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ORIGINAL ARTICLE

Model-Based Meta-Analysis for Quantifying Paclitaxel Dose Response in Cancer Patients

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Model-based meta-analysis of dose response is a sophisticated method to guide dose and regimen selection. In this report, the effects of paclitaxel dose and regimen (weekly or every 3 weeks) on the efficacy and safety in cancer patients were quantified by model-based meta-analysis of 29 monotherapy trials. Logistic regression models were developed to assess the relationship between dose and objective response rate or neutropenia rate. Survival models were developed to assess the relationship between dose and overall survival or progression-free survival. Paclitaxel efficacy (e.g., objective response rate, median overall survival, and progression-free survival) is correlated with average dose per week (mg/m^2/week), whereas safety (e.g., neutropenia rate) is correlated with dose per administration (mg/m^2). Weekly paclitaxel regimen at 65–80 mg/m^2 is supported to have comparable to better efficacy and lower neutropenia incidence than an every-3-week regimen at 175 mg/m^2.

Paclitaxel is a potent mitotic inhibitor that is an effective chemotherapy for treating solid tumors.[1–4] It is widely used to treat breast cancer (BC), both in adjuvant and metastatic settings,[5–8] with an approved dose of 175 mg/m^2 every 3 weeks (q3w).[4]

An optimal dose and schedule is important for obtaining the best safety–efficacy profile for chemotherapeutic agents. Based on the Norton–Simon's hypothesis (i.e., chemotherapy results in a rate of regression of tumor volume which is proportional to the rate of growth of an unperturbed tumor of that size), dose-dense therapy is considered to be more efficacious for cancer treatment, which could minimize tumor regrowth between cycles of chemotherapy.[9–11]

Recent clinical studies have shown that dose-dense paclitaxel administration (e.g., weekly or qw regimen) had better efficacy than q3w regimen.[12–15] Clinical trials of qw paclitaxel in BC have demonstrated promising efficacy and acceptable tolerability.[16–20] A randomized phase III trial[14] reported that qw paclitaxel is more effective than q3w administration in metastatic BC. The neoadjuvant study found that BC patients receiving qw paclitaxel had a higher pathologic complete response rate than patients with q3w schedule.[13] The Intergroup E1199 BC adjuvant study that compared qw to q3w paclitaxel (and docetaxel) after four cycles of doxorubicin and cyclophosphamide showed a significant improvement in disease-free survival favoring the weekly schedule of paclitaxel.[15] Katsumata *et al.*[21] highlighted the long-term results of dose-dense paclitaxel and carboplatin for ovarian cancer treatment in which after a median follow-up of 76.8 months, median progression-free survival (PFS) and overall survival (OS) were significantly longer in the dose-dense treatment group than in the conventional treatment group.

Besides therapeutic benefits for efficacy, weekly dosed taxanes were reported to be associated with a lower incidence of febrile neutropenia.[22–25] Seidman *et al.*[14] reported that improved efficacy of the qw regimen was accompanied by increased neurotoxicity but did not influence overall quality-of-life scores. In general, qw regimen appears well tolerated.[16–20]

Meta-analysis refers to methods of contrasting and combining results from different studies for identifying patterns among study results, sources of disagreement among those results, or other interesting relationships that may be revealed in the context of multiple studies.[26] For clinical trial data, meta-analysis of summary-level efficacy and safety data from multiple trials provides a quantitative framework for comparative efficacy and safety assessment.

For dose-dense therapy, in addition to running clinical trials for direct comparison of efficacy and safety, a systemic review and meta-analysis of randomized controlled trials was reported to assess dose-dense chemotherapy (including various regimens) in BC.[27] The results suggest that dose-dense chemotherapy yields better overall and disease-free survival, particularly in women with hormone receptor-negative BC. By using meta-analysis for paclitaxel-containing chemotherapy, efficacy and safety of q3w vs. qw paclitaxel in different cancer types and treatment settings were compared.[28–30] The analyses by Ginés *et al.*,[29] using 17 trials in BC patients, and Huang and Campbell,[30] using 5 trials in non–small-cell lung cancer (NSCLC) patients, suggested that weekly paclitaxel has a trend to provide better efficacy. Gao *et al.*[28] reported that qw regimens had similar OS and PFS rates as q3w regimen in NSCLC patients from five trials. Huang and Campbell,[30] by summarized data from 10 trials in solid tumors, reported that grade 3–4 neutropenia and grade 3 peripheral sensory neuropathy incidences were observed less frequently after qw paclitaxel dosing when compared with the q3w regimen. Gao *et al.*[28] reported that the q3w regimen had more frequent adverse events (AEs) than qw in NSCLC patients.

Together, most of the clinical trials and meta-analysis which evaluated efficacy and safety for dose-dense paclitaxel suggested a trend of larger therapeutic window and a better

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safety–efficacy profile for qw paclitaxel compared with q3w regimen and provided support for the Norton–Simon hypothesis. The meta-analysis reviewed above summarized data across q3w vs. qw regimens but not across different paclitaxel doses. The optimal dose and schedule for a chemotherapeutic agent can make the difference between a good and a poor response or even between success and failure.[12] It is important to quantify not only the effects of treatment but also the effects of dose and regimen on the response outcomes, using model-based meta-analysis (MBMA).[31] To date, no quantitative relationship using summary-level efficacy and safety data across trials has been established between different paclitaxel dose and regimen vs. efficacy or safety end points. It is important to explore this relationship based on literature data on paclitaxel monotherapy to guide the selection of dosing regimens in clinical practice, provide reference for evaluating the safety and efficacy of new molecular entities when given in combination with paclitaxel, and provide an estimation of efficacy and safety for a historical control arm of paclitaxel monotherapy.

