses and 1 complete response) both according to RECIST 1.1 and CGIC criteria. At median follow-up of 28.5 months, median PFS was 16.7 months, median OS was 65.4 months. • Median received dose intensity (DI) was 86% and 80% of the projected DI for nab-paclitaxel and carboplatin respectively. • No treatment-related grade 4 AEs. Most relevant treatment-related grade 3 AEs were: asthenia (10%), hypertransaminasemia (10%), neutropenia (20%), thrombocytopenia (20%) and anemia (10%). • No HSR observed
Limitations	• Retrospective cohort study with no comparator that cannot support causal conclusions about the intervention due to high risk of selection bias and confounding.

Detail	Description
	• Very small sample size • Lack of external validity due to selection bias

Table 24: Summary of Studies Addressing Gaps – Wang et al. (2023)[12]

Detail	Description
Evidence gap	No RCTs were identified that provided information on the efficacy and safety of nab-paclitaxel in patients with ovarian cancer
Study design	• A retrospective cohort study without comparison group

Population	• Inclusion criteria:
	  ○ Patients 18 years to 75 years of age
	  ○ Histologically confirmed epithelial OC, fallopian tube cancer, or primary peritoneal cancer
	  ○ FIGO stage I-IV cancer
	  ○ Received platinum combined with nab-paclitaxel as first-line chemotherapy including neoadjuvant chemotherapy and adjuvant chemotherapy.
	• Exclusion criteria:
	  ○ Ovarian tumours of low malignant potential
	  ○ Abdominal or pelvic radiotherapy
	  ○ Central nervous system or brain metastases
	  ○ Other malignancies in the last 5 years with the exception of cured cervical cancer in situ or non-melanoma skin cancer
	  ○ Previous grade ≥ 2 sensory or motor neuropathy

Interventions	• Intravenous nab-paclitaxel on day 1 of every 3-week cycle at 260mg/m2 • Platinum drugs (carboplatin, nedaplatin, lobaplatin) were administered after nab-paclitaxel.
Key findings	• Seventy-two patients (median age, 54.5 years; range 20.0-79.0 years) were evaluated. • The median follow-up duration was 25.6 months, and the median PFS was 26.7 (95% CI, 24.0 to 29.3) months in the whole patient population. • The most common grade 3-4 AES include anemia (15.3%), white blood cell decreased (11.1%), neutrophil count decreased (20.8%). • No drug-related HSRs occurred.
Limitations	• Retrospective cohort study with no comparator that does not support causal conclusions about the intervention due to high risk of selection bias and confounding.

Detail	Description
	• Small sample size • Lack of external validity due to selection bias

FIGO = International federation of Gynecology and Obstetrics

Economic Evidence

As this review is part of the CADTH non-sponsored reimbursement review program in which an application filed by a sponsor is absent. The economic review will consist of only a cost comparison for nab-paclitaxel compared with alternate taxane administration procedures for patients with or without hypersensitivity reactions to taxanes.

CADTH Analyses

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plans. Nab-paclitaxel is not indicated by Health Canada as a replacement for other taxanes in the case of hypersensitivity reactions but is sometimes used as such in clinical practice. Pricing for all products was based on wholesale pricing from IQVIA DeltaPA[22] and may not reflect actual prices paid by public plans.

In order to compare the cost of nab-paclitaxel to the other taxanes in a tumour-agnostic way, CADTH compared the most common doses of each taxane when used in 21-day cycles as well as in weekly cycles recommended in Cancer Care Ontario drug regimen monographs[23] and used in the comparative clinical trials identified within this review.[4-9] Drug acquisition costs and related assumptions for these example regimens can be found in Table 25. Using publicly available costs, the aforementioned dosing assumptions, and a patient body surface area of 1.8m^2, nab-paclitaxel has a greater drug acquisition cost than paclitaxel and docetaxel in most settings. Results may differ by jurisdiction if there are differences in their list prices or funded regimens compared to those presented in Table 25.The various taxanes have different premedication requirements and different infusion times which affect their total costs as detailed in Table 26.

When considering patients who have not experienced an HSR and when taxanes are used in typical 21-day regimens, CADTH estimated that the standardized 28-day cost of nab-paclitaxel ($6,193 per patient) was $134 more than that of paclitaxel ($6,059 per patient) and $3,144 to $4,805 more than that of docetaxel ($1,388 to $3,049 per patient). When typical weekly regimens are considered (3 weeks on, 1 week off), the estimated standardized 28-day cost of nab-paclitaxel ($5,545 to $8,167 per patient, depending on dose) ranged from conferring a savings of $471 to an incremental cost of $2,150 per patient relative to that of paclitaxel ($6,017 per patient), and incremental costs of $2,744 to $6,548 per patient relative to that of docetaxel ($1,619 to $2,802 per patient).

When considering a population of patients who have had an HSR to paclitaxel or docetaxel, administration protocols and their associated costs depend on the severity of the reaction. According to clinical expert opinion obtained by CADTH, patients who experience a mild (Grade 1) to moderate (Grade 2) HSR often receive additional premedication and a slowed taxane infusion, while those experiencing a severe (Grade 3) HSR may undergo a full taxane desensitization protocol.[24] Both scenarios increase the time and costs associated with taxane administration relative to administration costs for patients who have not had an HSR.

For patients requiring a slowed infusion due to a mild to moderate HSR to a 21-day regimen of paclitaxel or docetaxel, the estimated standardized 28-day cost of instead using typically infused nab-paclitaxel is $136 to $404 less expensive than that of the slowed paclitaxel infusion ($6,329 to $6,597 per patient), and $2,874 to $4,535 more expensive than that of slowed docetaxel infusion ($1,658 to $3,319 per patient, Table 26). For weekly regimens, the estimated standardized 28-day cost for typical use of nab-paclitaxel ranged from a savings of $1,076 to increased costs of $1,542 per patient relative to slowed paclitaxel ($6,625 per patient) and was $2,135 to $5,940 more expensive than slowed docetaxel ($2,227 to $3,410 per patient).

For patients requiring a full desensitization protocol due to a severe HSR to a 21-day regimen of paclitaxel or docetaxel, the estimated standardized 28-day total cost of instead using typically infused nab-paclitaxel is $670 less expensive than that of the desensitization protocol of paclitaxel ($6,864 per patient) and $1,803 to $3,464 more expensive than that of the desensitization protocol of docetaxel ($2,729 to $4,391 per patient, Table 26). For weekly regimens, the estimated standardized 28-day total cost for typical use of nab-paclitaxel is $868 to $3,490 less expensive per patient than that of the desensitization protocol for paclitaxel ($6,625 per patient) and ranged from a savings of $275 to increased costs of $3,530 per patient compared to that of the desensitization protocol for docetaxel ($4,637 to $5,820 per patient). According to clinical expert input obtained by CADTH, when a

patient requires a slowed infusion or desensitization protocol due to an HSR, they are likely to continue to receive the same administration protocol for subsequent cycles of taxane therapy and thus these cost-differences are amplified by the duration of the patient's treatment.

