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A systematic review and meta-analysis of nab-paclitaxel mono-chemotherapy for metastatic breast cancer.

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ABSTRACT

Background: Various clinical trials and real-life studies have tried to explore the value of nab-paclitaxel mono-chemotherapy for metastatic breast cancer (MBC). The safety and efficacy of nab-paclitaxel needs to be systematically evaluated.

Methods: Electronic searches for prospective clinical trials containing nab-paclitaxel monotherapy for MBC were performed. Requisite data were extracted, integrated and analyzed from the included studies according to different purposes using systematic review and meta-analysis.

Results: 22 studies with 3287 MBC patients were included. 1685 MBC patients received nab-paclitaxel as first-line therapy, 640 patients as further-line therapy, and 962 patients as mixed-line therapy. 1966 MBC patients (60.40%) received nab-paclitaxel weekly, while 1190 patients (36.56%) received nab-paclitaxel triweekly and 99 patients (3.04%) biweekly. The overall incidence of all grades neutropenia, leukopenia, peripheral sensory neuropathy, and fatigue was 52% (95% CI, 38%-66%), 58% (95% CI, 43%-73%), 58% (95% CI, 48%-68%), and 49% (95% CI, 41%-56%) respectively. The overall response rate (ORR) was 40% (95% CI, 35%-45%) and the clinical benefit rate (CBR) was 66% (95% CI, 59%-73%) following nab-paclitaxel monotherapy. The median progression free survival (PFS) was 7.64 months (95% CI, 6.89-8.40 months) and the median overall survival (OS) was 24.51 months (95% CI, 21.25-27.78 months). According to the meta-regression analysis, grade 3/4 neutropenia occurred less frequently in Her-2 negative patients compared with all population (P=0.046). Patients who received first-line nab-paclitaxel monotherapy showed higher ORR (P=0.006) and longer PFS (P=0.045). Patients who received further-line therapy was demonstrated to have shorter median OS versus first- and mixed-line therapy. Efficacy outcomes were not affected by the administration schedule. However, patients appeared to have more superior ORR (P=0.044) and longer PFS (P=0.03) along with the increasing dosage of nab-paclitaxel under the same schedule.

Conclusions: Both weekly and triweekly nab-paclitaxel mono-chemotherapy were proved to be effective for MBC with generally reasonable toxicity profiles. Higher

ORR, longer PFS and OS would be achieved in patients treated with nab-paclitaxel as first line. Increasing nab-paclitaxel dosage would result in better tumor control (higher ORR and PFS). Changing nab-paclitaxel schedule had no benefit on ameliorating the overall survival.

Keywords: nab-paclitaxel, metastatic breast cancer, safety, efficacy, meta-analysis

Introduction

Approximately one fourth of patients with earlier localized breast cancer will eventually develop recurrent or metastatic breast cancer (MBC) [1]. Once breast cancer becomes metastatic it is rarely curable, even if mortality has been decreasing steadily in the developed countries in the last decade [2]. Although no randomized evidence exists comparing therapy with observation in women with MBC, it is widely recommended that women with MBC should receive some form of systemic therapy during the course of their disease [3]. Chemotherapy has been the cornerstone in the treatment of MBC patients for many years, and it is generally accepted that taxanes are among the most active single agents [4].

The clinical approval of taxanes for MBC began with paclitaxel in 1994, continued with docetaxel in 1996, and still updated with nanoparticle albumin-bound paclitaxel (Abraxane, nab-paclitaxel) in 2005 [5]. Although paclitaxel and docetaxel had proven to be clinical beneficial, their hydrophobic chemical formulations had presented obvious limitations [6]. Nab-paclitaxel was developed to eliminate the solvent-related toxicities typically associated with taxanes administration. More importantly, this colloidal suspension was also designed to preferentially deliver paclitaxel to tumors by biologically interacting with albumin receptors that mediated drug transport [7]; in vitro studies had demonstrated a 4.5-fold increase in paclitaxel transport across endothelial cells for nab-paclitaxel compared to conventional taxanes [8].

Since Ibrahim NK firstly reported 300 mg/m2 nab-paclitaxel monotherapy in a triweekly style resulting in a 48% overall response rate (ORR) for 63 MBC patients in a phase II trial [9], various clinical trials and real-life studies tried to explore the safety and activity of nab-paclitaxel in treating MBC. Most recently, in the NABUCCO observational study Marschner N reported the nab-paclitaxel monotherapy could offer a 37.2% ORR, a 68.3% clinical benefit rate (CBR), a 5.9 months of median time to progression (TTP) and a 15.6 months of median overall survival (OS) with lower (5%) grade 3/4 treatment-related adverse events (TRAEs) in 697 MBC patients, [10]. Head-to-head clinical comparisons between

nab-paclitaxel and conventional taxanes were not lacking, with two pivotal phase II/III clinical trials reported by Gradishar WJ [11, 12], coincidentally demonstrated superior efficacy and safety of nab-paclitaxel compared with paclitaxel (175 mg/m2, q3w) or docetaxel (100 mg/m2, q3w), with a statistically higher ORR and clinically significant prolongation of progression-free survival (PFS) with shorter infusion schedules (30 minutes) and no premedication. However, opposite results still existed. In a phase II multicenter trial with 197 Her2 negative MBC, Tamura K reported similar efficacy outcomes in patients treated with weekly nab-paclitaxel (150 mg/m2) and triweekly docetaxel (75 mg/m2). Nab-paclitaxel did not show superiority in PFS compared with docetaxel [13]. In the CALGB 40502 study, Rugo HS also failed to demonstrate superiority of nab-paclitaxel given weekly compared with paclitaxel in 542 MBC patients with increased overall toxicity. They suggested weekly paclitaxel should remain the preferred microtubule inhibitor for treating patients with MBC in the first-line setting [14]. Therefore, considering a proportion of studies on nab-paclitaxel monotherapy were single-arm, non-randomized phase II trials with rather small sample size, the safety and efficacy of nab-paclitaxel needed to be excavated deeply and thoroughly.

Although nab-paclitaxel was initially approved by US Food and Drug Administration (FDA) with a recommended triweekly 260 mg/m2 dosage for MBC, evidence suggested that a weekly nab-paclitaxel regimen could also be feasible for patients with MBC inspired by weekly paclitaxel administration appearing to be the optimal schedule for MBC [7]. In fact, a retrospective study reported by Dent S showed inferior ORR (4.7% vs. 14.3%), CBR (57.1% vs. 76.2%), and shorter median OS (10.8 months vs. 13.6 months) in the triweekly nab-paclitaxel group compared with weekly nab-paclitaxel group [15]. Gradishar WJ also demonstrated better disease control for nab-paclitaxel qw 3/4 regimens (100 mg/m2 and 150 mg/m2) versus a q3w regimen as monotherapy, and nab-paclitaxel at 150 mg/m2 qw 3/4 resulted in a 33.8 months OS longer than historically achieved with single-agent taxanes therapy in MBC [16]. However, in the NABUCCO study, efficacy superiority with respect to better tumor control and longer survival outcomes had not

been obtained in the weekly nab-paclitaxel group [10]. Irrespective of the survival outcomes, weekly nab-paclitaxel regimen seemed to increase paclitaxel-related toxicity. Tamura K reported 150 mg/m2 qw 3/4 nab-paclitaxel monotherapy would result in 78% of grade 3/4 neutropenia and 22% of grade 3/4 neuropathy in 98 MBC patients [13]. Decreased quality of life (QOL) due to more TRAEs in MBC patients seemed to disobey the goal of MBC treatment [17]. Since no tailored regimens were strongly recommended, variable studies with different nab-paclitaxel dosage and schedule came into clinical practice [18], and these data called into question which regimen of nab-paclitaxel was the optimal setting for MBC.

To date, nab-paclitaxel had seemed been suggested quite important as a single agent for first-line or further-line treatment of MBC [19]. Since it was hard to interpret all the information into a clear conclusion in terms of the value of nab-paclitaxel in metastatic setting due to the limitation of every single study, here we reviewed the clinical evidence with nab-paclitaxel as a single agent in metastatic settings treatment, with the goal of understanding the safety and efficacy followed by nab-paclitaxel mono-chemotherapy. Furthermore, evidence-based optimal regimen and schedule of nab-paclitaxel for MBC was also explored by meta-regression analysis and subgroup analysis.

Methods

Study search strategy

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [20], a systematic search was independently performed by 2 investigators (Shan CX and Lu HL) using electronic databases including PubMed/Medline, ClinicalTrial.gov and the Cochrane Center Register of Controlled Trials to identify articles published between March 2005 and March 2020, using the following search keywords :"nab-paclitaxel or albumin-bound paclitaxel or abi-007 or Abraxane, and metastatic breast cancer". The "related articles" function was used to broaden the search. All abstracts, studies and citations were checked for additional material when appropriate. In addition, abstracts from annual meetings of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology Conference (ESMO) and San Antonio Breast Cancer Symposium (SABCS) were retrieved for relevant abstracts using similar search terms. No language restrictions were made.

Study selection criteria

Abstracts or full-text articles were initially screened, and then selected or rejected by the two reviewers (Shan CX and Lu HL) on the basis of the inclusion and exclusion criteria described below.

Inclusion criteria: (1) Designed prospective trials, including both observational studies and interventional studies. (2) Phase II clinical trials, phase III clinical trials and cohort studies. (3) Single arm, two arms or multi-arms trials which contained the treatment group of nab-paclitaxel monotherapy were all included. (4) The exact data of dichotomous-type information and continuous-type information, by which the standard deviation or standard error could be calculated, should be provided so as to integrate each single weight in each study.

Exclusion criteria: (1) Retrospective observational studies. (2) Total sample capacity < 10 cases. (3) Studies with the same research subjects published repeatedly

by different journals.