MBMA for an exposure–response analysis in oncology trials has rarely been reported, potentially due to significant heterogeneity across trials. This paper is the first report to summarize the quantitative relationship between the paclitaxel dosing regimen and efficacy/safety in cancer patients using a mixed-effect modeling approach, based on the summary-level efficacy and safety data from 29 published paclitaxel monotherapy trials. The MBMA approach reported here for dose–response analysis is applicable for other oncology drugs.

RESULTS

Literature database for paclitaxel monotherapy
The clinical outcome database with paclitaxel monotherapy was used for this analysis. Forty-nine phase I, II, and III trials from 55 publications, encompassing 95 treatment arms and trial summary information for 4,244 patients, were included in the database. In total, 35 trials were conducted in BC patients and the other 14 trials were conducted in ovarian, glioblastoma, lung, or mixed patient populations with different tumor types. Among the 49 trials, 28 trials involving 2,926 patients received 120–250 mg/m² q3w doses of paclitaxel monotherapy and

19 trials involving 1,283 patients received 60–150 mg/m² qw doses of paclitaxel monotherapy. In another two trials involving 35 patients, paclitaxel was administered only once at various dose levels (49.5, 75, 105, 135, 180, or 825 mg/m²). For MBMA, objective response rate (ORR), OS, and PFS were selected as the three representative efficacy end points. Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity for paclitaxel.[4] Incidence of neutropenia was selected as a representative safety event. A total of 29 trials (**Supplementary Information Part III**) containing data for ORR, OS, PFS, and/ or neutropenia rates were used for MBMA (**Table 1**). All studies included for analysis used the Cremophor EL containing formulation for paclitaxel.

Model-based meta-analysis
ORR analysis. The model correlating paclitaxel dosing regimen with ORR was developed from the data set including 29 trials, with 35 treatment arms involving 3,070 BC patients (**Table 1**). Exploratory plots suggested that ORR correlated

Table 1 Overview of paclitaxel trials included in the model-based meta-analysis of dose–response

End points	ORR	OS	PFS	Neutropenia rate
No. of trials	29	15	16	24
qw	13	6	9	11
q3w	16	9	7	13
Dose range (mg/m²)	80–250	80–250	80–250	70–250
qw dose range (mg/m²)	80–100	80–100	80–100	70–150
q3w dose range (mg/m²)	135–250	135–250	135–250	140–250
Breast carcinoma/ mixed or others	29/0	15/0	16/0	21/3
No. of arms	35	19	20	35
No. of patients	3,070	2,749	2,693	1,886
Treatment duration (weeks)				
Median (range)	19 (3–271)	51 (3–300)	39 (1–185)	16 (8–271)
Percentage of patients receiving prior chemotherapy (%)				
Median (range)	69 (0–100)	70 (0–100)	69 (0–99)	68 (0–100)

ORR, objective response rate; OS, overall survival; PFS, progression-free survival; qw, weekly; q3w, every 3 weeks.

Table 2 Parameters estimated for the meta-analysis of the final dose–response model (**Equations 1–4 in Supplementary Information Part I** define the parameters for the models and example scripts are provided in Supplementary Information Part II)

Parameters (units)	ORR	OS	PFS	Neutropenia rate (grade 2, 3, and 4)	Neutropenia rate (grade 3 and 4)
Dose unit	mg/m²/week	mg/m²/week	mg/m²/week	mg/m²	mg/m²
Intercept, e_0 (% response)	15.3 (26.4)	1.17 (1.8)	3.36 (2.0)	0.62 (7.17)	0.55 (9.77)
Linear slope, k (1/dose unit)	0.0146 (39.7)	−1.4 (22.3)	−0.821 (18.7)	–	–
Maximum drug effect, E_{max} (% response)	–	–	–	99.9 (fix)*	99.9 (fix)*
Dose for reaching 50% E_{max}, ED_{50} (mg/m²)	–	–	–	69.4 (7.47)	82.3 (13.0)
Hill coefficient, γ	–	–	–	3.03 (35.5)	2.28 (23.8)
SD of intertrial variability (%)	48.6 (16.6)	21.4 (27.8)	24.8 (17.9)	59.9 (18.7)	52.6 (18.4)
SD of residual variability (%)**	4.32	5.53	5.34	10.7	8.91

Parameter estimates are reported in mean (% RSE).
ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RSE, relative SE.
*Fix to 100% neutropenia based on observed data (use 99.9% for logit scale computation).
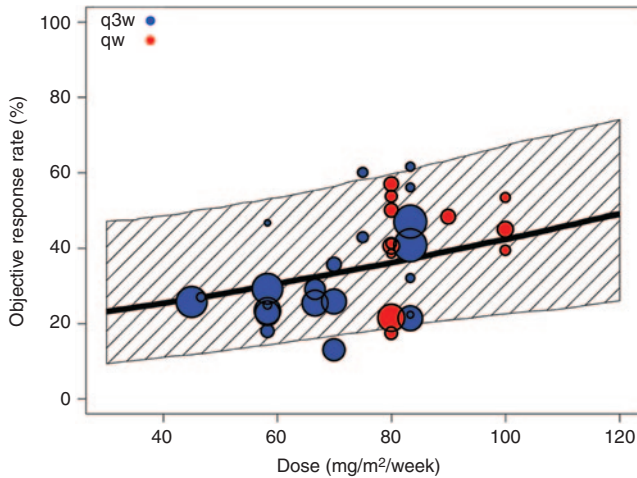**SD of the difference between each observed and model-predicted values for each data point used in modeling.