Table 25: CADTH Drug Cost Comparison Table for Common Taxane Doses in Chemotherapy Regimens

Treatment	Strength / concentration	Vial Size	Price	Typical Dose	Drug Cost per Dose ($)	Average Drug Cost per 28 Days ($)	Incremental Drug Cost per 28 days Nab-paclitaxel vs Comparator ($)
21-Day Regimens							
Nab-Paclitaxel (Abraxane)	**2 mg/mL**	**100 mg (50 mL)**	**971.0000**	**260 mg/m^2 on Day 1, repeating every 21 days[a]**	**4,544**	**6,059**	**Reference**
Paclitaxel (generics)	6 mg/mL	30 mg (5 mL) 96 mL (16 mL)	374.0000 1,196.8000	175 mg/m^2 on Day 1, repeating every 21 days[b]	3,927	5,236	823
Docetaxel (various, generics)	10 mg/mL	80 mg (8 mL) 160 mg (16 mL)	970.2000 1,850.0000	75 to 100 mg/m^2 on Day 1, repeating every 21 days[c]	1,561 to 2,081	2,081 to 2,775	3,284 to 3,978
	20 mg/mL	80 mg (4 mL) 160 mg (8 mL)	497.0000 990.0000		835 to 1,114	1,114 to 1,485	4,574 to 4,945
Weekly Regimens (3 weekly doses then 1 week off)							
Nab-Paclitaxel (Abraxane)	**2 mg/mL**	**100 mg (50 mL)**	**971.0000**	**100 to 150 mg/m^2 Days 1, 8, and 15, repeating every 28 days[d]**	**1,748 to 2,622**	**5,243 to 7,865**	**Reference**
Paclitaxel (generics)	6 mg/mL	30 mg (5 mL) 96 mL (16 mL)	374.0000 1,196.8000	80 mg/m^2 Days 1, 8, and 15, repeating every 28 days[e]	1,795	5,386	-142 to 2,480
Docetaxel (various, generics)	10 mg/mL	80 mg (8 mL) 160 mg (16 mL)	970.2000 1,850.0000	30 to 35 mg/m^2 Days 1, 8, and 15, repeating every 28 days[f]	624 to 728	1,873 to 2,185	3,058 to 5,992
	20 mg/mL	80 mg (4 mL) 160 mg (8 mL)	497.0000 990.0000		334 to 390	1,002 to 1,169	4,074 to 6,863

All prices are from the IQVIA Delta PA (accessed April 2024),[22] unless otherwise indicated and do not include dispensing fees. Patients are assumed to have a body surface area of 1.8m^2. Treatment is assumed to occur in specialized cancer centres and thus no wastage is included.

Note: This table is not intended to imply that the taxane doses listed within it should be considered interchangeable or equivalent, although the paclitaxel and nab-paclitaxel doses are generally consistent with those compared in the randomized controlled trials identified by CADTH in the clinical sections of this review.[4-9] The example regimens provided are not exhaustive, nor does this table include all doses of taxanes currently in use.

[a] Example regimens include NPAC+PERT+TRAS for HER2 positive unresectable locally recurrent or metastatic breast cancer, NPAC for 2nd line treatment of locally advanced or metastatic blader cancer progressing on platinum-based chemotherapy, CRBPNPAC for patients with endometrial, ovarian, or cervical cancer with severe hypersensitivity to paclitaxel.[23]

[b] Example regimens include PACL+PERT+TRAS for HER2 positive unresectable locally recurrent or metastatic breast cancer, PACL for 2nd line treatment of metastatic bladder cancer progressing on platinum-based chemotherapy, CRBPPACL for patients with endometrial, ovarian, vulvar, or cervical cancer with various criteria. [23]

[c] Example regimens include DOCE+PERT+TRAS for HER2 positive unresectable locally recurrent or metastatic breast cancer, DOCE for treatment of advanced or metastatic bladder/urothelial cell carcinoma in patients who have failed to respond or relapsed on cisplatin-based chemotherapy, CRBPDOCE for the treatment of advanced or recurrent epithelial ovarian, fallopian tube and primary peritoneal cancers. [23]

[d] Example regimens include NPAC(W) for the treatment of metastatic breast cancer in patients who cannot tolerate paclitaxel or docetaxel therapy, NPAC(W) for the treatment of metastatic melanoma, NPAC(W) for second-line treatment of locally advanced or metastatic urothelial bladder cancer after failure of a platinum-containing regimen.[23]

[e] Example regimens include PACL(W) and PACL(W)+TRAS for the treatment of metastatic breast cancer, PACL(W) for second-line treatment of metastatic bladder cancer progressing on platinum-based chemotherapy, PACL(W) for the treatment of recurrent or metastatic carcinoma of the head and neck.[23]

[f] Example regimens include DOCE(W) for the treatment of metastatic breast cancer, DOCE(W) for the treatment of advanced or recurrent squamous cell cancer of the head and neck [23]

Table 26: CADTH-Estimated Administration and Total Costs for Nab-Paclitaxel Compared to Other Taxanes in Patients with and without Hypersensitivity Reactions

Treatment	Premedication Cost per Dose ($)[a]	Infusion Time (Hours)[b]	Infusion Cost ($)[c]	Total Administration Cost per Dose ($)	Drug Cost per Dose[d]	Total Cost per Dose	Average Total Cost per 28 Days ($)	Incremental Total Cost of Nab-Paclitaxel vs Comparator per 28 days ($)
21- Day Regimens								
Nab-Paclitaxel (HSR or non-HSR)	**0**	**0.5**	**101**	**101**	**4,544**	**4,645**	**6,193**	**Reference**
Paclitaxel (non-HSR)	13	3	604	617	3,927	4,544	6,059	134
Paclitaxel (mild to moderate HSR)	15	4 to 5	805 to 1,006	820 to 1,021	3,927	4,544	6,329 to 6,597	-136 to -404
Paclitaxel (severe HSR)	13	6	1,207	1,221	3,927	5,148	6,864	-670
Docetaxel (non-HSR)	4	1	201	205	835 to 2,180	1,041 to 2,287	1,388 to 3,049	3,144 to 4,805
Docetaxel (mild to moderate HSR)	6	2	402	408	835 to 2,180	1,244 to 2,489	1,658 to 3,319	2,874 to 4,535
Docetaxel (severe HSR)	4	6	1,207	1,212	835 to 2,180	2,047 to 3,293	2,729 to 4,391	1,803 to 3,464
Weekly Regimens (3 weekly doses then 1 week off)								
Nab-Paclitaxel (HSR or non-HSR)	**0**	**0.5**	**101**	**101**	**1,748 to 2,622**	**1,848 to 2,722**	**5,545 to 8,167**	**Reference**
Paclitaxel (non-HSR)	9	1	201	210	1,795	2,006	6,017	-471 to 2,150
Paclitaxel (mild to moderate HSR)	11	2	402	413	1,795	2,208	6,625	-1,076 to 1,542
Paclitaxel (severe HSR)	9	6	1,207	2,017	1,795	3,012	9,035	-868 to -3,490
Docetaxel (non-HSR)	4	1	201	205	334 to 728	540 to 937	1,619 to 2,802	2,744 to 6,548
Docetaxel mild to moderate HSR)	6	2	402	408	334 to 728	742 to 1,137	2,227 to 3,410	2,135 to 5,940
Docetaxel (severe HSR)	4	6	1,207	1,212	334 to 728	1,546 to 1,940	4,637 to 5,820	-275 to 3,530

HSR= hypersensitivity reaction.

Note: Some calculations may appear off due to rounding.

[a] Premedication includes dexamethasone, diphenhydramine, and ranitidine for paclitaxel and dexamethasone for docetaxel.[25] Hydrocortisone has been added to slowed taxane regimens. Desensitization protocols assume typical premedication use and do not include the potential longer-term use of over-the-counter antihistamines as these are likely at the patient's expense. Types of premedication and dosages are based on the respective regimen monographs,[23] the Anti-Emetic Recommendations from Cancer Care Ontario,[26], Management of Cancer Medication-Related Infusion Reactions: Drug Table from Cancer Care Ontario,[27] and clinical expert opinion obtained by CADTH. Premedication recommended for non-taxane agents within a regimen are not included.

[b] Infusion times for patients without an HSR are from the respective regimen monographs from Cancer Care Ontario.[23] Patients who have experienced a mild to moderate (Grade 1 or 2) HSR were assumed to receive a slowed infusion, with infusion times approximated based on clinical expert input obtained by CADTH. Patients who have experienced a severe HSR (Grade 3) were assumed to undergo a desensitization protocol, with infusion times calculated using the 3-step, 12-bag Protocol Calculation Tool, available from Cancer Care Ontario.[28]

[c] Derived from Sohi et al., 2019,[29] a systematic review which reported a median chemotherapy administration cost in Canada of US$128 per hour (2019 dollars). When converted to Canadian dollars[30] and inflated to 2024,[31] the median cost per hour is $201.