Quality assessment

Methodological quality of randomized controlled trials (RCTs) was assessed by Cochrane Collaboration tool with six domains: random sequence generation, allocation concealment, blinding of investigators, participants and outcome assessor, completion of outcome data, selective reporting. All of the domains should be graded as “low risk”, “high risk” or “unclear risk” of bias. If no less than 4 “low risk” domains were identified in the trial with none “high risk” domain, the trial was considered with low risk and high quality.

The Newcastle-Ottawa Scale was used to evaluate the quality of cohort study. Grading criteria included: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study, comparability of cohorts on the basis of the design or analysis, assessment of outcome, enough time to follow up, adequate follow-up. The maximum score was nine.

For non-randomized trials, quality assessment was performed by Methodological Index for Non-randomized Studies (MINORS). For trials without control group, eight criteria were required for evaluation: clear object, consecutive participants, collection of expected result, terminal point could properly reflect the purpose, objectivity of endpoint evaluation, long enough to follow up, the rate of lost to follow up was less than 5%, estimation of sample size. For those with control group, four additional criteria were also required: appropriate choice of control group, patients were selected at the same period, comparability of two groups, optimal statistical analysis. The criteria were graded from zero to two points according to the information reported rarely, inadequately or in detail. The maximum score was sixteen or twenty-four.

Data extraction

The two reviewers independently extracted details from each eligible study which

comprised (1) information and quality of the research: first author, year of publication, study design, treatment line, population, sample capacity; (2) nab-paclitaxel regimen including the dosage and schedule; (3) The assessment data of trials containing multiple groups were initially divided into single nab-paclitaxel mono-chemotherapy group and other groups, and then extracted individually; (4) toxicity profile, including the incidence of all grades and grade 3/4 of neutropenia, leukopenia, peripheral sensory neuropathy and fatigue; (5) disease control rate, including ORR and CBR; (6) survival endpoints, including median PFS and median OS. Specifically, the assessment data of repeated trials published in different journals at different time was extracted based on the latest and the most detailed article. Furthermore, if the safety and efficacy outcomes were both assessed by radiologist and investigator independently in certain studies, we retrieved the data provided by the investigator.

Statistical analysis

All trials referring to nab-paclitaxel monotherapy was firstly split into each individual group according to nab-paclitaxel administration dosage and schedule. The outcome measures included the incidence of TRAEs, the disease control rate (ORR, CBR), and median survival time (median PFS, median OS). Data analysis in our study was performed with STATA (version 14.0) software. For the ratio analysis, we performed single-arm meta-analysis and adopted the “metaprop” command set in STATA for data integration. Additional “ftt” command set was applied if the level of rate was unusual high or low. For the survival outcome analysis, median PFS or median OS with its sampling error were utilized for data integration. The sampling error could be retrieved through the literature data base, while, it could also be calculated with the formula of the upper bound minus the lower bound of 95% confidence interval (CI)/2*1.96. If significant heterogeneity did exist between the recruited studies ($I^2 > 50\%$), we adopted a random-effects model, if not, a fixed-effects model was applied. The publication bias was checked through “Begger” and “Egger” method in STATA, and further represented through funnel

plot analysis. We performed meta-regression analysis to demonstrate the potential risk factors affecting each single outcome of nab-paclitaxel monotherapy after removing the included studies with significant heterogeneity. If the risk factor did exist, meta-regression subgroup analysis was further performed to demonstrate the difference between individual groups due to the specified risk factor.

Results

Identification and characteristics of studies

We ultimately identified 22 independent studies published between March 2005 and March 2020 [9, 10, 12, 13, 16, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37]. A flow chart representing selection of studies is shown in Figure 1. Totally 11 RCTs, 10 non-randomized trials and 1 cohort study were included. The quality of 11 RCTs were all demonstrated with low risk (Grade A). The only one cohort study was also evaluated as high quality with full score. Based on the criteria of MINORS, five non-randomized trials scored zero point in sample size estimation criteria for bare report (Ibrahim NK 2005, Hurria A 2015, Blum JL 2007, Marschner N 2018, Bernardo A 2017), one trial scored one point for inadequate information (Yamamoto S 2017), and another one trial (Bernardo A 2017) also scored one point in follow-up domain for higher rate (>5%) of lost to follow-up. The details of study quality were shown in Table 1. The baseline characteristics of the included studies for metastatic breast cancer were summarized in Table 2.

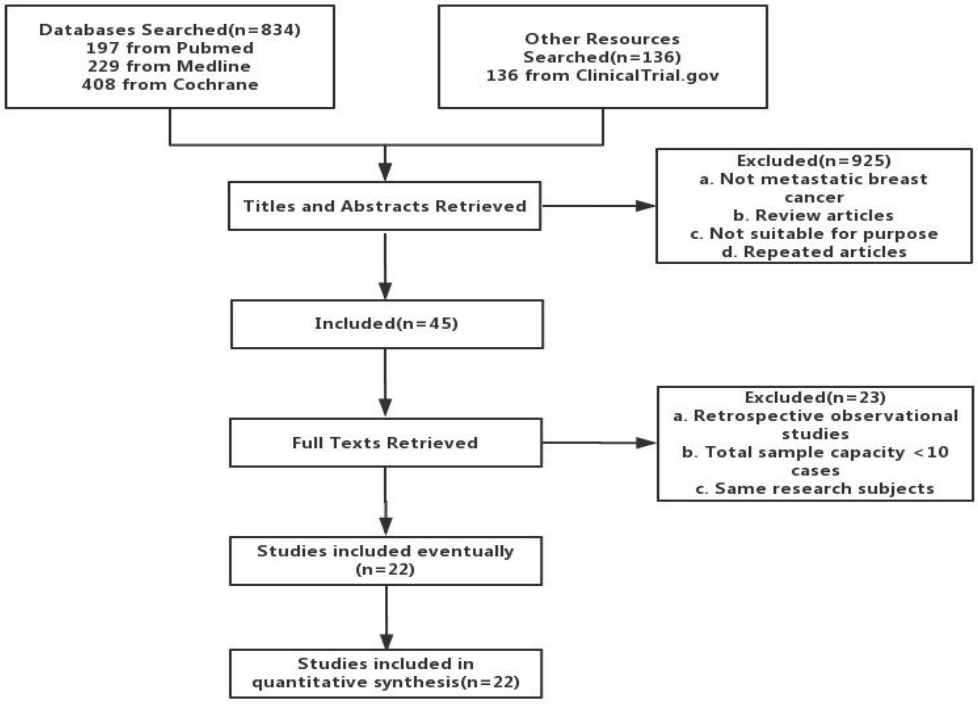


Figure 1 Study retrieval flow diagram

Table 1 Quality assessment of the included studies

Author	Year	Cochrane	NOS	MINORS	MINORS
Gradishar WJ	2005	Grade A			
GUAN ZZ	2009	Grade A			
Gradishar WJ	2012	Grade A			
Ranade AA	2013	Grade A			
Andres FT	2015	Grade A			
Jain MM	2016	Grade A			
Tamura K	2017	Grade A			
Gennari A	2018	Grade A			
Ciruelos E	2019	Grade A			
Hara F	2019	Grade A			
Schmid P	2019	Grade A			
Brezden B	2013		9		
Ibrahim NK	2005			14	
Mirtsching B	2011			16	
Fabi A	2015			16	
Hurria A	2015			16	
Palumbo R	2015			16	
Yamamoto S	2017			15	
Hurria A	2019			14	
Blum JL	2007				22
Bernardo A	2017				21
Marschner N	2018				22

Nab-paclitaxel treatment patterns

Totally 3287 MBC patients treated with nab-paclitaxel monotherapy were included in the current study. In our analysis, there were 1685 (51.26%) MBC patients who received nab-paclitaxel as first-line therapy, 640 patients (19.47%) as further line therapy, and the rest 962 MBC patients (29.27%) as mixed (first or further) line therapy. Furthermore, a majority of MBC patients (n=1966, 60.40%) had nab-paclitaxel administered weekly, 1190 MBC patients (36.56%) had nab-paclitaxel administered triweekly, and 99 MBC patients (3.04%) with biweekly 150mg/m2 nab-paclitaxel administration. Among 1190 MBC patients with triweekly nab-paclitaxel schedule (q3w), despite of 194 patients (16.30%) being administered at an imprecise reported dosage of 220-260 mg/m2, 192 patients (16.13%) were

Table 2 Baseline characteristics of the included studies for metastatic breast cancer

Author+Year	Study Design	Sample Size (N)	Treatment Line	Nab-paclitaxel Monotherapy Regimen	Treatment Related Adverse Events (TRAEs)								Efficacy Outcomes			
					Neutropenia (%)		Leukopenia (%)		Neuropathy (%)		Fatigue (%)		ORR (%)	CBR (%)	Median PFS (Months)	Median OS (Months)
					All grades	3/4 grade	All grades	3/4 grade	All grades	3/4 grade	All grades	3/4 grade				
Ibrahim NK 2005	Phase II Multicenter	63	Mixed	300mg/m^2 q3w	9	51	91	24	64	11	40	13	48			14.8
		39	First	300mg/m^2 q3w									64			
		24	Further	300mg/m^2 q3w									21			
Gradishar WJ 2005	Phase III RCT Multicenter	229	Mixed	260mg/m^2 q3w		30		7		10		7	33			15.2
		97	First	260mg/m^2 q3w									42			
		132	Further	260mg/m^2 q3w									27			13.2
Blum JL 2007	Phase II Multicenter	106	Further	100mg/m^2 qw 3/4	49	18	62	19	25	8	37	5	14	26	3	9.2
		75	Further	125mg/m^2 qw 3/4	64	34	66	36	51	19	45	12	16	37	3.5	9.1
Guan ZZ 2009	Phase II RCT Multicenter	104	Further	260mg/m^2 q3w	69	42	64	24	76	7	17		54	71	7.6	17.8
Mirtsching B 2011	Phase II Multicenter	72	First	125mg/m^2 qw 3/4	14	11	11	1.4	54	8.3	58	6.9	42.2	68.8	14.5	29
Gradishar WJ 2009/2012	Phase II RCT Multicenter	76	First	100mg/m^2 qw 3/4	80	25			58	9	34	0	63	83	7.5	22.2
		74	First	150mg/m^2 qw 3/4	92	44			68	22	47	4	74	91	14.6	33.8
		76	First	300mg/m^2 q3w	93	44			73	21	36	5	46	72	10.9	27.7
Brezden B	Phase II Multice	47	First	100mg/m^2 qw 3/4	14.9	9			46.8	0	70		30	51	6	20.9