Figure 1 Observed and model-predicted objective response rate vs. paclitaxel dose per week (mg/m^2/week). Black solid line represents typical model prediction and dashed area represents 95% prediction interval. Points represent observed values with size indicating relative patient numbers in each arm.

with average paclitaxel dose per week (mg/m^2/week) but not with the dose per administration of paclitaxel (mg/m^2). Using a linear logistical regression model, the probability of objective response linearly increases with average paclitaxel exposure in mg/m^2/week with the slope significantly different from zero (**Table 2**). Covariate analysis suggested that dose frequency (qw vs. q3w), percentage of patients who received prior chemotherapy, and treatment duration were not significant covariates of the model. The model prediction of ORR vs. average paclitaxel dose (mg/m^2/week) and its 95% prediction interval (PI) are illustrated in **Figure 1**, with observed data overlaid in the plot. The simulated change of ORR with average dose matched the overall trend and spread of the observed data.

OS and PFS analysis. OS and PFS parametric proportional hazard models were developed separately using the digitized survival data of BC patients collected in the database. The dosing regimen vs. OS model was developed from 15 trials involving 19 treatment arms and 2,749 BC patients, and the dosing regimen vs. PFS model was developed from 16 trials involving 20 arms and 2,693 patients (**Table 1**). Exploratory plots suggest that the qw regimen had a better median OS and PFS compared with the q3w regimen. Similar to ORR, median OS and PFS correlated with paclitaxel dose per week (mg/m^2/week) but not with the dose level of paclitaxel (mg/m^2). Parametric proportional hazard models with the baseline hazard assumed to be constant across time was found to well describe the OS or PFS profiles after paclitaxel treatment. The logarithmic hazard functions of OS or PFS were found to linearly correlate with average paclitaxel doses in mg/m^2/week, with the slope significantly different from zero (**Table 2**). Covariate analysis suggested that dose frequency (qw vs. q3w) and percentage of patients who received prior chemotherapy were not significant covariates in the OS or PFS models. The model simulated OS and PFS of each individual trial are provided in **Figure 2**. In most of the trials, observed

survival results were within the 95% confidence interval (CI) of the simulated ranges, suggesting that the model well described the OS and PFS data. Model simulated median OS and PFS vs. average dose per week (mg/m^2/week) and 95% PI agreed with observed values (**Figure 3**).

Neutropenia incidence analysis. The model using the dosing regimen vs. the reported incidence of neutropenia was developed from 24 trials including 35 treatment arms and 1,886 cancer patients. The percentages of patients with grade 2–4 or grade 3–4 neutropenia in each treatment arm were used for the analysis. Exploratory plots suggested that the qw regimen, with a lower range of doses per administration, resulted in a lower incidence of neutropenia than the q3w regimen, and the incidence of neutropenia has a correlation with the dose level of paclitaxel in mg/m^2, but not with the paclitaxel dose per week in mg/m^2/week. Logistical regression models with a sigmoidal and saturable dose–response relationship were found to best describe the correlation between the administered paclitaxel dose (mg/m^2) and the neutropenia incidence. ED_{50} values were estimated to be 69.4 and 82.3 mg/m^2 for grade 2–4 neutropenia and grade 3–4 neutropenia, respectively (**Table 2**). Covariate analysis suggested that dose frequency (qw vs. q3w) was not a significant covariate of the model, which could be due to the correlation between dose frequency and dose per administration. The models testing covariates of treatment duration or percentage of patients who received prior chemotherapy were not converged potentially due to limited data for a relatively complex model. Model prediction of neutropenia rate vs. dose per administration (mg/m^2) and 95% PI is consistent with observed data (**Figure 4**).

Model simulation: comparison of paclitaxel safety and efficacy at q3w vs. qw regimens