[d] As calculated in Table 25.

Of note, based on the experiences described in the patient input received by CADTH for this review, patients who experienced HSRs to taxanes required hospitalization. Clinician input indicated that some patients experience recurrent infusion reactions despite desensitization. As such, there are potential differences in hospital resource use between nab-paclitaxel, paclitaxel, and docetaxel for patients with or without HSR, as well as potentially in related resources such as outpatient or general practitioner visits. Although these components have been identified as important to patients, the clinical review did not identify data within the clinical assessment to quantify such differences in resource use, and therefore they have not been included within the cost analysis.

Issues for Consideration

- **Generic nab-paclitaxel may be available:** According to the Health Canada Drug Product Database, a generic of nab-paclitaxel imported by Apotex Inc. is also marketed in Canada in 100 mg vials. No pricing or claims data were available through IQVIA DeltaPA or Pharmastat for this product at the time of this review (as of April 3, 2024).[22,32] If this product is available at a lower cost than Abraxane-brand nab-paclitaxel, then the cost of treatment with nab-paclitaxel may be lower than estimated. If the generic price of nab-paclitaxel is 55% of the reference brand within three months after market entry of a single source generic, consistent with the pCPA pan-Canadian Tiered Pricing Framework,[33] then the standardized 28-day drug acquisition cost of nab-paclitaxel 21-day regimens would be $3,332 per patient, while the drug acquisition cost of nab-paclitaxel weekly regimens would be $2,884 to $4,326 per patient. At these costs, nab-paclitaxel would be less expensive than paclitaxel (using publicly listed prices) regardless of administration protocol, and less expensive than docetaxel desensitization protocols (using publicly listed prices) when used weekly but within the range of docetaxel desensitization costs when used every 21 days.
- **Cabazitaxel is available for prostate cancer:** Cabazitaxel, another taxane, is approved and funded in combination with prednisone for the treatment of some forms of prostate cancer.[23] As the current regimen in which cabazitaxel is funded does not overlap with those of paclitaxel or nab-paclitaxel, a direct substitution is unlikely. Thus, cabazitaxel has not been included in the current cost comparison. When used at a dose of 20 to 25 mg/m^2 every 3 weeks, the drug acquisition cost of cabazitaxel for a patient with a body surface area of 1.8m^2 is $3,944 to $4,930 per standardized 28 days.[22] This regimen of cabazitaxel is typically infused over an hour and would therefore have administration costs similar to those of 21-day regimens of docetaxel outlined in Table 26.
- **Healthcare resource use:** Aside from cost considerations, nab-paclitaxel administration is associated with less infusion chair time and thus less nurse monitoring time than administration of paclitaxel or docetaxel, particularly when slowed or using a desensitization protocol. Additionally, while administration costs have been approximated in CADTH's analysis using estimated infusion time as a multiplier,[29] this does not fully account for differences in pharmacy and nursing time requirements between typical or slowed infusions and those requiring a full 3-bag, 12-step desensitization protocol.[28] As chair time, nursing time, and pharmacy time are limited resources in public healthcare settings, the use of regimens requiring fewer of such resources may have benefits to the healthcare system beyond those captured when considering administration cost differences alone.
- **Patient expenses:** When patients require longer infusion times due to HSRs, it is likely that they or their caregivers will require additional time off work compared to those whose taxane can be administered over its typical infusion timeframe. This is especially true when full desensitization protocols, which effectively take a full day, are required. Longer infusion times due to HSRs are also likely to incur additional expenses for patients such as more parking fees or requiring additional over-the-counter antihistamines or other premedication not reimbursed by public plans.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on December 19th, 2023.

Discussion

Summary of Available Evidence and Interpretation of Results

Note that no evidence was found via the systematic review for the population of interest, specifically for patients who have developed taxanes-induced HSR. Hence, the comparative information suffers from population indirectness. The evidence presented is about the benefits and harms of nab-paclitaxel versus traditional taxanes are in patients without HSR. The evidence is also based on comparative evidence with paclitaxel, instead of all available taxanes including paclitaxel, docetaxel or cabazitaxel.

The main evidence base for this review is comprised of six open-label phase III RCTs comparing nab-paclitaxel with paclitaxel in three tumour sites including breast cancer[4-7], NSCLC[8] and gastric cancer[9]. The overall survival, the progression-free survival and the pathological complete response (in the neoadjuvant setting of breast cancer) were the efficacy endpoints included for this review, some demonstrating either non-inferiority or marginal benefits with the use of nab-paclitaxel when compared with paclitaxel in the different tumour settings.

Overall Survival: This outcome was informed by 5 studies across 3 cancers (early and metastatic breast cancer, NSCLC and gastric cancer). The risk of bias is with some concerns. In the study by Socinski et al.[8], non-inferiority was demonstrated for overall survival when nab-paclitaxel was compared to paclitaxel. This analysis appeared post-hoc without multiplicity adjustment. Shitara et al.[9] evaluated overall survival in gastric cancer. There was non-inferiority for one dose comparison (between nab-paclitaxel weekly and paclitaxel weekly treatment groups). However, the non-inferiority hypothesis was not rejected when nab-paclitaxel every 3 week treatment arm was compared to paclitaxel weekly treatment arm. This does not infer inferiority. Instead, the evidence was insufficient to prove non-inferiority. In metastatic breast cancer study by Gradishar et al.[7], the study tested for superiority. However, limited information was provided (p-value), where the null hypothesis was rejected. Without confidence interval, it would not be possible to estimate the uncertainties. In the extension study by Untch et al.,[11], the overall survival was based on hazard ratios of 0.82 with CI between 0.59 to 1.16. The null hypothesis was not rejected. With such a wide confidence interval, it introduces uncertainty about which treatment could have favoured. Gianni et al[10] published an event-free survival analysis with only a p-value (0.245) with no measures of precision. Hence, there is also uncertainty about which group would have favoured.

Based on the evidence presented, it seems that there are some cancers which suggest non-inferiority of nab-paclitaxel versus traditional taxanes.

Progression Free Survival: This outcome was informed by 3 studies across 3 cancers (metastatic breast cancer, NSCLC and gastric cancer). There are some concerns for risk of bias. In the study by Jain et al.[6], it tested for superiority. There is limited information provided beyond p values and medians. The null hypothesis was not rejected. However without measures of precisions, there would be uncertainty about how wide the confidence interval might be and if there is potential for either group being favoured. Socinski et al.[8] showed non-inferiority. The study appears to be post-hoc without multiplicity adjustment. In gastric cancer, Shitara et al[9] tested for superiority. The null hypotheses were not rejected. For the comparison between weekly nab-paclitaxel and paclitaxel treatment arms, the confidence interval shows potential for benefit when nab-paclitaxel weekly group was compared to paclitaxel weekly (HR 0.88, CI 0.73 to 1.06, p=0.176) or little-to-no difference when nab-paclitaxel every 3 week group was compared to paclitaxel weekly group (HR 1.03, CI 0.85 to 1.24, p=0.778). Given the evidence, it appears that there is some signal from one study to support non-inferiority with limitations.

Pathological Complete Response: This outcome was informed by two studies in early breast cancer. There are also some concerns for risk of bias. This is an early surrogate outcome for overall survival with potential concerns for validity as efficacy endpoints [34,35]. Overall, there is some inconsistency in the findings, as one study found nab-paclitaxel to be superior[4] whereas in the other[5], the null hypothesis was not rejected.

HRQoL: While HRQoL was available from two studies, with one study in breast cancer and another study in gastric cancer [7,9], the high risk of bias with the evidence (e.g. open label, high missing data) renders it difficult to arrive at any meaningful conclusions.

In addition, three retrospective cohort studies without a control group[12-14] were included as they evaluated the use of nab-paclitaxel in gynecological malignancies, an area identified to have unmet needs within the current treatment landscape. Two of these studies[13,14]

specifically looked at individuals who have developed prior HSRs from the traditional taxanes, the findings provide some clinical experience with the use of nab-paclitaxel in this population. However, these studies included few patients, were single-centre, and lacked comparator groups, which limits the ability to draw causal conclusions.