2013	nter	76	First	100mg/m^2 qw 3/4	17.1	9			57.9	0	72		28	57	6.7	20
Ranade AA	Phase II RCT	55	Mixed	220mg/m^2 q3w		28				1.5			40	67		
2013	Multice nter	53	Mixed	300mg/m^2 q3w		38				17			40	72		
Palumbo R 2015	Phase II Multice nter	52	Further	260mg/m^2 q3w	77	21.2	88.5	25	48.1	5.8	27	0	48.1	76.9	8.9	
Fabi A 2015	Phase II Single-c enter	42	Further	Mixed	95	70	95	25	80	12	72	13	23.8	50	4.6	
		32	Further	125mg/m^2 qw 3/4									28.1	50		
		10	Further	260mg/m^2 q3w									10	50		
Hurria A 2015	Phase II Multice nter	39	Mixed	100mg/m^2 qw 3/4	26	3	36	5	8	0	31	5	31	69	5.7	19.4
Andres FT 2015	Phase II RCT Multice nter	21	Mixed	100mg/m^2 qw 3/4	38	14			48	5	54	10	38	52	3.7	
Jain MM 2016	Phase III RCT Multice nter	58	Mixed	260mg/m^2 q3w	33	21	28	16	60	17	36	7	43	75	7.9	
Yamamot o S 2017	Phase II Multice nter	35	Mixed	180mg/m^2 q3w		46				0			23	51	6.5	44.7
Tamura K 2017	Phase II RCT Multice nter	98	First	150mg/m^2 qw 3/4	97	78	96	58	88	22	33	1	61.2	96.9	11.2	42.4
Bernardo A	Cohort	209	Further	Mixed	9.4	3			29.9	2.1	27.4	1.7	32.1	57.7		18

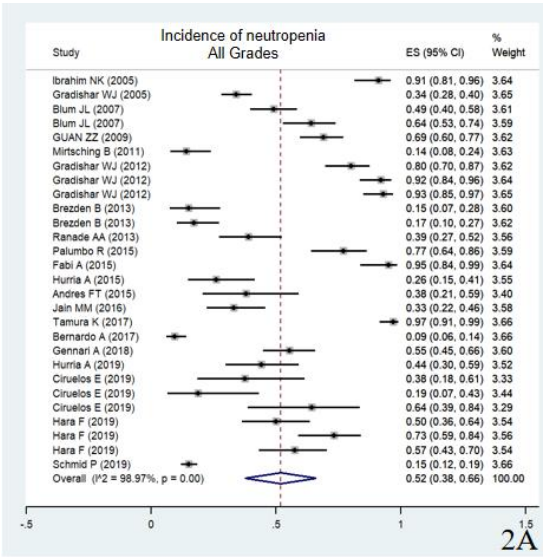
2017		68	Further	125mg/m^2 qw 3/4	8.7	1.1			17.4	2.2	12	1.1	31.5	54.3		16.9
		121	Further	260mg/m^2 q3w	9.9	4.2			38	2.1	37.3	2.1	32.4	59.9		18
Gennari A 2018	Phase II RCT	83	First	150mg/m^2 q2w	55.4	21.7			69.5	8		48.2	47	65.1	7.9	25.8
	Multicenter	86	First	100mg/m^2 qw 3/4	68.6	27.9			73.2	5.8		46.5	54.7	68.6	9	26.2
		86	First	75mg/m^2 qw	72.2	24.4			70	5.8		10.5	44.7	60.5	8.5	25.5
Marschner N 2018	Cohort Multicenter	697	Mixed	Mixed		4		7.5	39.6	4.3	20.8	1.3	37.2	68.3	5.9	15.6
		491	Mixed	≤150mg/m^2 qw									39.1	68.8	6	16.3
		194	Mixed	220-260mg/m^2 q3w									33	67.5	5.7	15.1
Hurria A 2019	Phase II Multicenter	40	Mixed	100mg/m^2 qw 3/4	44	11	18	3	10	5	55	5	35	75	6.5	21.2
Ciruelos E 2019	Phase II RCT	16	First	100mg/m^2 qw 3/4	37.5	0	50.1	6.3	81.3	0	43.9	6.3	37.5			
	Multicenter	14	First	150mg/m^2 q2w	18.8	0	25.1	6.3	62.6	0	87.6	0	12.5			
		16	First	150mg/m^2 qw 3/4	64.2	50	50	28.6	78.6	35.7	64.3	14.3	42.9			
Hara F 2019	Phase II RCT	48	Mixed	180mg/m^2 q3w	50	14.6	60.4	14.6	81.3	8.3	70.8	0	37.8		6.8	
	Multicenter	45	Mixed	220mg/m^2 q3w	73.3	37.7	77.8	26.6	84.4	8.9	77.8	0	44.1		7.3	
		47	Mixed	260mg/m^2 q3w	57.4	25.4	66	19.1	91.5	31.9	80.9	2.1	48.7		6.7	
Schmid P 2018/2019	Phase III RCT Multicenter	449	First	100mg/m^2 qw 3/4	15	8.2			23	2.7	44	3	45.9	72.4	5.5	18.7

administered at the dosage of 300 mg/m2, 621 patients (52.18%) were at 260 mg/m2, 100 patients (8.40%) were at 220 mg/m2, and 83 patients (6.97%) were at 180 mg/m2. Among 1966 MBC patients with weekly nab-paclitaxel schedule, 956 patients (48.62%) were administered at the dosage of 100mg/m2 qw 3/4, 247 patients (12.56%) were at 125mg/m2 qw 3/4, 186 patients (9.5%) were at 150mg/m2 qw 3/4, and 86 patients (4.4%) were at 75mg/m2 qw. Still, 491 MBC patients (24.97%) with weekly nab-paclitaxel monotherapy in the NABUCCO study were reported with administration at ≤150mg/m2 qw schedule.

Nab-paclitaxel monotherapy safety profiles

All 3287 MBC patients were included in the safety analysis. Neutropenia, leukopenia, peripheral sensory neuropathy and fatigue were the four chosen representative TRAEs of nab-paclitaxel monotherapy.

According to our study, 22 included studies with 31 individual groups reported the incidence of treatment related neutropenia after nab-paclitaxel monotherapy in 3287 MBC patients. After data integration, the overall incidence of all grades neutropenia was 52% (95% CI, 38%-66%), and the incidence of grade 3/4 neutropenia was 24% (95% CI, 16%-32%) (Figure 2A2B). 19 individual groups reported the incidence of chemotherapy related leukopenia with the overall incidence of all-grades leukopenia was 58% (95% CI, 43%-73%), and the incidence of grade 3/4 leukopenia was 17% (95% CI, 11%-24%) (Figure 2C2D). Together 3287 MBC patients in 31 individual groups reported the incidence of all grades and grade 3/4 peripheral sensory neuropathy. The overall incidence of all grades peripheral sensory neuropathy was 58% (95% CI, 48%-68%), and the incidence of grade 3/4 peripheral sensory neuropathy was only 8% (95% CI, 5%-10%) (Figure 2E2F). 27 individual groups reported the incidence of treatment related fatigue. The overall incidence of all grades fatigue was 49% (95% CI, 41%-56%), and the incidence of grade 3/4 fatigue was 5% (95% CI, 2%-8%) following nab-paclitaxel administration (Figure 2G2H).



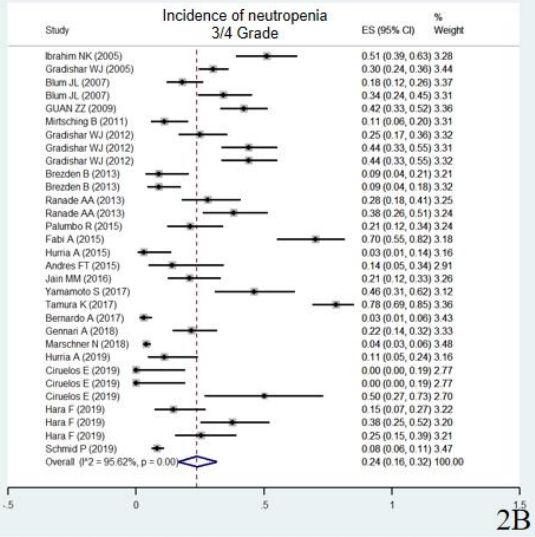
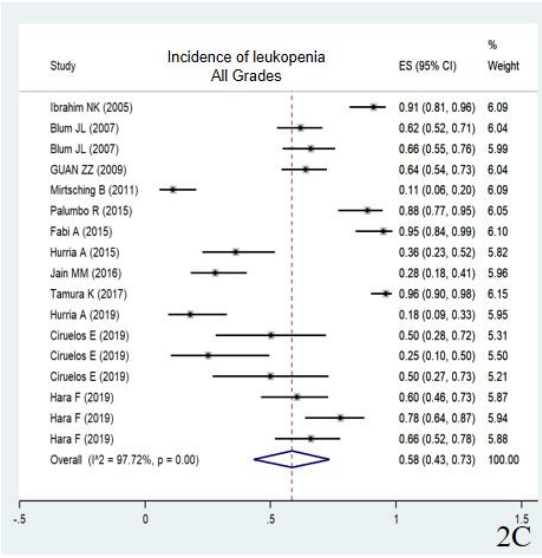