Based on the label, the recommended paclitaxel dose is 175 mg/m^2 q3w for BC.[4] However, the current dose of paclitaxel in clinical practice is 65–80 mg/m^2 qw for BC.[32] Thus, a comparison of the safety and efficacy of the qw vs. q3w regimens is presented in **Figure 5** based on the models. Weekly paclitaxel at 65 mg/m^2 is predicted to achieve an ORR of 31.9% (95% CI: 26.9–37.2%), median OS of 12.4 months (95% CI: 10.5–14.9), and median PFS of 4.4 months (95% CI: 3.8–5.1); the grade 2–4 neutropenia incidence is 12.2% (95% CI: 4.4–24.2%) and grade 3–4 neutropenia incidence is 6.6% (95% CI: 3.5–15.0%). ORR, PFS, and OS are correlated with the average dose per week, which is similar for the 175 mg/m^2 q3w and the 65 mg/m^2 qw regimen. Thus, paclitaxel at a dose of 175 mg/m^2 given q3w is predicted to achieve an ORR of 29.8% (95% CI: 24.1–36.1%), median OS of 10.9 months (95% CI: 8.8–13.4), and median PFS of 4.1 months (95% CI: 3.5–4.8), similar to the 65 mg/m^2 qw regimen. However, the incidence of grade 2–4 neutropenia at 175 mg/m^2 given q3w increased to 80.7% (95% CI: 58.3–84.8%) and the incidence of grade 3–4 neutropenia increased to 66.0% (95% CI: 54.0–71.5%). These results suggest that the qw regimen at a dose similar to the subdivided qw dose in the standard q3w regimen would result in a comparable efficacy while significantly reducing the incidence of neutropenia. Additionally, the qw regimen also allows administration
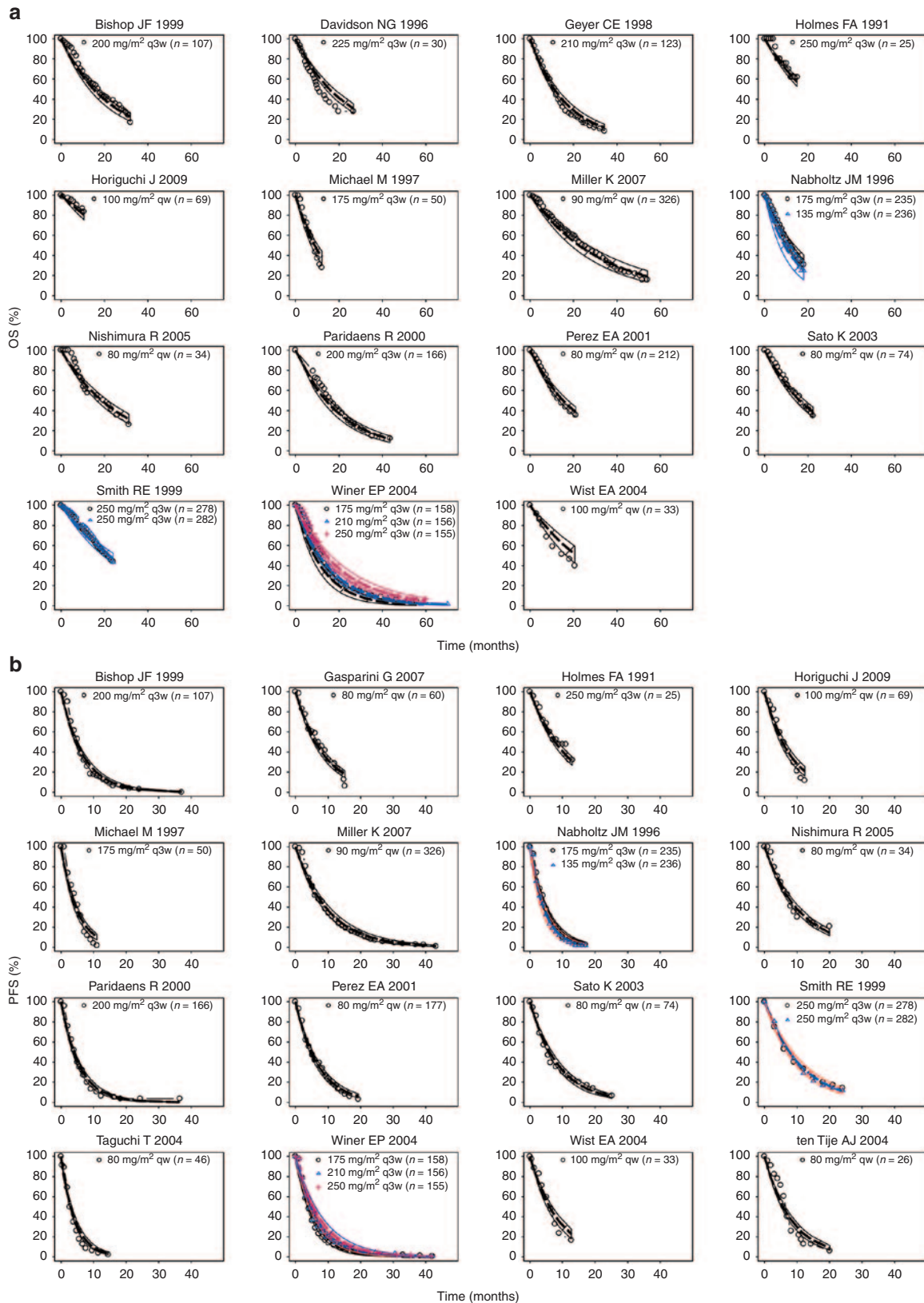
Figure 2 Observed and model-predicted OS and PFS curves for each arm of each trial. (**a**) Overall survival (OS) and (**b**) progression-free survival (PFS). Dashed lines represent typical model prediction and shaded areas represent 95% confidence interval based on model parameter uncertainty. Black open circles represent observed data digitized from the original publications for each arm.
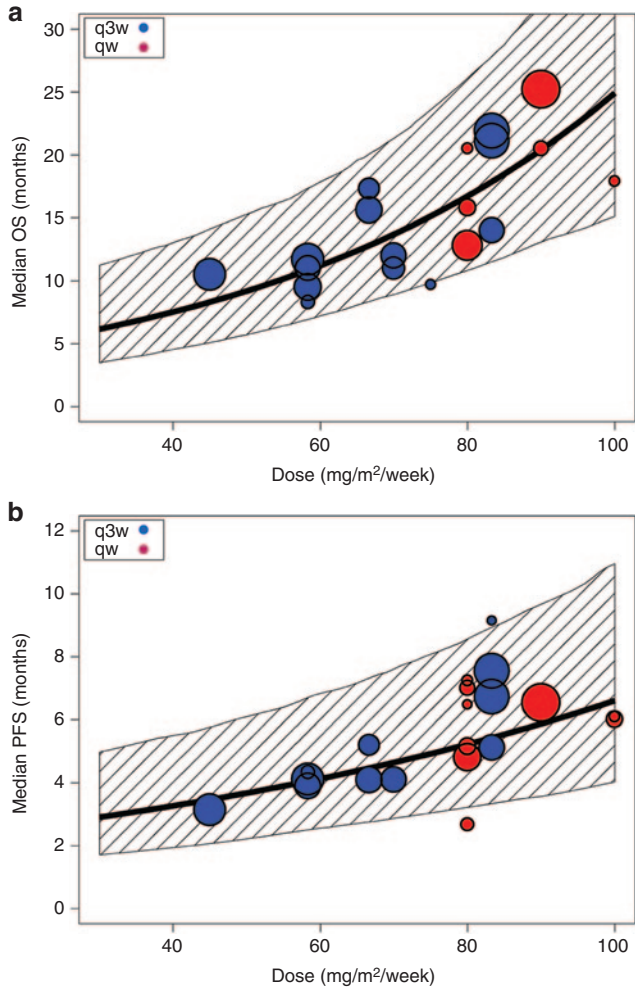
Figure 3 Observed and model-predicted median OS and median PFS vs. paclitaxel dose per week (mg/m²/week). (**a**) OS and (**b**) PFS. Black solid line represents typical model prediction and dashed area represents 95% prediction interval simulated using the models. Points represent observed median OS with size indicating relative patient numbers in each arm. OS, overall survival; PFS, progression-free survival; qw, weekly; q3w, every 3 weeks.