Harms including AEs, SAEs, WDAEs, and deaths due to AE were evaluated. However, the reporting isn't consistent across studies, rendering it difficult for direct comparison. In general, serious adverse event involving death was rare. However, withdrawal due to adverse event would be as expected for chemotherapies. Harms of special interest included HSRs, neutropenia, neuropathy and fatigue were evaluated in this review. Based on 5 of the 6 included studies[4-7,9], the HSRs or allergic reactions were reported. Details of incidences related to neutropenia, neuropathy and fatigue were also reported.

It should be noted that in summation the above comparative evidence does not address the role of nab-paclitaxel following a taxane reaction, and thus does not directly apply to the patient population for which this evidentiary summary is submitted.

Overall, the incidence of HSR was higher in the paclitaxel treatment arms (e.g.6 % or less) when compared with the nab-paclitaxel treatment arms (2% or less) in all included studies. Note that 4 of the 6 studies[6-9] have criteria to exclude patients with pre-existing HSR to taxanes, so the true incidences to taxanes could have been higher. These differences may be of clinical relevance when deciding on a regimen for patients with previous hypersensitivity reactions. Also, only one study provided the definition of HSR and other remaining studies did not provide additional details on either the definition(s) of HSR or the severity of the HSRs being noted. Note that hospitalization as a result of HSR was not evaluated or captured in the clinical evidence.

Overall, neutropenia is commonly reported in both nab-paclitaxel and paclitaxel treatment arms. In the study by Gianni et al., any grade neutropenia was reported in 41.8% CI 36.5 to 47.3) in the nab-paclitaxel arm compared to 36.4% (CI 31.3 to 41.8) in the paclitaxel treatment arm. Neutropenia may also be influenced by the dose administered, frequency of the regimen as well as other concurrent cytotoxic therapies that can contribute to neutropenia. In 4 studies that have also reported febrile neutropenia which is often associated to worse outcomes, the incidence is overall low (3% or less) and does not appear to be different between group. One potential outlier is in gastric cancer where 11% experienced grade 3 febrile neutropenia in the nab-paclitaxel every 3 weeks treatment group, when compared to nab-paclitaxel weekly group (2%) and paclitaxel weekly group (2%). In addition, Jain et al. .[6] reported that grade 3 and 4 febrile neutropenia with 3% from the nab-paclitaxel 260mg/m^2 group, 2% in the paclitaxel 260mg/m^2 group and 7% in the paclitaxel 295mg/m^2, suggesting this harm may be connected to the dose intensity. Further investigation would be needed.

As reported in the 6 included studies, neuropathy appeared to be more common among the nab-paclitaxel treatment arms, if receiving the same dose. For example in the study by Gianni et al., any grade peripheral neuropathy was reported in 62.9% (CI 57.5 to 68.1) in the nab-paclitaxel treatment arm versus 53.7% (CI 48.2 to 59.2) in the paclitaxel treatment arm. One exception is in Socinski et al. (2012) where taxanes were administered together with carboplatin which could also contribute to neuropathy. In the study by Jain et al. [6], the paclitaxel treatment arm with higher dose appeared to have highest any grade neuropathy (64%) and grade 3 and 4 neuropathy (21%) as compared to other two treatment arms (58 – 60% for any grade neuropathy, 8-17% for grade 3 and 4 neuropathy).

Fatigue was reported in 5 of the 6 included studies. Based on the descriptive statistics, patients in the nab-paclitaxel treatment arms had a higher or similar incidence of fatigue in most studies when compared with the paclitaxel treatment arms. The one exception is with the study by Socinski et al. (2012) in NSCLC where the paclitaxel treatment arm reported higher incidence of grade 3 fatigue with 6% versus 4% in nab-paclitaxel treatment arm. This was, however, informed by few events.

Cost

Based on wholesale prices and when considering commonly used 21-day regimens, the drug acquisition cost of nab-paclitaxel (average $6,059 per patient per 28-days) is more expensive than that of paclitaxel (average $3,097 per patient per 28-days) and docetaxel (average $835 to $2,081 per patient per 28-days). When considering commonly used weekly regimens (3 weeks on, 1 week off), the drug acquisition cost of nab-paclitaxel (average $5,243 to $7,865 per patient per 28-days) is generally more expensive than that of paclitaxel (average $5,386 per patient per 28-days) and docetaxel (average $1,002 to $2,185 per patient per 28-days). However, as nab-paclitaxel requires less time to infuse than paclitaxel and docetaxel, associated administration costs for nab-paclitaxel are lower. When considering a patient population who have had an HSR to paclitaxel or docetaxel, these administration

cost differences are magnified due to the need to slow infusions of the drug causing the reaction (in the case of a mild to moderate HSRs) or use a full desensitization protocol (in the case of severe HSRs).

For patients requiring a slowed infusion due to a mild to moderate HSR when receiving a 21-day regimen of paclitaxel or docetaxel, when drug acquisition, administration and premedication costs are included, the standardized 28-day total cost of nab-paclitaxel (at the typical rate of infusion) is $136 to $404 less per patient than that of the slowed paclitaxel infusion and $2,874 to $4,535 more per patient than that of slowed docetaxel infusion. For weekly regimens, the standardized 28-day total cost for nab-paclitaxel (at the typical rate of infusion) ranged from a savings of $1,076 per patient to increased costs of $1,542 per patient relative to slowed paclitaxel infusion and $2,135 to $5,940 more per patient than slowed docetaxel infusion.

For patients requiring a full desensitization protocol due to a severe HSR when using a 21-day regimen of paclitaxel or docetaxel, when drug acquisition, administration, and premedication costs are included, the standardized 28-day total cost of nab-paclitaxel (at the typical rate of infusion) is $670 less per patient than the desensitization protocol of paclitaxel and $1,803 to $3,464 more per patient than the desensitization protocol of docetaxel. For weekly regimens, the standardized 28-day total cost for nab-paclitaxel (at the typical rate of infusion) is $868 to $3,490 less per patient than that of the desensitization protocol for paclitaxel and ranged from a savings of $275 to increased costs of $3,530 per patient compared to that of the desensitization protocol for docetaxel. These incremental costs are based on publicly available wholesale prices and may not reflect actual prices paid by Canadian public drug payers.

Conclusions

Based on the evidence included in this review, there is limited and inconsistent evidence to suggest nab-paclitaxel may be comparable to paclitaxel in the treatment of patients in some solid organ tumours. This is based on efficacy outcomes in overall survival and progression free survival in studies evaluating the comparison in early breast cancer, metastatic breast cancer, NSCLC and gastric cancer. The population reviewed includes any patients with solid organ tumours requiring taxanes as their treatments, as opposed to the requested population which is in patients with previous HSRs.

The proportion of patients experiencing adverse event was not consistently reported in all included studies. However, serious adverse event due to death was rare. The incidence of HSR from the nab-paclitaxel group was 6% or less, whereas the incidence from the paclitaxel group was 2% or less. Both nab-paclitaxel and paclitaxel can cause neutropenia, neuropathy and fatigue. Other factors can contribute to these side effects such as dose intensity and regimen.