Figure 2A Incidence of all grades neutropenia

Figure 2B Incidence of grade 3/4 neutropenia



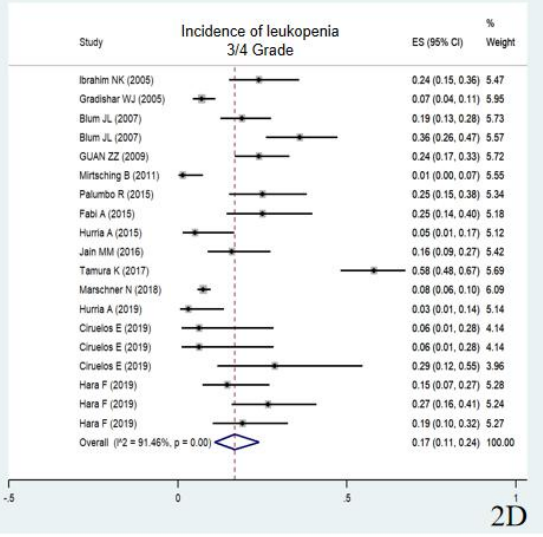


Figure 2C Incidence of all grades leukopenia

Figure 2D Incidence of grade 3/4 leukopenia

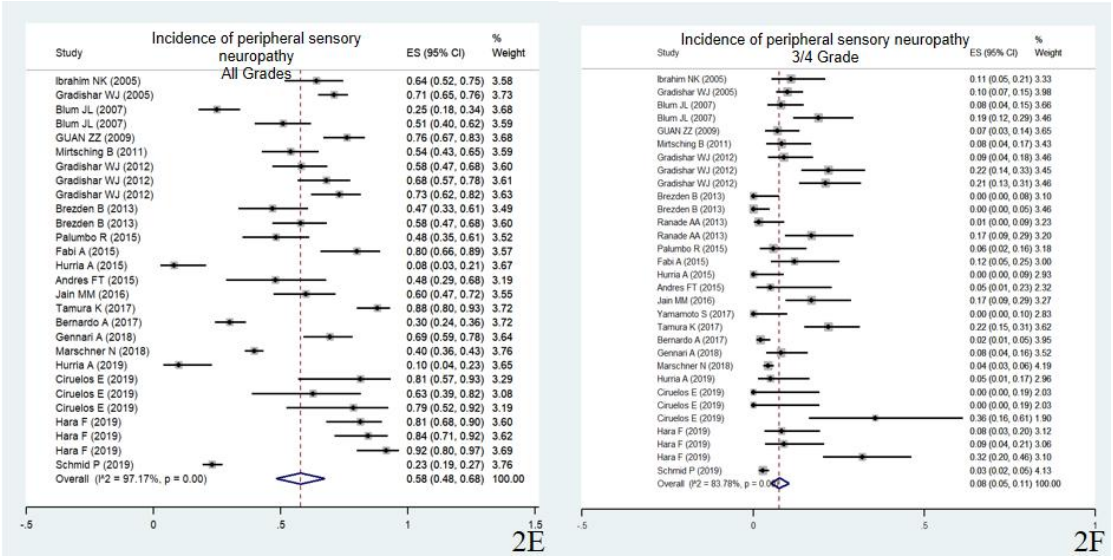


Figure 2E Incidence of all grades peripheral sensory neuropathy

Figure 2F Incidence of grade 3/4 peripheral sensory neuropathy

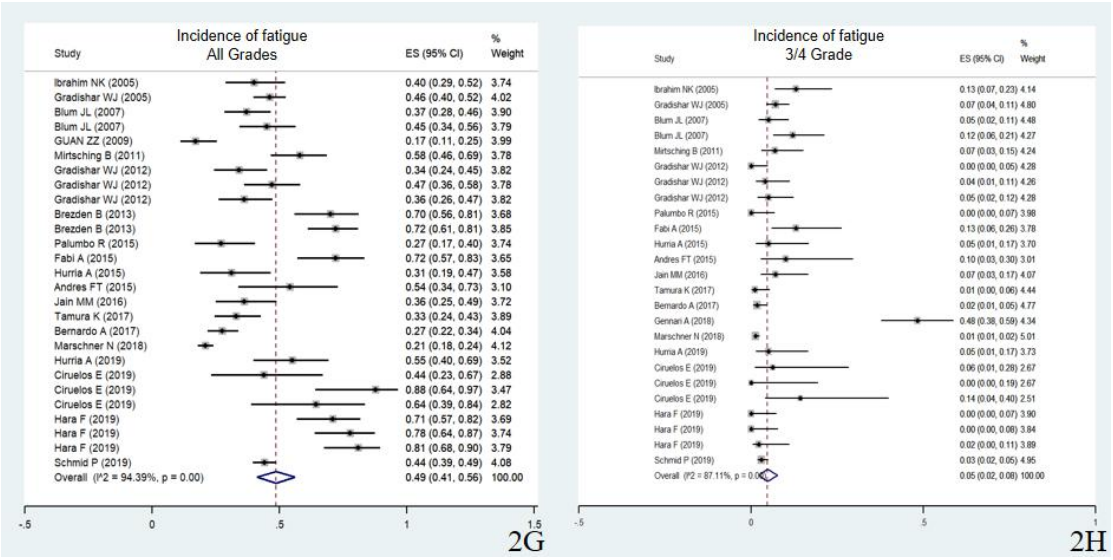


Figure 2G Incidence of all grades fatigue

Figure 2H Incidence of grade 3/4 fatigue

Risk factors affecting TRAEs

According to the results of meta-regression analysis, treatment lines, nab-paclitaxel dosage, nab-paclitaxel schedule did not affect the incidence of all grades neutropenia and grade 3/4 neutropenia. However, grade 3/4 neutropenia occured less frequently in Her-2 negative patients compared with all population (Coef value=0.063, *P*=0.046). All grades leukopenia seemed to occur more frequently in MBC patients treated with nab-paclitaxel as further-line therapy (Coef

value=0.366, *P*=0.056). Treatment lines, patient population, the schedule of nab-paclitaxel administration did not contribute to the development of all grades and grade 3/4 peripheral sensory neuropathy. However, the dosage of nab-paclitaxel monotherapy seemed to be a potential independent risk factor affecting the incidence of grade 3/4 peripheral sensory neuropathy (Coef value=0.201, *P*=0.078) as *P* value almost reached 0.05. Meanwhile, obvious clinical trend can be noted that grade 3/4 peripheral sensory neuropathy were more frequently recorded in patients with higher nab-paclitaxel dosage group compared with patients with lower dosage group (Figure 3A). Nab-paclitaxel related all grades fatigue occurred more frequently in MBC patients with further-line monotherapy (Coef value=-0.239, *P*=0.032).

Nab-paclitaxel monotherapy efficacy outcomes

All 3287 MBC patients were included in the efficacy analysis. ORR, CBR, PFS, and OS were the chosen efficacy endpoints index of nab-paclitaxel monotherapy.

33 individual groups reported the ratio of ORR as the major efficacy of nab-paclitaxel monotherapy. After data integration, the cumulative ratio of ORR was 40% (95% CI, 35%-45%). 25 individual groups reported the ratio of CBR with the cumulative ratio being 66% (95% CI, 59%-73%). Additionally, complete remission (CR) was noted in 23 individual groups and the cumulative ratio of CR was only 3% (95% CI, 2%-5%). Partial remission (PR) and stable disease (SD) were higher than CR with the cumulative ratio reaching 38% (95% CI, 32%-44%) and 28% (95% CI, 24%-31%), respectively.

23 individual groups with 2399 MBC patients reported the outcome of PFS after nab-paclitaxel monotherapy. The median PFS ranged from 3.7 to 14.6 months and the overall median PFS was 7.64 months (95% CI, 6.89-8.40 months). The outcome of OS was reported in 14 studies with 17 individual groups containing 2472 MBC patients. The median OS ranged from 15.2 to 44.7 months and the overall median OS was 24.51 months (95% CI, 21.25-27.78 months).

Risk factors affecting efficacy outcomes

According to the meta-regression analysis, we found that patients treated with nab-paclitaxel monotherapy in further line would suffer from unfavorable lower ORR (Coef value=-0.18, *P*=0.006) compared with the patients in other lines. In the subsequent subgroup analysis, the value of ORR was 48.2% (95% CI, 41%-45%) in patients treated with nab-paclitaxel in the first line, while 40.1% (95% CI, 35.1%-45%) in the mixed line (first or further line), and 27.2% (95% CI, 20.1%-34.3%) in the further line. Similar result and statistical significance were also obtained concerning to CBR (Coef value=-0.176, *P*=0.037), with CBR valued 55.3% (95% CI, 43.2%-67.4%) in the further line, 68.7% (95% CI, 62.5%-75%) in the first line, and 68.8% (95% CI, 63.5%-74%) in the mixed line. The schedule of nab-paclitaxel administration (weekly, biweekly or triweekly) did not affect the ORR (Coef value=-0.212, *P*=0.116). However, under the same schedule of nab-paclitaxel administration, patients appeared to have more superior ORR along with the increasing dosage of nab-paclitaxel (Coef value=0.081, *P*=0.044) (Figure 3B).