Figure 4 Observed and model-predicted neutropenia incidence vs. paclitaxel dose (mg/m²). (**a**) Neutropenia grade 2, 3, and 4 and (**b**) neutropenia grade 3 and 4. Black line represents model prediction and dashed area represents 95% prediction interval. Points represent observed data with size indicating relative patient numbers in each arm. qw, weekly; q3w, every 3 weeks.

of a higher average dose to achieve better efficacy. This is supported by the simulation that a dose of 80 mg/m² given qw has a higher ORR of 36.9% (95% CI: 32.1–41.8%), a longer median OS of 16.7 months (95% CI: 14.4–19.4), and a longer median PFS of 5.2 months (95% CI: 4.6–5.9), compared with the label dose of 175 mg/m² given q3w. Grade 2–4 neutropenia rate and grade 3–4 neutropenia rate for the 80 mg/m² qw regimen is predicted to be 29.0% (95% CI: 17.7–38.1%) and 13.6% (95% CI: 8.8–22.0%), respectively, which is substantially lower than the neutropenia rate for 175 mg/m² given q3w.

DISCUSSION

The MBMA modeled the relationship between paclitaxel dose (average dose per week or dose per administration) and efficacy (ORR, OS, and PFS) in BC patients or neutropenia incidence in cancer patients treated with paclitaxel monotherapy, integrating literature data from multiple trials. The results
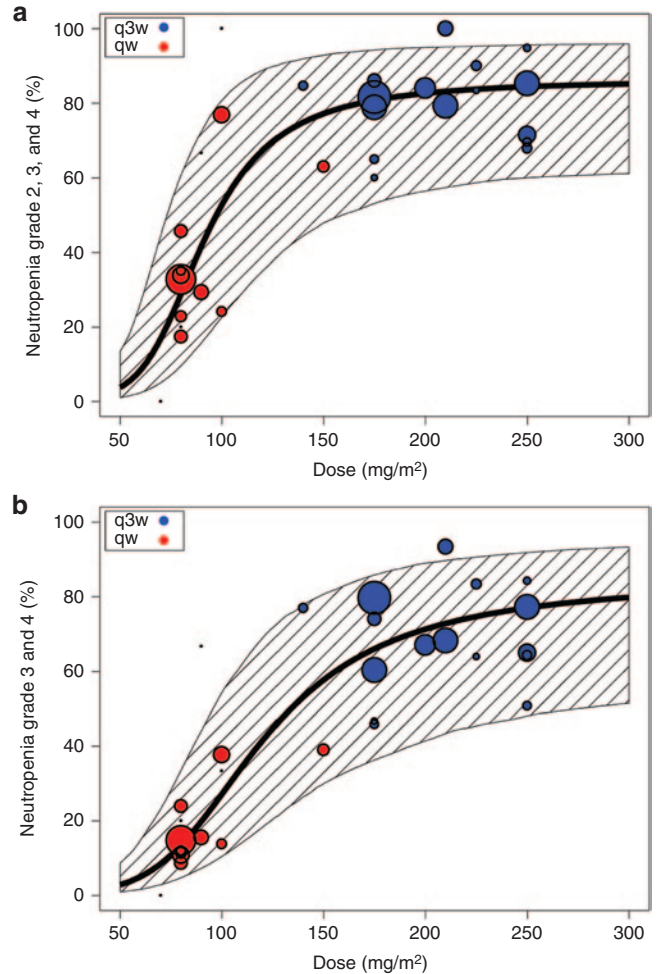
suggest that the efficacy end points are correlated with the average dose per week, whereas the neutropenia rate is correlated with the dose per administration. The qw regimen has a lower dose per administration but a similar to higher dose per week compared to the q3w regimen (**Table 1**; **Figures 1**, **3** and **4**). Consequently, qw paclitaxel is associated with a better safety–efficacy profile with a lower neutropenia rate and comparable to increased ORR, PFS, and OS compared to q3w regimen, in BC patients. This finding is consistent with the Norton–Simon hypothesis,[10,11] meta analysis,[27,29] and most clinical studies[12–15,19] in BC patients. Patients receiving qw regimen may experience longer duration of reduced neutrophil counts due to more frequent dosing. However, the nadir may be shallower compared with the q3w regimen, due to a lower dose per administration.[33] The duration of low neutrophil counts are not consistently reported in the literature. The neutropenia incidence modeled here is of more clinical relevance.