Results of the cost-comparison demonstrate that while the drug acquisition cost of nab-paclitaxel is more expensive than that of paclitaxel and docetaxel used in similar regimens, administration costs are lower. When considering patients with a mild to moderate HSR to paclitaxel or docetaxel, the total cost per 28 days of using typically administered nab-paclitaxel was within the range of costs for similar regimens of slowed paclitaxel infusion (range: cost savings of $1,076 to increased costs of $1,542 per patient) and more expensive than similar regimens of slowed docetaxel infusion (range: increased costs of $2,135 to $5,940 per patient). For patients with a severe HSR to paclitaxel or docetaxel, the total cost per 28 days of using typically administered nab-paclitaxel was less expensive than the desensitization protocol for similar regimens of paclitaxel (range: cost savings of $868 to $3,490 per patient) but was generally more expensive than the desensitization protocol for similar regimens of docetaxel (range: cost savings of $275 to increased costs of $3,530 per patient). These incremental costs are based on wholesale prices and may not reflect actual prices paid by Canadian public drug payers. A generic version of nab-paclitaxel has marketing authorization from Health Canada; if it is available to public payers at a reduced price, the cost associated with nab-paclitaxel would be less than estimated and the assessment of comparative costs may change. To consider this alongside the healthcare resource implications associated with any differences in comparative clinical benefits, a cost effectiveness analysis of nab-paclitaxel would be required.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: December 19, 2023

Alerts: Biweekly search updates until project completion

Search filters applied: None

Limits

- Conference abstracts: excluded

Table 27:Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.ae	Adverse effects (MEDLINE) / Adverse drug reaction (Embase) subheading
*****	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily

Syntax	Description
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

1 Albumin-bound paclitaxel/
2 ((nab or nabs) adj2 paclitaxel*).ti,ab,kf,rn,nm.
3 Nabpaclitaxel*.ti,ab,kf,rn,nm.
4 Abraxane*.ti,ab,kf,rn,nm.
5 (ABI-007 or "ABI 007" or abi-007 or "abi 007").ti,ab,kf,rn,nm.
6 (paclitaxel* adj2 (protein or albumin or nanoparticle* or nano particle* or nanodeliver* or nano deliver*)).ti,ab,kf,rn,nm.
7 QY511JBA21.rn,nm.
8 or/1-7
9 Drug hypersensitivity/ or anaphylaxis/
10 (paclitaxel* or taxane* or taxoid* or abraxane* or taxol*).ti,ab,kf.
11 and/9-10
12 Taxoids/ae
13 ((paclitaxel* or taxane* or taxoid* or abraxane* or taxol*) adj4 (hypersensitiv* or hyper sensitiv* or HSR or HSRs or allerg*)).ti,ab,kf.
14 or/11-13
15 and/8,14
16 15 use medall
17 *Paclitaxel/ and (protein or albumin or nanoparticle* or nano particle* or nanodeliver* or nano deliver*).ti,ab,kf,dq,ot.
18 ((nab or nabs) adj2 paclitaxel*).ti,ab,kf,dq,ot.
19 Nabpaclitaxel*.ti,ab,kf,dq,ot.
20 Abraxane*.ti,ab,kf,dq,ot.
21 (ABI-007 or "ABI 007" or abi-007 or "abi 007").ti,ab,kf,dq,ot.
22 (paclitaxel* adj2 (protein or albumin or nanoparticle* or nano particle* or nanodeliver* or nano deliver*)).ti,ab,kf,dq,ot.
23 or/17-22
24 Drug hypersensitivity/ or Anaphylaxis/
25 (paclitaxel* or taxane* or taxoid*).ti,ab,kf,dq,ot.
26 and/24-25
27 Taxoids/ae
28 ((paclitaxel* or taxane* or taxoid*) adj4 (hypersensitiv* or hyper sensitiv* or HSR or HSRs or allerg*)).ti,ab,kf,dq,ot.
29 or/26-28
30 and/23,29
31 30 use oemezd
32 or/16,31
33 conference abstract.pt.
34 32 not 33

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.
[Search -- Studies with results | nabpaclitaxel, taxane hypersensitivity]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.
[Search terms -- nabpaclitaxel, taxane hypersensitivity]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.
[Search terms -- nabpaclitaxel, taxane hypersensitivity]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search terms -- nabpaclitaxel, taxane hypersensitivity]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search terms -- nabpaclitaxel, taxane hypersensitivity]

Grey Literature

Search dates: December 7, 2023 – December 8, 2023

Keywords: nabpaclitaxel, taxane hypersensitivity

Limits: None

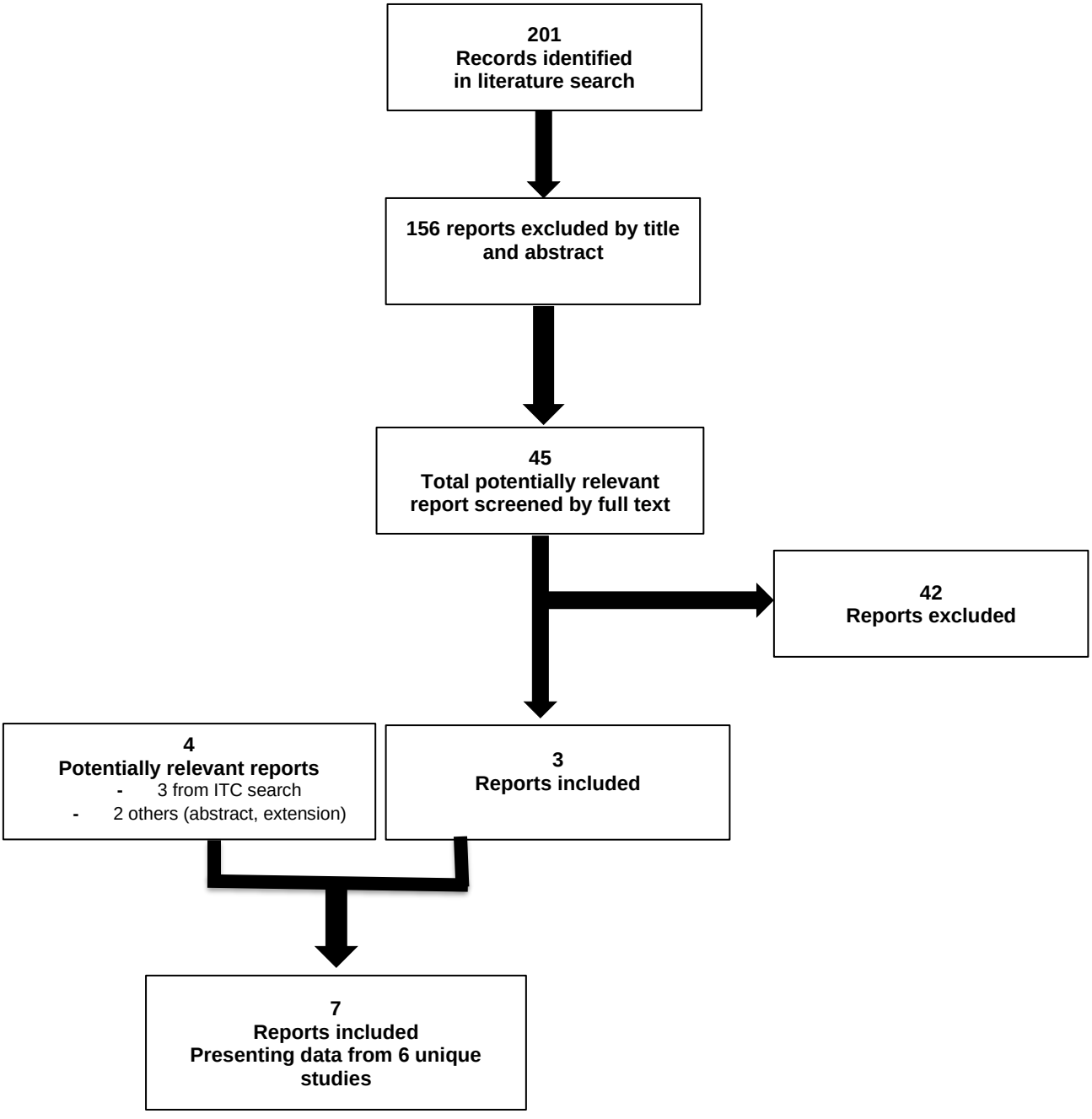
Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Study Selection

Figure 3: Flow Diagram for Inclusion and Exclusion of Studies

Alt text: 201 records were identified, 195 were excluded by title and abstract, while no electronic literature and no grey literature potentially relevant full text reports were retrieved for scrutiny. In total 6 reports of 6 randomized controlled trials are included in the review.