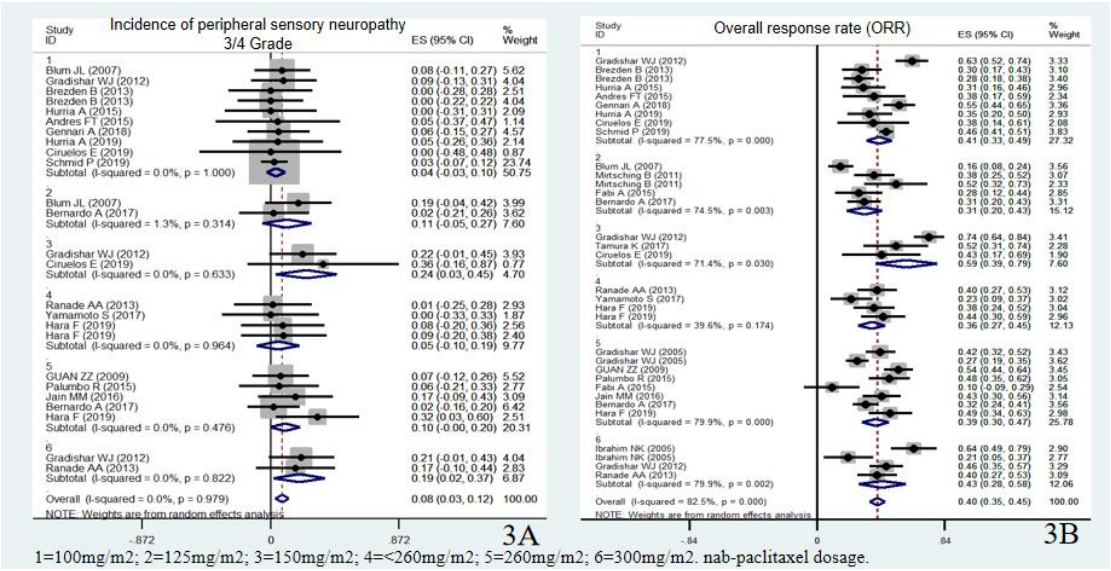


Figure 3A Incidence of grade 3/4 peripheral sensory neuropathy related to different nab-paclitaxel dosage

Figure 3B Overall response rate related to different nab-paclitaxel dosage

Patients who received first line nab-paclitaxel monotherapy was demonstrated to have longer median PFS versus mixed line therapy. The median PFS was 8.01

months (95% CI, 6.83-9.18 months) in the first line group and 6.55 months (95% CI, 5.69-7.4 months) in the mixed line group, respectively. Patients who received further line nab-paclitaxel monotherapy was demonstrated to have rather shorter median OS versus first and mixed line therapy. Median OS values were 16.18 months (95% CI, 13.41-18.94 months), 24.41 months (95% CI, 20.4-28.42 months), and 28.44 months (95% CI, 12.75-44.13 months) by further, first, and mixed line therapy, respectively. Similarly, just like the ORR, the schedule of nab-paclitaxel administration (weekly, biweekly or triweekly) did not affect the median PFS (Coef value=-2.77, *P*=0.162) and median OS (Coef value=6.27, *P*=0.623). Median PFS was 6.94 months (95% CI, 5.92-7.96 months) for weekly and 7.71 months (95% CI, 6.90-8.52 months) for q3w nab-paclitaxel monotherapy. However, under the same schedule of nab-paclitaxel administration, patients appeared to have longer PFS along with the increasing dosage of nab-paclitaxel (Coef value=2.68, *P*=0.03). This significance was not found with respect to the median OS (Coef value=6.27, *P*=0.62). Risk factors affecting nab-paclitaxel monotherapy related adverse events and efficacy outcomes were presented in Table 3.

Table 3 Risk factors affecting nab-paclitaxel monotherapy related adverse events and efficacy outcomes by meta-regression analysis

Effect Index	Risk Factors	Coef. value	Std. Err.	T value	*P* value	95% Confidence Interval
Incidence of neutropenia 3/4 grade	Her2 negative	-0.136	0.063	-2.14	0.046	-0.268 to -0.003
Incidence of leukopenia all grades	Treatment line	0.366	0.148	2.48	0.056	-0.014 to 0.746
Incidence of neuropathy 3/4 grade	Nab-paclitaxel dosage	0.201	0.107	1.87	0.078	-0.025 to 0.427
Incidence of fatigue all grades	Treatment line	-0.239	0.100	-2.40	0.032	-0.455 to -0.024
Overall response rate (ORR)	Treatment line	-0.180	0.059	-3.03	0.006	-0.302 to -0.058
	Nab-paclitaxel dosage	0.171	0.081	2.11	0.044	0.005 to 0.338
Clinical benefit rate (CBR)	Treatment line	-0.176	0.077	-2.29	0.037	-0.340 to -0.012
Progression free survival (PFS)	Treatment line	1.398	0.635	2.20	0.045	0.036 to 2.760
	Nab-paclitaxel dosage	2.683	1.114	2.41	0.030	0.295 to 5.071
Overall survival (OS)	Treatment line	-18.909	8.210	-2.30	0.040	-36.797 to -1.021

DISCUSSION

Taxanes are regarded as the most widely used and effective single antitumor agents in the treatment of metastatic breast cancer [38]. Although proven beneficial, the solvent-based toxicities and high incidence of TRAEs restricted the long-term maintenance therapy of paclitaxel and docetaxel. Nab-paclitaxel, a relatively younger member of taxanes family, has gained increasing favor in treating MBC due to its special antitumor characteristics and low toxicities in the past 15 years. Although a proportion of studies reported nab-paclitaxel monotherapy with acceptable safety profiles, higher disease control rates and improved survival in the management of MBC [9, 16, 39, 40], no systematic data was provided. These limitations could pose a specific question what exactly nab-paclitaxel monotherapy could provide for MBC patients concerning to both TRAEs and clinical benefits.

In our study, the safety profiles of nab-paclitaxel mono-treatment were firstly analyzed. It was known that neutropenia and leukopenia were the most common hematologic adverse events (AEs) of nab-paclitaxel, and some authors even reported the incidence of grade 3/4 neutropenia after nab-paclitaxel monotherapy could be higher than 50% [14]. Actually, according to our analysis, after integrating each single individual group, the overall incidence of all grades neutropenia and leukopenia was 52% and 58%, the incidence of grade 3/4 neutropenia and leukopenia was 24% and 17%, respectively. Furthermore, across to the majority of studies, these hematologic adverse events were generally considered uncomplicated and could be rapidly resolved after treatment interruption, dose reduction and granulocyte colony-stimulating factor (G-CSF) supplement. Although neutropenia and leukopenia were known as dose-limiting, we found the incidence of all grades and grade 3/4 neutropenia and leukopenia were not correlated with the nab-paclitaxel dosage and schedule which indicated neutropenia or leukopenia might not be a dose or schedule-dependent adverse event. We still found that Her2 expression status seemed to be correlated with the incidence of grade 3/4 neutropenia, as the incidence of 3/4 grade neutropenia was significantly lower in the Her2-negative population, however, this reason was still unknown yet.

Peripheral sensory neuropathy is a common and a specific adverse event of taxanes-based therapy. In our analysis, following nab-paclitaxel monotherapy, the overall incidence of all grades peripheral sensory neuropathy was 58%, and grade 3/4 neuropathy was 8%. Interestingly, unlike hematologic AEs, we found that the nab-paclitaxel dosage seemed to be a potential risk factor affecting the incidence of grade 3/4 peripheral sensory neuropathy. Although statistical significance had not obtained, relatively obvious trend could be noted that grade 3/4 peripheral sensory neuropathy were more frequently recorded in patients with higher nab-paclitaxel dosage group compared with patients with lower dosage group. Furthermore, in the fixed weekly or triweekly nab-paclitaxel monotherapy, the incidence of grade 3/4 peripheral sensory neuropathy increased if nab-paclitaxel dosage increased. This was in accordance with the results of Ciruelos E as they found the grade 3 peripheral neuropathy was deemed to be taxanes-related, which is known to be cumulative [35].

Concerning to the efficacy outcomes, our analysis showed nab-paclitaxel monotherapy could provide a 40% ORR, a 60% CBR, a median PFS of 7.64 months and a median OS of 24.51 months for the overall population of patients with MBC who received various doses, schedules, and regimens of nab-paclitaxel across all lines of therapy. Still, in MBC patients who received nab-paclitaxel monotherapy in the first line treatment, the nab-paclitaxel efficacy outcomes could be more encouraging with a 48.2% ORR, a 68.7% CBR, a median PFS of 8.01 months and a median OS of 24.41 months. These results are more superior than the previous real-life study with sizeable sample, which showed a median time to next therapy or death (TNTD) of 6.1 months, a median OS of 17.4 months in patients receiving nab-paclitaxel monotherapy for ≥ first-line treatment of MBC [19]. In the current study, we proved treatment line and nab-paclitaxel dosage were the risk factors affecting ORR and median PFS. Patients treated with nab-paclitaxel monotherapy in further or mixed line would endure lower ORR and shorter median PFS compared with patients in first line, and patients appeared to have better ORR or longer PFS along with the increasing dosage of nab-paclitaxel.

Nab-paclitaxel can be used as a triweekly schedule, but it is also justifiable to

administer it in various weekly schedules in metastatic MBC. It is particular true that different opinions exist among the experts regarding the optimal schedule of nab-paclitaxel [41]. Findings from a randomized study by Gradishar in 2009 suggested that nab-paclitaxel provided weekly for 3 weeks at a dose of 150 mg/m2 followed by 1 week of break is more effective in terms of PFS than is 100 mg/m2 nab-P provided weekly [11]. In our study, we find that weekly administration schedule was more frequently used compared with triweekly schedule. However, according to our analysis, no matter which nab-paclitaxel schedule (weekly, biweekly or triweekly) was chosen, the nab-paclitaxel efficacy outcomes were not affected. The recently published NABUCCO study also showed no differences in terms of clinical activity of nab-paclitaxel according to the schedule used [10]. This finding is of particular interest for the clinical practice. As the schedule of nab-paclitaxel administration is not proven to be corelated with the efficacy outcomes, we suggested that nab-paclitaxel can be safely used with the weekly as well as the triweekly schedule, leaving the choice to the physician according to the patient's needs and preference, with a careful balance between activity and potential toxicity. In a word, nab-paclitaxel offers flexible scheduling. Moreover, treatment line rather than the nab-paclitaxel dosage was demonstrated to be the only risk factor affecting median OS. Indeed, assessment of OS was considered to be more objective than PFS. These findings might partially guide us how nab-paclitaxel could be used in clinical practice on the basis of the current data, that is for patients with higher tumor burden (visceral metastatic disease or > 2 metastatic lesions) who needs immediate disease control could receive maximum-tolerated dosage of nab-paclitaxel, such as 300mg/m2 q3w or 150 mg/m2 qw 3/4. These regimens would bring patients with better ORR and longer PFS, but the overall survival might not be changed.