Whether qw regimen provides a favorable safety–efficacy profile in other cancer types needs further analysis. Gao *et al.*[28] compared by meta-analysis the qw vs. q3w regimens of
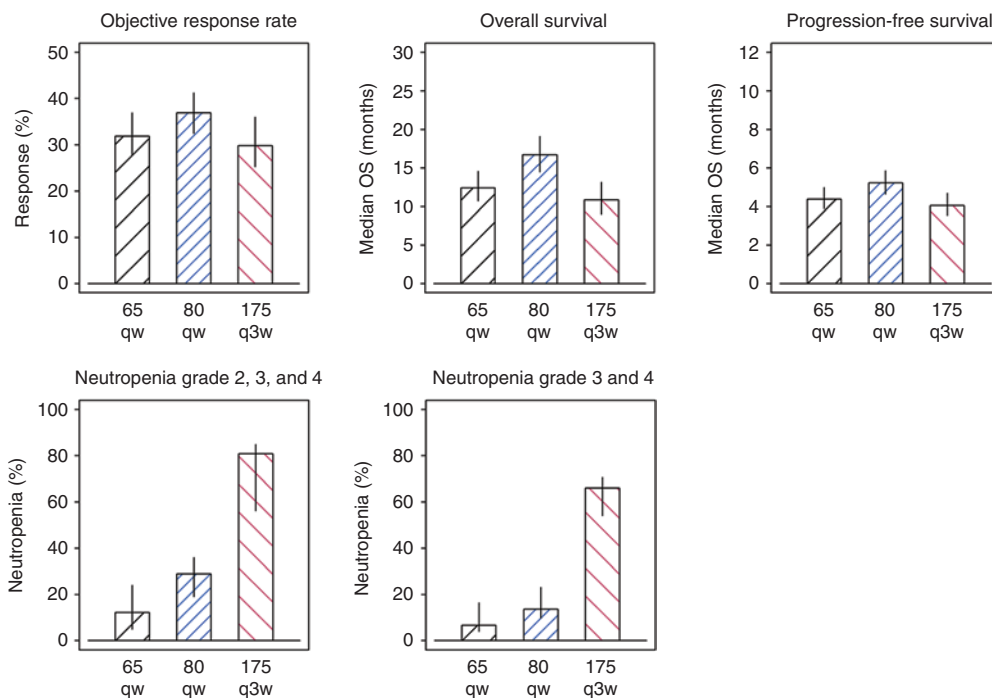
Figure 5 Simulated efficacy (objective response rate, overall survival, and progression-free survival) and safety (neutropenia incidence) of paclitaxel at typical qw and q3w regimens in clinical practice: 65 mg/m² qw, 80 mg/m² qw, and 175 mg/m² q3w. Error bars represent 95% confidence interval based on model parameter uncertainty. qw, weekly; q3w, every 3 weeks.

paclitaxel in NSCLC patients and reported similar OS and PFS rates and less frequent AEs for qw compared with q3w regimen. Huang and Campbell[30] found that a higher response rate is observed with qw paclitaxel regimen in NSCLC patients, and qw regimen resulted in a lower neutropenia incidence in solid tumors. For ovarian cancer treatment, Scambia *et al.*[34] commented that among 14 randomized dose-intensity studies assessing first-line treatment of qw paclitaxel combined with q3w carboplatin, only the Japanese Gynecological Oncology Group 3016 trial[21] showed improved survival with the qw regimen. Preliminary results of MITO-7 study[35] suggested similar PFS and OS for q3w vs. qw paclitaxel and carboplatin and fewer alopecia, neuropathy, and febrile neutropenia with the qw regimen. Overall, there are some evidences that qw regimen offers a larger therapeutic window by providing either better efficacy or lower toxicity in these tumor types. Ongoing trials, such as GOG262 study (NCT01167712) in ovarian epithelial cancer, will provide new data.

Dose–response relationships for the incidence of other AEs after paclitaxel treatment were also explored by graphs (data not shown). Limited data suggest that the incidences of alopecia and arthralgia/myalgia had moderate correlation with paclitaxel dose per administration instead of average dose per week, and qw regimen is associated with reduced incidence of alopecia and arthralgia/myalgia. No apparent correlation with dose was found for the incidence of mucositis or stomatitis, potentially due to limited data. For peripheral neuropathy, although there was a trend of positive correlation between neuropathy incidence and dose within q3w regimen trials, there was no apparent correlation with dose per administration, average dose per week, or cumulative dose using data pooled from qw and q3w regimens (data not shown). From literature, the

meta-analysis by Huang and Campbell[30] reported that grade 3 peripheral sensory neuropathy incidences were less frequent for qw paclitaxel compared with q3w. Oppositely, in a randomized phase III trial, grade 2 and 3 sensory neuropathy was encountered in 21 and 24% of patients receiving qw paclitaxel vs. 21 and 12% receiving q3w paclitaxel, respectively; grade 2 and 3 motor neuropathy was noted in 8 and 9% of qw vs. 5 and 4% of q3w regimen.[14] Together, qw regimen with a lower dose per administration may reduce the incidence of some acute toxicity, but it is inconclusive whether the qw regimen is beneficial in reducing chronic toxicity such as neurotoxicity.