Appendix 3: Risk of Bias Assessment

Table 28: Risk of Bias Assessment Per Outcome Within Each RCT Using RoB2

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Gianni et al. 2018 (ETNA) [5]						
Pathological Complete Response	**Low** Randomization was done centrally via computed-generated blocks, and stratification was by cooperative research group, disease stage and tumour subtype. No apparent baseline imbalances.	**Low** Although the study was open label, longer infusion time for nab-paclitaxel could expose participants to become aware of their assigned interventions and potential AEs. However, these interventions were unlikely to affect outcomes.	**Some concerns** Although about 8.5% (paclitaxel group) and 9.1% (nab-paclitaxel group) discontinued from taxane, an intention-to-treat analysis was conducted; The distribution of patients who withdraw consent, discontinued from study and reasons for missing assessment was not available.	**Some concerns** pCR was assessed by a local pathologist according to provided guidelines. No info on whether person was blinded.	**Low** Data appeared to have been analysed according to pre-specified plan.	**Some concerns**
Harms		**Some concerns** Dose reductions or treatment delays were allowed which could underscore the true harms. It is unclear whether this is by protocol or at the discretion of the clinicians.	**Some concerns** Some missing data with potential of bias. For example, 3-4% of randomized patients were excluded in the safety reports.	**Some concerns** All safety outcomes are reported for both groups. No apparent reason to believe outcomes have been influenced by knowledge of intervention. However, some outcomes of harm are subjective (e.g., fatigue)		**Some concerns**
Gradishar et. al.[7]						
Overall Survival	**Some concerns**. 1:1 randomization was done, although the detailed methods were not described. randomization and allocation concealment methods were not described	**Low** Open label and any otential deviations were apparent. Any deviations to the interventions were unlikely to affect the overall survival outcome.	**Some concerns** Intention to treat analysis was done on the efficacy endpoints. However, censoring details were not available.	**Low** Overall survival outcome is unlikely to be influenced by knowledge of intervention received.	**Low** Data appeared to have been analysed according to pre-specified plan.	**Some concerns**
HRQoL		**Some concerns** Different infusion time and premedication requirements may affect QoL results.	**Some concerns**. No detailed information on number of patients completed the questionnaires.	**High risk** Quality-of-life measurements were reported with European Organisation for		**High risk**

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
		Unclear if these deviations align with protocol.	Only mean scores were provided in the publication.	Research and treatment of Cancer Quality of Life Question C30.Some concerns with open label and whether it is a validated tool		
Harms		**Low** AE-related discontinuations, dose reductions and dose delays were infrequent (3% to 7%) in both treatment arms, with no statistically significant differences noted between the groups.	**Low** All 454 patients in the ITT population were included in the safety analysis.	**Some concerns** All safety outcomes are reported for both groups. No apparent reason to believe outcomes have been influenced by knowledge of intervention. However, some outcomes of harm are subjective (e.g., fatigue)		**Some concerns**
Jain et al. 2016[6]						
Progression Free Survival	**Some concerns** .Randomisation was done using a computer-generated randomization code. Description of allocation concealment was not provided.	**Low** All three treatment arms received similar regimens other than the intervention and comparators. Both arms had same infusion time and no premedications. Different diluents were used for reconstitutions. No apparent deviations noted.	**Some concerns** Intention to treat analysis was done on the efficacy endpoints.Some concerns with large proportion of patients who withdrew consent (>205). 6-7% withdraw due to losses to follow up.	**Low** Progression free survival is unlikely to be influenced by knowledge of intervention received.	**Low** Data appeared to have been analysed according to pre-specified plan.	**Some concerns**
Harms			**Some concerns** Intention to treat analysis was done on the efficacy endpoints.Some concerns with large proportion of patients who withdrew consent (>205). 6-7% withdraw due to losses to follow up.	**Some concerns** All safety outcomes are reported for both groups. No apparent reason to believe outcomes have been influenced by knowledge of intervention. However, some outcomes of harm are subjective (e.g., fatigue)		**Some concerns**
Shitara et al. 2017[9]						

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Overall Survival	Some concerns Randomization in a 1:1:1 ratio using a randomisation sequence generated using the minimisation method and done centrally using a validated computerised system. The minimisation method was applied to balance the three groups using the following stratification factors: previous use of docetaxel, presence of peritoneal metastases, and ECOG performance status. However, there are some baseline imbalances pertaining to previous chemotherapies.	Low The study allowed different infusion time and premedication requirements However, these interventions were unlikely to affect outcomes.	Low Overall survival and progression-free survival were analysed in the full analysis set, which included all randomly assigned patients who received at least one dose of the allocated drug and who met the eligibility criteria.	Some concerns Overall survival and progression-free survival outcomes are unlikely to be influenced by knowledge of intervention received. However, some outcomes of harm are subjective (e.g., fatigue)	Some concerns Data appeared to have been analyzed with some deviations not fully explained in the publication. For example, how patients were enrolled if they had no measurable lesions.	Some concerns
Progression Free Survival						Some concerns
HRQoL		Some concerns Although the study was open label, longer infusion time for nab-paclitaxel could expose participants to become aware of their assigned interventions and potential AEs and lead to their interpretation of QoL	High Quality of life were assessed in the full analysis set. However, there were significant missing data at later time course, resulting in potential of bias.	High The mean EQ-5D index score was used to assess QoL. The open label and self reporting nature of the tool may introduce bias.	Low Data appeared to have been analysed according to pre-specified plan.	High
Harms		Low Different infusion time and premedication requirements could expose participants to become aware of their assigned interventions. However, these interventions were unlikely to affect outcomes.	Some concerns Toxicities were analysed in the safety analysis set (as-treated population set). This has potential to introduce bias. If patients who discontinued treatments (and loss to follow) due to toxicities, they would not be captured in the safety data.	Some concerns All safety outcomes are reported for both groups. No apparent reason to believe outcomes have been influenced by knowledge of intervention. However, some outcomes of harm are subjective (e.g., fatigue)	Low Data appeared to have been analysed according to pre-specified plan.	Some concerns
Socinski et al. 2012[8]						
Overall Survival	Low Randomization conducted 1:1 and stratified by disease stage, age, sex, histology and geographic region.	Some concerns Although the study was open label, longer infusion time for nab-paclitaxel could expose participants to become aware of their	Low Efficacy endpoints were evaluated using intent-to-treat population. ~ 7% excluded for the treated population.	Low Overall survival and progression-free survival outcomes are unlikely to be influenced by knowledge of intervention received.	Low Data appeared to have been analysed according to pre-specified plan.	Some concerns

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Progression Free Survival		assigned interventions and potential AEs. . However, these interventions were unlikely to affect the efficacy outcomes. Overall high discontinuation (18%) from treatment due to "investigator's discretion and 13% due to "patient discretion" may bias the outcome.	.			Some concerns
Harms		Some concerns Dose reductions or treatment delays were allowed which could underscore the true harms. 46% in the nab-paclitaxel group and 23% in the paclitaxel group had a taxne dose reduction.	Low Toxicities were analysed in the safety analysis set (as-treated population set). This has potential to introduce bias. However, the resulted in 2% patients removed only.	Some concerns All safety outcomes are reported for both groups. No apparent reason to believe outcomes have been influenced by knowledge of intervention. However, some outcomes of harm are subjective (e.g., fatigue)	Low Data appeared to have been analysed according to pre-specified plan.	Some concerns
Untch et al. 2016 (GeparSepto GBG 69)[4]						
Pathological Complete Response	Low 1:1 randomization using dynamic allocation and Pocock minimisation by breast cancer subtype, Ki67 and SPARC expression	Low Although the study was open label, longer infusion time for nab-paclitaxel could expose participants to become aware of their assigned interventions and potential AEs. However, these interventions were unlikely to affect outcomes.	Some concerns All patients who started therapy after randomization were included in the modified intention-to-treat population There are some concerns with missing assessments.	Low Pathological complete response was defined as no invasive or non-invasitve tumour residuals in breast and axillary lymph nodes after neoadjuvant therapy. This is not directly influenced by the allocation of intervention of the participants.Pathologists were also blinded to the assignments.	Low Data appeared to have been analysed according to pre-specified plan.	Some concerns
Harms			Low About the same number of patients (605 and 601) were included in the safety analysis.	Some concerns All safety outcomes are reported for both groups. No apparent reason to believe outcomes have been influenced by	Low Data appeared to have been analysed according to pre-specified plan.	Some concerns