In this systematic review and meta-analysis, we demonstrated nab-paclitaxel mono-chemotherapy was a low-toxic and effective strategy in palliative management for MBC patients. Both weekly and triweekly nab-paclitaxel mono-chemotherapy were proved to be effective for MBC. Higher ORR, longer PFS and OS would be

achieved in patients treated with nab-paclitaxel as first line. Increasing nab-paclitaxel dosage would result in better tumor control (higher ORR and PFS), however, changing nab-paclitaxel schedule had no benefit on ameliorating the survival outcomes.

Conclusions

According to our research, the following conclusions can be drawn: (1) Both weekly and triweekly nab-paclitaxel mono-chemotherapy were proved to be effective for MBC with generally reasonable toxicity profiles. (2) Higher ORR, longer PFS and OS would be achieved in patients treated with nab-paclitaxel as first line. (3) Increasing nab-paclitaxel dosage would result in better tumor control (higher ORR and PFS).(4) Changing nab-paclitaxel schedule had no benefit on ameliorating the survival outcomes. In general, nab-paclitaxel has a distinct advantage in the treatment of MBC, which can be a superior option in clinical strategy.

Ethical approval and Consent to participate Not applicable.

Consert for publication Written informed consent for publication was obtained from all participants.

Availability of supporting All data are fully available without restriction.

Conflict of interest None of the authors have the potential competing interests in this manuscript.

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Authors' contributions

Research design Chengxiang Shan.

Systematic search and Study selection Chengxiang Shan and Haili Lu.

Data analysis and interpretation Chengxiang Shan.

Initial manuscript writing Chengxiang Shan, Haili Lu, Siluo Zha and Wei Zhang.

Manuscript revision All authors.

Final approval of manuscript All authors.