It is reported that paclitaxel pharmacokinetics is nonlinear and is related to infusion duration,[4] potentially due to the Cremophor EL containing formulation.[36,37] Multicompartmental population pharmacokinetic models were established to address nonlinearity across multiple doses (100–250 mg/m² q3w) with majority of data for 135 mg/m² or above.[38–42] By simulation using a model established in solid tumors,[38] the typical values for area under the concentration–time curve are 4.03 and 22.4 µg/ml × h after a single dose of 80 and 240 mg/m² given by 1-h infusion, 3.21 and 19.3 µg/ml × h by 3-h infusion, and 2.33 and 9.54 µg/ml × h by 24-h infusion, suggesting a more than dose-proportional increase of exposure. Weekly regimen of 80 mg/m² will have ~27–50% lower total area under the concentration–time curve compared with q3w regimen of 240 mg/m², for a 3-week cycle with the same average dose per week. Because dose–concentration relationship is nonlinear, quantitative comparison across doses and schedules are confounded, and extrapolation of the dose–response relationship to doses and schedules outside the modeling data should be used with caution. This analysis supported the choice of qw over q3w regimen for the doses included in the modeling. Future work to assess area

under the concentration–time curve–response relationship may allow better quantitative comparison of schedule effect on efficacy and safety and extrapolation across dosing regimens.

MBMA of summary-level efficacy and safety data provides a quantitative approach for comparative exposure–efficacy and exposure–safety assessments.[31] By integrating the results from trials with different dose regimens, the dose–response relationships were quantified. Modeling dose response is usually difficult from a single study as most of them tested only one dose regimen. One challenge of MBMA is to normalize differences in patient population across the trials, since the efficacy and safety response are influenced by prognostic factors. This challenge may be tackled by combining a mixed-effect modeling approach with covariate analysis. In the current analysis, covariates including dosing frequency (q3w vs. qw), percentage of patients who received prior chemotherapy, and treatment duration were explored while other clinically relevant covariates were not consistently reported in the literature. Given these non-tested covariates contribute to patient heterogeneity, and the limited number of arms with covariates tested, the results of covariate analysis should be interpreted with caution.

Selection of either average dose or dose per administration as a predictor for efficacy or neutropenia was based on observed data. Dosing frequency was not identified as a significant covariate for efficacy and safety end points tested. In clinical practice, the qw schedule is associated with a lower dose per administration but similar to higher dose per week compared to the q3w schedule (**Table 1**; **Figures 3** and **4**). As a result, the schedule effect on efficacy or safety could not be separated out, when dose level per administration or average dose per week is included in the model. The nonlinear dose–concentration relationship further confounded quantitative comparison of schedules. An evaluation of stratified relationship per schedule was not feasible due to the limited range of doses for each schedule.

Dose delay and dose reduction are recommended for paclitaxel treatment–related bone marrow suppression (primarily neutropenia).[4] The paclitaxel label states that[4] a 20% dose reduction in subsequent therapy is recommended for grade 4 neutropenia (<500 cells/mm^3) continuing for 7 days or more. The scheduled dose was used for our analysis. It is considered a more appropriate exposure measurement for the assessment of dose–safety relationship instead of the actual dose, since patients received the scheduled dose before neutropenia occurrence, while the actual dose is resulted from dose delay and dose reduction after AE occurrence so may be confounded for dose–neutropenia assessment. The actual doses might be more accurate for exposure–efficacy analysis. However, this information is not consistently available from literature.

The data used in this meta-analysis were identified through a thorough literature review. A potential bias of this analysis could be publication related. However, a study by Takeda *et al.*[43] on the publication bias of anticancer medicines for BC suggests that observational analysis of the published and unpublished trials did not indicate any particular biases in terms of whether positive results were more likely to be fully published than nonsignificant ones. The heterogeneity across trials due to difference in patient characteristics were accounted for by mixed-effect modeling. The distribution of the random effect parameter is found to be approximately normal.

Most studies are single-arm trials with one dose level. Thus, for MBMA of ORR or neutropenia rate, data are limited to model both between-trial variability and residual (within-trial) variability. Nonetheless, there are a few trials with multiple arms which provided some information for the estimation of residual variability. However, the information to differentiate between-trial variability and residual variability could be limited and model simulation using the estimated variability should be interpreted with caution.

By simulating the dose–efficacy and dose–safety relationships of paclitaxel monotherapy, the model supports qw paclitaxel for a better safety–efficacy profile. By applying similar analysis approach to other drugs, dedicated clinical trials for regimen comparison may be reduced. The model is also useful for interpretation of safety and efficacy outcomes for the combination of paclitaxel with a new molecular entity by comparing to historical paclitaxel single agent data summarized by the model.

METHODS
Paclitaxel monotherapy clinical trial database
A thorough literature search of published paclitaxel monotherapy related clinical trial data was performed using the online PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) and the following key words: paclitaxel single agent, paclitaxel monotherapy, paclitaxel alone, paclitaxel weekly, paclitaxel every three weeks, neutropenia, thrombocytopenia, pharmacokinetic, and BC. The publication type was specified to be "clinical trial." Nonduplicated trials with relevant efficacy and safety information were selected (**Supplementary Information Part III**). Efficacy and safety results were extracted from the tables, figures, or text, along with the patient and treatment information. The OS and PFS curves were digitized and recorded in the database. The data included in this database were extracted for MBMA.