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
				knowledge of intervention. However, some outcomes of harm are subjective (e.g., fatigue)		

Appendix 4: Other Relevant Information from Included Studies

Table 29 : Patient disposition of included RCTs

Included RCTs	Tumour Type	Patient Disposition
GeparSepto-GBG 69[4]	Early Breast Cancer	Among the 1373 patients screened for eligibility, 1229 underwent randomisation with 616 allocated to the nab-paclitaxel treatment arm and 613 allocated to the paclitaxel treatment arm. Nab-pacitaxel treatment arm Among the 616 patients assigned to this treatment arm, 606 patients started treatment and were included in the modified ITT analysis of primary endpoint. 1 patient in the nab-paclitaxel treatment arm received paclitaxel by mistake, and as such, excluded from the safety analysis which included 605 patients. 162 patients discontinued taxane, or both epirubicin-cyclophosphamide. Of these, 123 discontinued taxane. 444 patients completed treatment with both taxane and epirubicin-cyclophoshamide. Paclitaxel treatment arm Among the 613 patients assigned to this treatment, 600 patients started treatment and were included in the modified ITT analysis of primary endpoint. 601 patients were included in the safety analysis. The additional 1 patient is from the other treatment arm where the patient mistakenly received paclitaxel. 123 patients discontinued taxane, or both epirubicin-cyclophosphamide. Of these, 80 discontinued taxane. 477 patients completed treatment with both taxane and epirubicin-cyclophosphamide.
Gianni et al. 2018[5]	Early Breast Cancer	814 patients were screened. Among the 695 patients who meet eligibility criteria for randomization, 346 patients were allocated to the nab-paclitaxel treatment arm and 349 patients were allocated to the paclitaxel treatment arm. Nab-paclitaxel treatment arm Of the 346 patients, 336 patients went on to receive treatment, 10 patients did not receive treatment, 6 patients withdrew consent and 4 patients did not start nab-paclitaxel treatment. Of the 336 patients who started treatment, 4 patients failed eligibility and 8 patients did not undergo surgery or pCR was not assessed. 346 patients were assessed in the intent-to-treat analysis. 32(9.5%) patients discontinued taxanes, 12 (3.5%) due to adverse events, 16 (4.6%) had progressive disease and 4 (1.2%) patients due to other reasons. Paclitaxel treatment arm Of the 349 patients, 336 patients received paclitaxel treatment. 13 patients did not receive paclitaxel treatment, 6 patients withdrew consent, 7 patients did not start paclitaxel treatment. Of the 336 patients who started treatment, 3 patients failed eligibility, 3 patients received nab-paclitaxel, 7 patients did not undergo surgery or pCR was not assessed. 349 patients were assessed in the intent-to-treat analysis.

Included RCTs	Tumour Type	Patient Disposition
		27(8.1%) patients discontinued taxanes, 12 (3.4%) due to adverse events, 1 (0.3%) due to patient's refusal to continue on a taxane, 10 (2.9%) had progressive disease and 4 (1.1%) patients due to other reasons.
Jain et al. (2016)[6]	Metastatic Breast Cancer	233 patients were screened. Among the 180 patients randomized, 58 patients were allocated to nab-paclitaxel treatment arm, 64 patients were allocated to the paclitaxel 260mg/m^2 treatment arm and 58 patients were allocated to the paclitaxel 295mg/m^2 treatment arm. Nab-paclitaxel treatment arm All 58 patients allocated to this treatment arm received treatment. All 58 patients discontinued treatment with the following reasons: 20 (34%) due to disease progression, 16 (28%) due to consent withdrawal, 9 (16%) due to unacceptable toxicity, 5 (9%) due to death, 4 (7%) due to lost to follow-up, 4 (75) due to investigator discretion. Paclitaxel 260mg/m^2/ treatment arm All 64 patients allocated to this treatment arm received treatment. All 64 patients discontinued treatment with the following reasons: 27 (42%) due to disease progression, 14 (22%) due to consent withdrawal, 8 (12%) due to unacceptable toxicity, 5 (8%) due to death, 4 (6%) due to lost to follow-up, 4 (6%) due to investigator discretion, 1 (2%) due to non-compliance and 1 (2%) due to having complete response. Paclitaxel 295mg/m^2 treatment arm All 58 patients allocated to this treatment arm received treatment. All 58 patients discontinued treatment with the following reasons: 18 (31%) due to disease progression, 11 (20%) due to consent withdrawal, 11 (20%) due to unacceptable toxicity, 7 (12%) due to death, 4 (7%) due to lost to follow-up, 3 (5%) due to investigator discretion.
Gradishar et al. (2005)[7]	Metastatic Breast Cancer	A CONSORT diagram was not included in the publication. Among the 460 patients enrolled and randomly assigned to treatment groups into the study, six patients (1%) did not receive study drug. The remaining 454 patients (229 patients in the nab-paclitaxel treatment arm and 225 patients in the paclitaxel treatment arm) were included in the modified intent-to-treat population. The number of patients discontinued was not reported.
Socinski et al. (2012)[8]	NSCLC	The number of patients screened was not reported. Among the 1052 patients randomly assigned, 521 patients were allocated to receive nab-paclitaxel with carboplatin and 531 patients were allocated to receive paclitaxel with carboplatin. 7 (1%) patients from each treatment arm were excluded, resulting in 514 (99%) patients from the nab-paclitaxel treatment arm who were treated and 524 (99%) patients from the paclitaxel treatment arm who were treated. The intent-to-treat population includes the 521 patients allocated to receive nab-paclitaxel with carboplatin and 531 patients allocated to receive paclitaxel with carboplatin. Nab-paclitaxel treatment arm Among the 514 patients, 3 (<1%) patients had therapy ongoing and 511 (>99%) patients had discontinued therapy. Reasons for discontinuation included progressive disease (275 patients [54%]), unacceptable toxicities (61 [12%]), adverse events (20 [4%]), investigator discretion (86 [17%]), protocol deviation (3 [>1%]), lost to follow up (1 [<1%]), other (0). Paclitaxel treatment arm

Included RCTs	Tumour Type	Patient Disposition
		All 524 allocated patients went on to receive treatment. All 524 (100%) patients had discontinued therapy. Reasons for discontinuation included progressive disease (265 [51%], unacceptable toxicities 62 [12%], adverse events (24 [5%]), investigator discretion (99 [19%]), patient discretion (67 [13%]), protocol deviation (4 [<1%]), lost to follow-up (1 [<1%]) and other (2 [<1%]).
Shitara et al. (2017)[9]	Gastric Cancer	The number of patients screened was not reported. Among the 741 patients enrolled, 247 patients were allocated to the nab-paclitaxel every 3 weeks treatment arm, 246 patients were allocated to the nab-paclitaxel weekly treatment arm and 248 patients were allocated to the paclitaxel weekly treatment arm. <u>Nab-paclitaxel every 3 weeks treatment arm</u> Among the 247 patients in the nab-paclitaxel every 3 weeks treatment arm, 3 patients were untreated and 244 patients received treatment. 243 patients were included in the full analysis set (1 patient was excluded). Of these 243 patients, 93 patients had no measurable lesions at enrollment and were excluded for measurement of overall response. 150 patients completed measurements for overall response. 232 patients discontinued treatment (160 had progressive disease, 15 investigator decision, 36 adverse events, 1 surgery [disease regression], 0 lost to follow-up, 2 due to other reasons) <u>Nab-paclitaxel weekly treatment arm</u> Among the 246 patients, 241 patients went on to receive treatment (5 patients were untreated). 240 patients were included in the full analysis set (1 excluded). Of these 240 patients, 90 patients had no measurable lesions at enrollment and were excluded for measurement of overall response. 150 patients completed measurements for overall responses. 221 patients discontinued treatment (173 had progressive disease, 13 investigator decision, 22 adverse events, 7 patient decision, 1 surgery [disease regression], 2 lost to follow-up and 2 due to other reasons). <u>Paclitaxel weekly treatment arm</u> Among the 248 patients, 243 patents went on to receive treatment (5 patients were untreated). 243 patients were included in the full analysis set. Of these, 74 patients had no measurable lesions at enrollment and were excluded for measurement of overall response. 169 patients completed measurements for overall response. 230 patients discontinued treatment (187 had progressive disease, 17 investigator decision, 17 adverse events, 7 patient decision, 1 surgery [disease regression], 0 lost to follow-up and 1 due to other reason.