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Figures

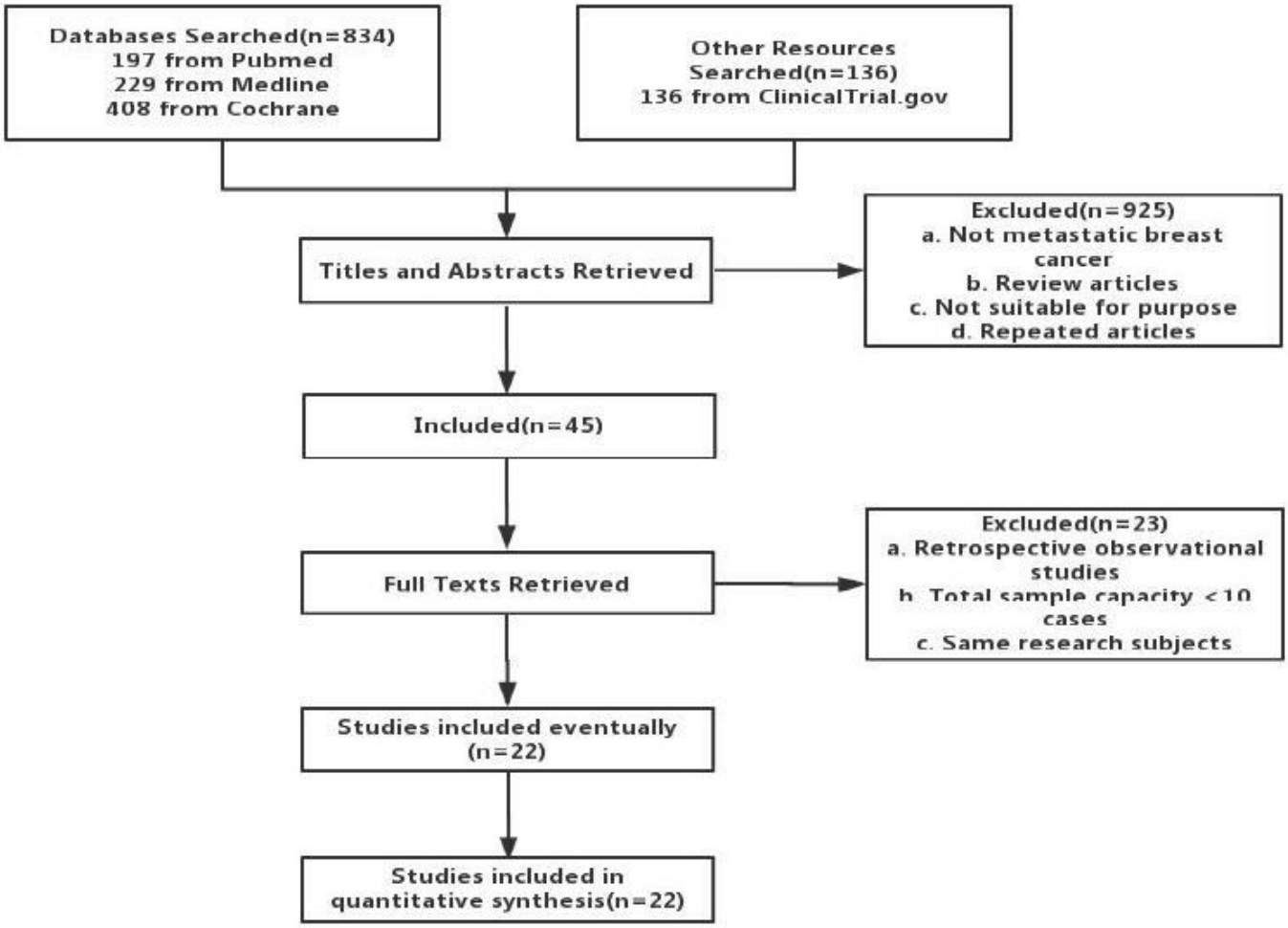

Figure 1

Study retrieval flow diagram

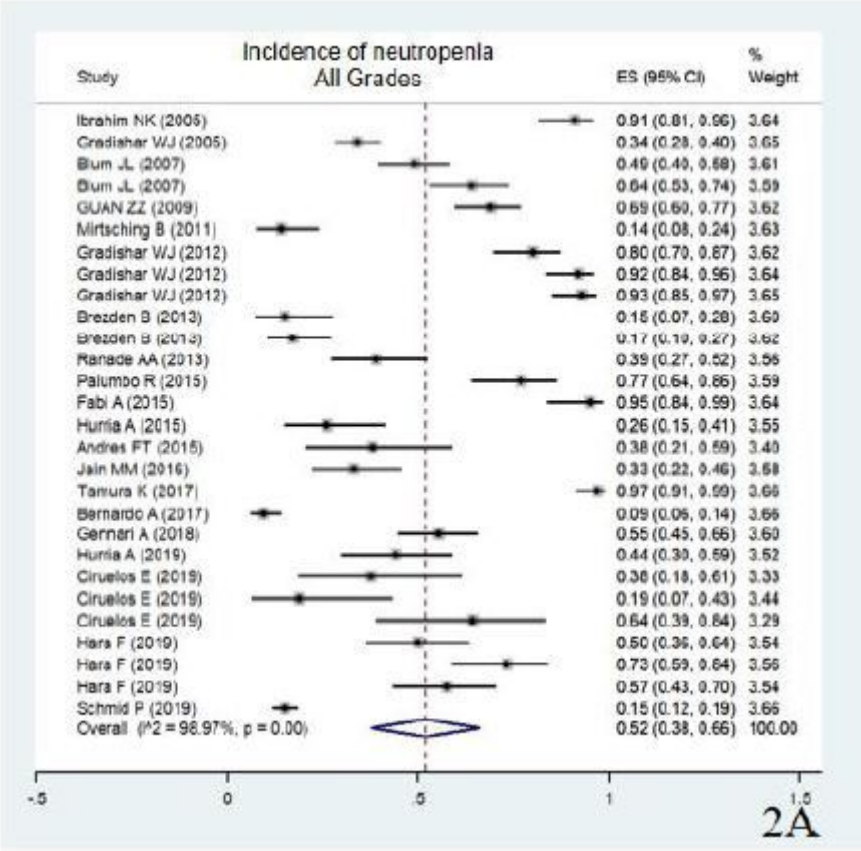

Figure 2

2A Incidence of all grades neutropenia

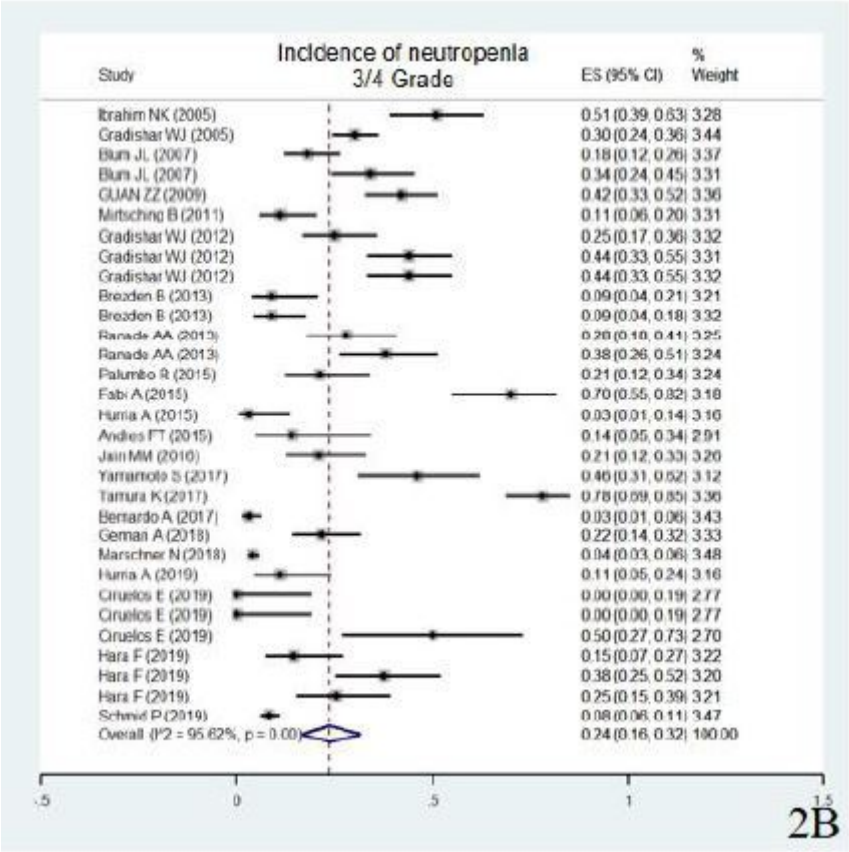

Figure 3

2B Incidence of grade 3/4 neutropenia

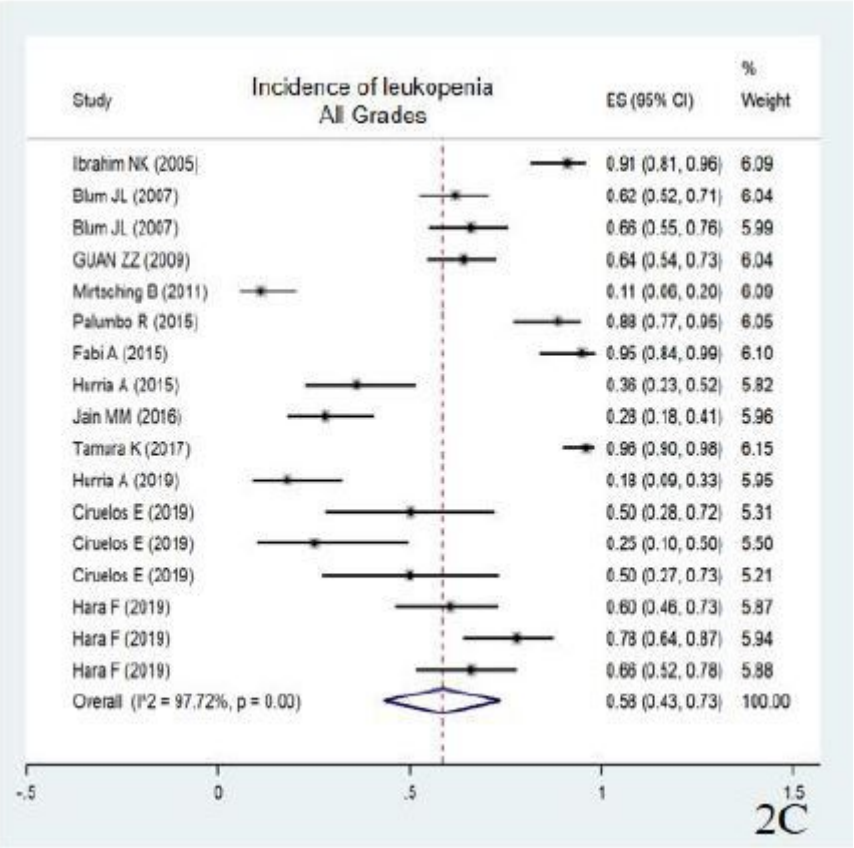

Figure 4

2C Incidence of all grades leukopenia

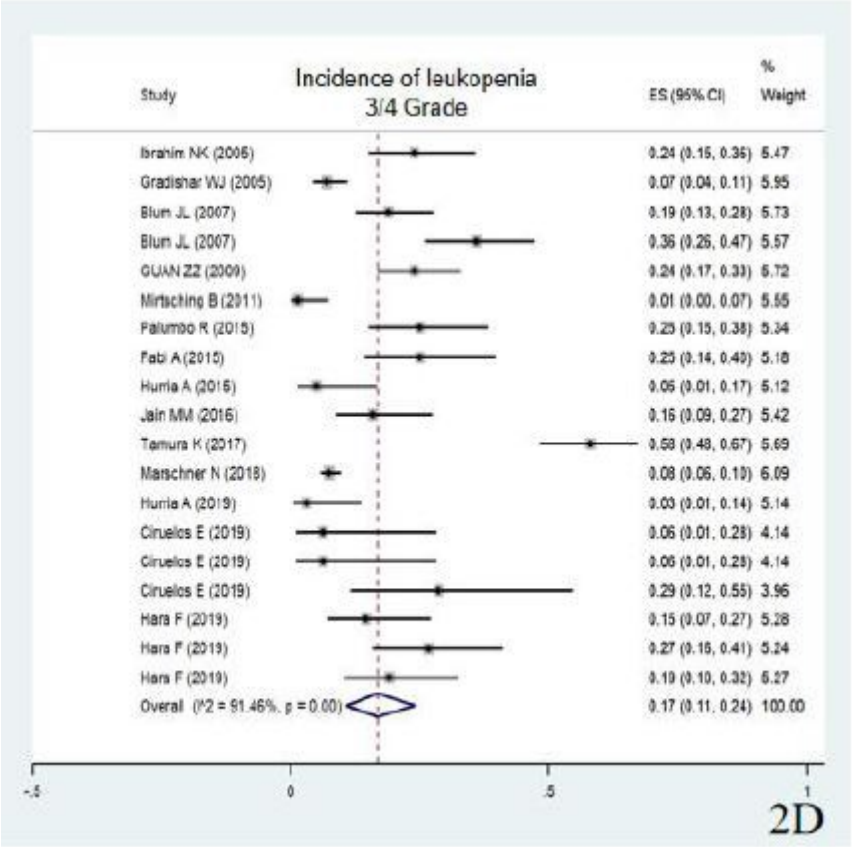

Figure 5

2D Incidence of grade 3/4 leukopenia

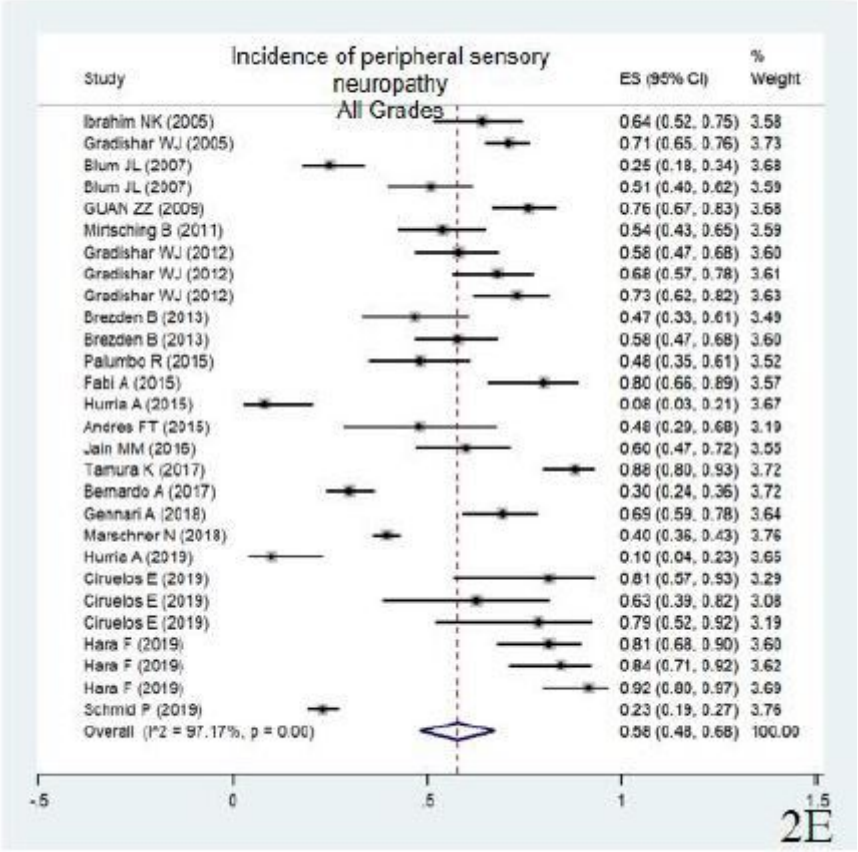

Figure 6