MBMA of paclitaxel dose–response relationship
Model building and diagnosis. The relationship between paclitaxel dosing regimen with multiple efficacy end points such as ORR (sum of partial response and complete response rates), PFS, and OS and multiple safety end points such as hematology-related AEs—including incidence of neutropenia (grade 2–4 or grade 3–4)—and other non–hematology-related AEs—such as peripheral neuropathy, arthralgia and/or myalgia, alopecia, mucositis, and stomatitis—were first explored by graphic analysis. The probability for each binary end point or the median time of time-to-event end points (PFS and OS) from each trial arm were plotted against the paclitaxel dose level (mg/m^2) and average dose per week (mg/m^2/week). The Kaplan–Meier PFS and OS curves digitized from the literature for each trial arm were also plotted in one figure with different dose and regimen of paclitaxel. The individual survival curves were fitted and the curve for median OS or PFS vs. average dose per week was then simulated and overlaid with observed data. For the chronic toxicity of peripheral neuropathy, the incidence with a cumulative dose of paclitaxel in mg/m^2 was explored. Potential data error or outliers were carefully examined in these exploratory plots.

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Based on the relationship shown in the plots, a few representative end points for safety and efficacy were selected for MBMA. A structure model using a mixed-effect modeling approach which included intertrial variability and residual variability was selected to describe the relationship between appropriate paclitaxel dose variables (dose level or average dose per week) and response. To account for the difference of patient numbers in each arm of each study, the model was weighted using $1/(SE)^{2,44}$ in which SE is the model prediction of observed data, so that more weight was given to the studies with larger patient numbers.

The impact of the selective covariate on the key fixed effect parameters of the dose–response model was then added to the base model to test the significance. The covariates for testing were selected based on the clinical relevance and data availability. The covariate examined for all the end points was dose frequency (qw vs. q3w) and percentage of patients with prior chemotherapy. The impact of treatment duration on ORR and neutropenia rate was also examined. The criterion for including the covariate was a change in log-likelihood ratio >6.8 for adding 1 parameter (Chi-square distribution for log-likelihood ratio test, $P < 0.01$).

Goodness-of-fit plots were used for model diagnostics. Model residual plots against predicted value and against time were used to examine for potential bias of the models. A simulated dose–response curve with 95% PI was overlaid with observed data to evaluate the model fitting performance. The 95% PI of each plot was obtained by simulating 1,000 trials with both the intertrial variability and model parameter uncertainty. To diagnose the model fitting for OS and PFS curves, the simulated curves with 95% CI obtained by simulating 1,000 repeats with model parameter uncertainty only was overlaid with the observed OS or PFS curve in each arm of each trial.

To compare the efficacy and safety at a clinically recommended dosing regimen such as 65–80 mg/m^2 for qw regimen and 175 mg/m^2 for q3w regimen, the estimated response for a trial with median placebo (e.g., intercept) response was simulated. The 95% CI of each plot was obtained by simulating 1,000 repeats with model parameter uncertainty.

Nonlinear mixed-effects model (*nlme*) in Splus Professional version 8.2 (TIBCO Software, Seattle, WA) was used for model development, exploratory plots, model simulation, and diagnostics.

Logistic dose–response models for modeling dose–ORR and dose–neutropenia incidence. Mixed-effect logistic regression models[45] were used to model the relationship between dose and ORR or neutropenia incidence (grade 2, 3, and 4 or grade 3 and 4).

The exploratory plots show that there is a correlation between paclitaxel dose in mg/m^2/week and ORR. Various models were tested and a linear model (**Equation 1 in Supplementary Information Part I and example S-plus script in Supplementary Information Part II**) was used to describe this relationship.

The exploratory plots also show that there is a correlation between the administered paclitaxel dose level in mg/m^2 and the neutropenia incidence. Linear, power, and E_{max} models were tested and a sigmoidal E_{max} dose–response model (**Equation 2 in Supplementary Information Part I**

and example S-plus script in Supplementary Information Part II) was used to describe this relationship.

Parametric proportional hazard survival models for modeling dose–OS or dose–PFS. The exploratory plots show that there is a correlation between paclitaxel dose in mg/m^2/week and median OS and PFS. Based on the exploratory data analysis, parametric proportional hazard survival models (**Equations 3 and 4 in Supplementary Information Part I**) were used to describe this relationship.

Author Contributions. D.L. and H.L. wrote the manuscript. J.Y.J., D.L., and A.J. designed the research. J.Y.J., D.L., H.L., N.Z., and R.W. performed the research. H.L., N.Z., D.L., J.Y.J., Y.G., and M.M.R. analyzed the data.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ Dedicated clinical studies and meta-analysis suggested that weekly paclitaxel offers a better safety–efficacy balance than an every-3-week regimen. However, MBMA was not applied to quantify dose–response relationships for efficacy and safety of paclitaxel given by weekly or every-3-week regimen.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ Are there dose–response relationships for efficacy and safety of paclitaxel monotherapy, based on MBMA of summary-level literature data of paclitaxel?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✔ MBMA suggested that paclitaxel efficacy is correlated with average dose per week, while neutropenia incidence is correlated with dose per administration. Compared to the every-3-week regimen, the weekly regimen with a lower dose per administration but a similar to higher dose per week may provide a better safety–efficacy profile.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✔ MBMA results supported the choice of weekly over every-3-week regimen for the doses included in the modeling, for a better balanced safety–efficacy profile.

Conflict of Interest. The authors declared no conflict of interest.

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Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (http://www.nature.com/psp)