Table 30: Treatment exposure of included RCTs

Included RCTs	Tumour Type	Treatment Exposure
GeparSepto-GBG 69[4]	Early Breast Cancer	Due to the imbalance of discontinuation and sensory neuropathy for nab-paclitaxel treatment group compared to paclitaxel treatment group, the independent data monitoring committee made a recommendation to adjust the nab-paclitaxel dose. The scientific committee reduced the dose from 150mg/m^2 to 125mg/m^2 weekly by means of a study amendment. In addition, the taxane dose was reduced in 182 (30%) of 605 patients in the nab-paclitaxel treatment arm versus 75 (12%) of the 601 in the paclitaxel treatment arm.
Gianni et al. 2018 Trial [5]	Early Breast Cancer	The median treatment duration (range) was 16 (4 to 21) weeks in the nab-paclitaxel treatment arm versus 16 (4 to 19.7) weeks in the paclitaxel treatment arm. The median number of cycles (range) was 4 (1-4) for both the nab-paclitaxel and paclitaxel treatment arms. Dose omissions occurred in 24 (7.1%) of patients in the nab-paclitaxel treatment arm and 20 (6.0%) of the patients in the paclitaxel treatment arm. Dose reduction occurred in 39 (11.6%) of patients in the nab-paclitaxel treatment arm. Among this group, 37 (11.0%) patients had a dose reduction due to any adverse event. Dose reduction occurred in 32 (9.6%) of patients in the paclitaxel treatment arm. Among this group, 28 (8.4%) of patients had a dose reduction due to any adverse event. Dose delay occurred in 123 (36.5%) of patients in the nab-paclitaxel treatment arm. Among this group, 69 (20.5%) patients had a dose delay due to any adverse event. Dose delay occurred in 104 (31%) of patients in the paclitaxel treatment arm. Among this group, 49 (15%) of patients had a dose delay due to any adverse event. The median days of delay due to adverse events was 7 (1-20) for both the nab-paclitaxel and paclitaxel treatment arms. The median relative dose intensity was 99.35% in the nab-paclitaxel treatment arm and 99.53% in the paclitaxel treatment arm. The relative dose intensity (%) is the ratio between the absolute and the intended dose intensity (mg/m^2/week) multiplied by 100.
Jain et al. (2016)[6]	Metastatic Breast Cancer	The mean (± standard deviation) cumulative doses administered during the trial were as follow: • In the nab-paclitaxel treatment arm: 2290mg ± 1293mg/m^2. • In the paclitaxel 260mg/m^2 treatment arm: 2026mg ± 1329mg/m^2. • In the paclitaxel 295mg/m^2 treatment arm: 2260mg ± 1823mg/m^2. The mean dose intensities were as follow: • In the nab-paclitaxel treatment arm: 137 ± 61mg/m^2. • In the paclitaxel 260mg/m^2 treatment arm: 155 ± 88mg/m^2 • In the paclitaxel 295mg/m^2 treatment arm: 186 ± 126mg/m^2 The mean number of cycles administered per patient were as follow: • In the nab-paclitaxel treatment arm: 5.9 ± 3.5 • In the paclitaxel 260mg/m^2 treatment arm: 5.2 ± 3.5 • In the paclitaxel 295mg/m^2 treatment arm: 5.07 ± 3.7 Treatment was administered without dose reduction in 88% (n = 51), 92% (n = 59) and 86% (n = 50) and 88% (n = 51) in the nab-paclitaxel treatment arm, paclitaxel 260mg/m^2 treatment arm and paclitaxel 295mg/m^2 treatment arm respectively. Unacceptable toxicity resulted in treatment discontinuation in 9 (16%), 8 (12%) and 11 (20%) patients in the nab-paclitaxel treatment arm, paclitaxel 260mg/m^2 treatment arm and paclitaxel 295mg/m^2 treatment arm respectively.

Included RCTs	Tumour Type	Treatment Exposure
Gradishar et al. (2005)[7]	Metastatic Breast Cancer	>99% of the nab-paclitaxel infusions were administered in 50 minutes or less and 81.5% of the paclitaxel infusions were administered over 30 minutes. 22.9% of patients in the paclitaxel treatment arm required longer than planned infusion time of 180 minutes. The actual delivered paclitaxel dose-intensity was 49% higher in the nab-paclitaxel treatment arm than the paclitaxel treatment arm. The mean dose delivered was 85.13, SD 3.118 mg/m^2 for the nab-paclitaxel treatment group and was 57.02, SD 3.008mg/m^2 per week for paclitaxel treatment group. At least six treatment cycles were administered to 129 patients (56%) in the nab-paclitaxel treatment arm and 112 patients (50%) in the paclitaxel treatment arm.
Socinski et al. (2012)[8]	NSCLC	The median number of cycles was 6 for both treatment arms. 350 patients in the nab-paclitaxel treatment arm and 358 patients in the paclitaxel treatment arm received six or fewer cycles of treatment. The median cumulative paclitaxel dose was 1,325mg/m^2 in the nab-paclitaxel treatment arm and 1,125mg/m^2 in the paclitaxel treatment arm. The median paclitaxel dose intensity was 82mg/m^2/week for the nab-paclitaxel treatment arm and 65mg/m^2/week for the paclitaxel treatment arm. Among the treated patients, 46% of the nab-paclitaxel treatment arm and 23% of the paclitaxel treatment arm had a taxane dose reduction, due to neutropenia (29% and 10%), thrombocytopenia (13% and 4%), anemia (6% and < 1%) and sensory neuropathy (2% and 6%). Despite more dose reduction in the nab-paclitaxel treatment arm, paclitaxel dose intensity was 26% greater and cumulative dose was 18% greater for nab-paclitaxel treatment arm over the paclitaxel treatment arm. Dose delays were more common in the nab-paclitaxel treatment arm (82%) compared with the paclitaxel treatment arm (54%).
Shitara et al. (2017)[9]	Gastric Cancer	The median treatment duration was 2.4 months (IQR 0.9 to 5.0) in the nab-paclitaxel every 3 weeks treatment arm, 3.7 months (IQR 1.9 to 6.7) in the nab-paclitaxel weekly treatment arm and 3.3 months (IQR 1.5 to 5.4) in the paclitaxel weekly treatment arm. The median total doses were 1399mg per patient (IQR 838 to 2599) in the nab-paclitaxel every 3 weeks treatment arm, 1890mg per patient (IQR 1025 to 2864) in the nab-paclitaxel weekly treatment arm and 1380mg per patient (IQR 768 to 2113) in the paclitaxel weekly treatment arm. Dose reductions occurred in 151 (62%) of the 244 patients in the nab-paclitaxel every 3 weeks treatment group, 88 (37%) of the 241 patients in the nab-paclitaxel weekly treatment group and 51 (21%) of the 243 patients in the paclitaxel weekly treatment group. Median relative dose intensities were 88.06% (IQR 75.82 to 100.00) in the nab-paclitaxel every 3 weeks treatment arm, 83.79% (IQR 69.85 to 94.12) in the nab-paclitaxel weekly treatment arm and 87.36% (IQR 75.94 to 96.00) in the paclitaxel weekly treatment arm.

Note that this information is not standardized due to variation in reporting among the included studies.