2E Incidence of all grades peripheral sensory neuropathy

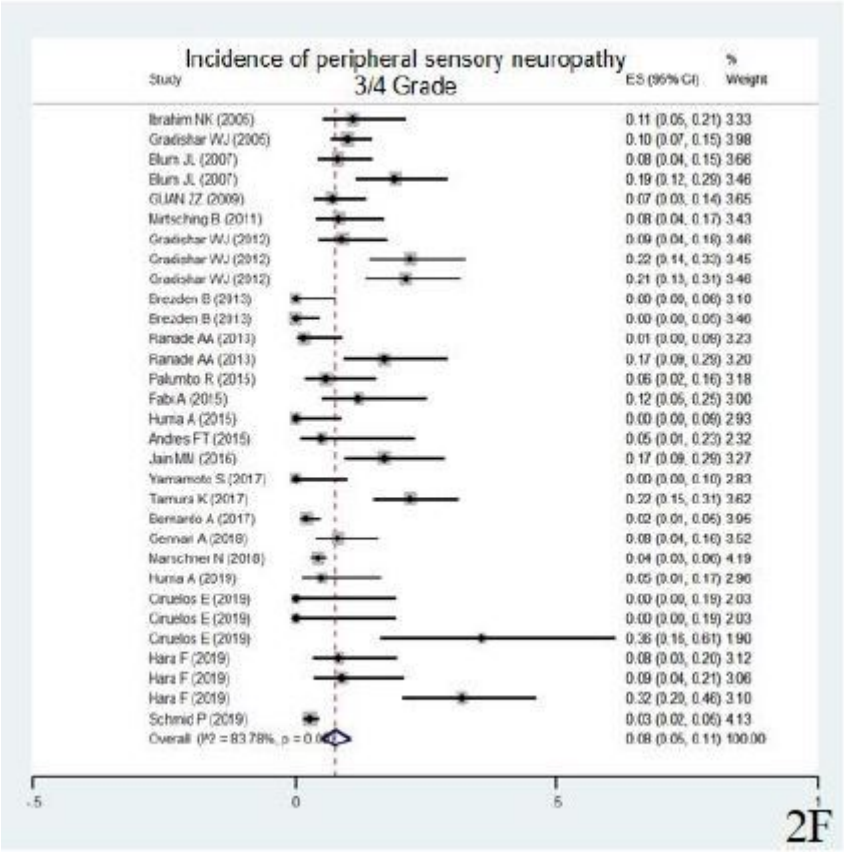

Figure 7

2F Incidence of grade 3/4 peripheral sensory neuropathy

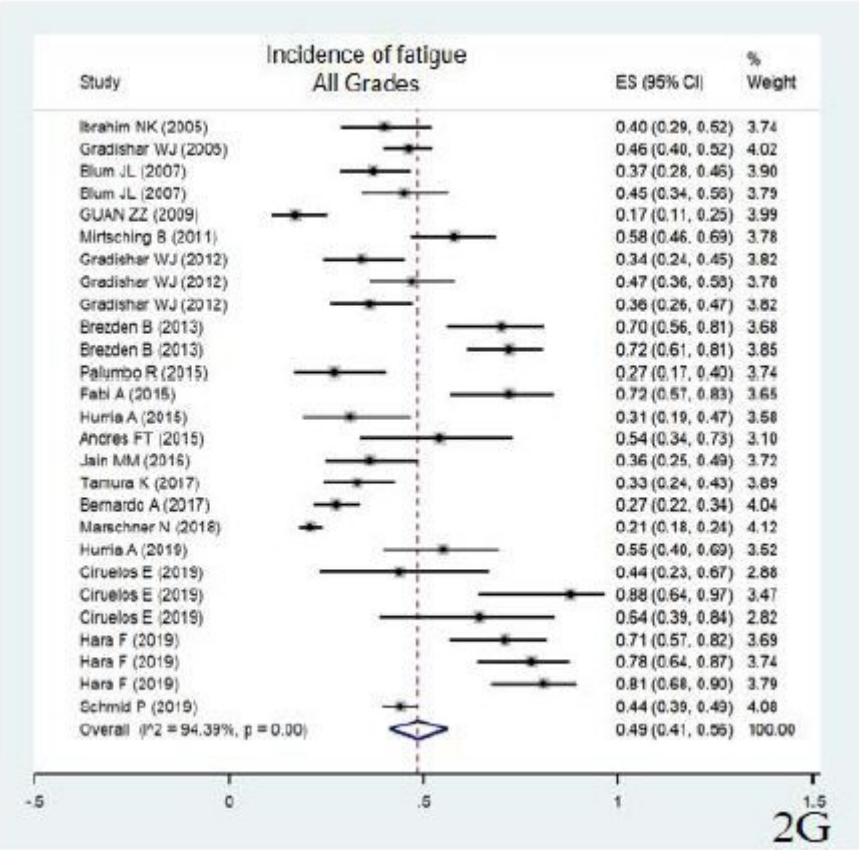

Figure 8

2G Incidence of all grades fatigue

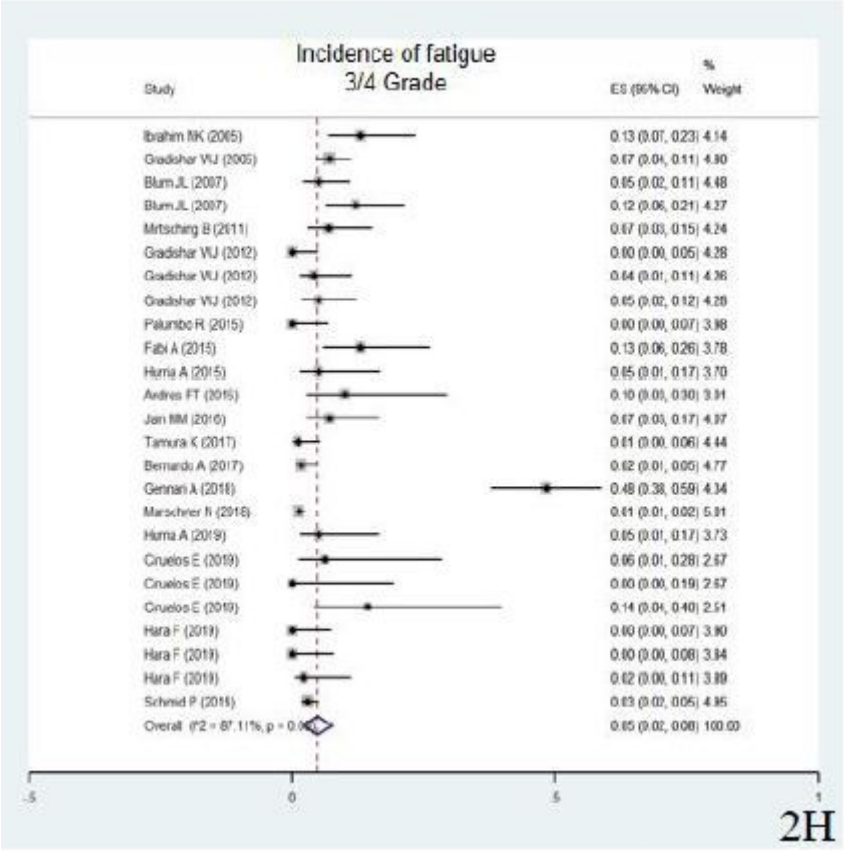

Figure 9

2H Incidence of grade 3/4 fatigue

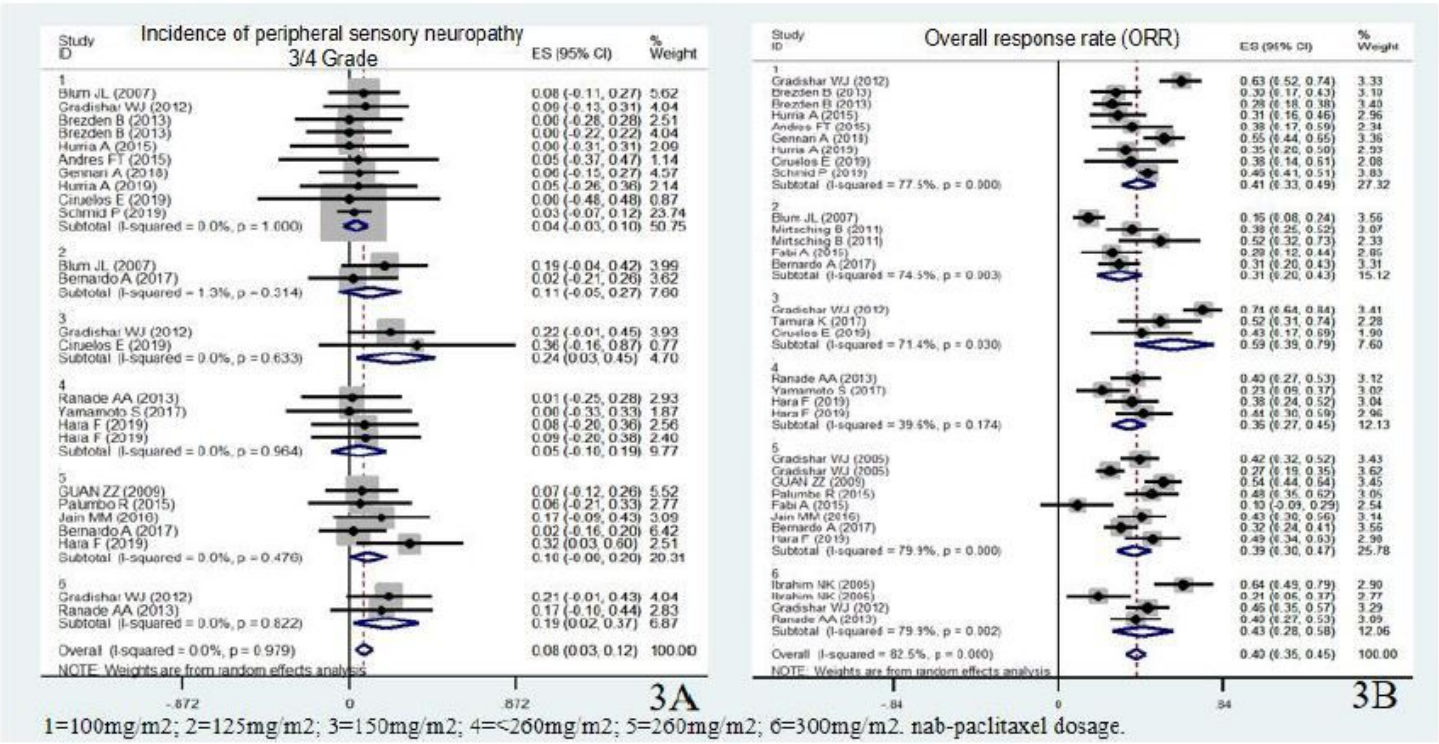

Figure 10

3A Incidence of grade 3/4 peripheral sensory neuropathy related to different nab-paclitaxel dosage 3B Overall response rate related to different nab-paclitaxel dosage