JPET Fast Forward. Published on October 2, 2020 as DOI: 10.1124/jpet.120.000053
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Time-to-event analysis of paclitaxel-associated peripheral neuropathy in advanced non-small cell lung cancer highlighting key influential treatment/patient factors

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Running title

Time-to-event analysis of paclitaxel peripheral neuropathy

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Other information on this page

- Number of text pages (36)
- Number of tables (4 in main section and 1 in supplementary data)
- Number of figures (4 in main section and 8 in supplementary data)
- Number of references (42)
- Number of words: abstract (250), introduction (584), discussion (1500)

List of non-standard abbreviations used in the manuscript

- CEPAC-TDM: Central European Society of Anticancer Drug Research Study of Paclitaxel Therapeutic Drug Monitoring
- FCM: full covariate model
- MI: multiple imputation
- PN: peripheral neuropathy
- PN2+: peripheral neuropathy grade≥2
- SI: single imputation
- TTE: time-to-event
- $T_{C>0.01\ \mu M}$: time of paclitaxel plasma concentration above 0.01 µM
- $T_{C>0.05\ \mu M}$: time of paclitaxel plasma concentration above 0.05 µM
- $T_{C>0.1\ \mu M}$: time of paclitaxel plasma concentration above 0.1 µM

Recommended section of the journal

Chemotherapy, Antibiotics, and Gene Therapy

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Abstract

Paclitaxel-associated peripheral neuropathy (PN), a major dose-limiting toxicity, significantly impacts patients' quality of life/treatment outcome. Evaluation of risk factors often ignores time of PN onset, precluding the impact of time-dependent factors, e.g. drug exposure, needed to comprehensively characterize PN. We employed parametric time-to-event (TTE) analysis to describe the time-course of risk of first occurrence of clinically relevant PN grades≥2 (PN2+, n=105, common terminology criteria v4.0) and associated patient/treatment characteristics, leveraging data from 365 patients (1454 cycles) receiving 3-weekly paclitaxel (plus carboplatin AUC=6 or cisplatin 80 mg/m^2) for ≤6 cycles. Paclitaxel was intravenously administered (3 h) as standard 200 mg/m^2 doses (n=182) or following pharmacokinetic-guided dosing (n=183). A cycle-varying hazard TTE model linking surge in hazard of PN2+ to paclitaxel administration (PN2+ proportions (i.e. cases/1000 patients), first day, cycle 1: 4.87/1000, cycle 6: 7.36/1000) and linear decline across cycle (last day, cycle 1: 1.64/1000, cycle 6: 2.48/1000) adequately characterized the time-varying hazard of PN2+. From joint covariate evaluation, PN2+ proportions (first day, cycle 1) increased by 1.00/1000 with 5-µmol·h/L higher paclitaxel exposure per cycle (AUC_{cycle}, most relevant covariate), 0.429/1000 with 5-year higher age, 1.31/1000 (smokers versus non-smokers), and decreased by 0.670/1000 (females versus males). Compared to 200 mg/m^2 3-weekly dosing, model-predicted cumulative risk of PN2+ was significantly higher (42%) with 80 mg/m^2 weekly dosing but reduced by 11% with 175 mg/m^2 3-weekly dosing. The established TTE modelling framework enables quantification and comparison of patient's cumulative risks of PN2+ for different clinically-relevant paclitaxel dosing schedules, sparing patients PN2+ to improve paclitaxel therapy.

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Significance statement

Characterization of risk factors of paclitaxel-associated peripheral neuropathy (PN) typically involves time-independent comparison of PN odds in patient subpopulations, concealing the impact of time-dependent factors e.g. changing paclitaxel exposure required to comprehensively characterise PN. We developed a parametric time-to-event model describing the time-course in risk of clinically-relevant paclitaxel-associated PN, identifying the highest risk in older, male, smokers with higher paclitaxel AUC_{cycle}. The developed framework enabled quantification of patient's risk of PN for clinically-relevant paclitaxel dosing schedules, facilitating future dosing decisions.

Key words: Peripheral neuropathy, paclitaxel exposure, time-to-event analysis, non-small cell lung cancer, dosing regimens, patient factors

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Introduction

Peripheral neuropathy (PN) is a major cumulative, often irreversible, dose-limiting toxicity of paclitaxel with significant impact on patient's quality of life and may influence treatment outcome (Stubblefield et al., 2009). Over twenty percent of patients receiving standard paclitaxel dosing (175 mg/m^2-200 mg/m^2, 3-weekly) against non-small cell lung cancer (NSCLC) experience clinically relevant PN (Joerger et al., 2016; Zhang et al., 2019). The currently accepted mechanism of paclitaxel-associated PN is through microtubule hyperstabilization, distorting the physiological cycle of microtubule depolymerization and repolymerization and subsequently interfering with axonal growth, intracellular transport and the structural integrity of neurons (Mielke et al., 2005; Gornstein and Schwarz, 2017). Paclitaxel-associated PN typically manifests with sensory symptoms such as pain, paresthesia, dysesthesia and numbness, primarily in the hands and feet, beginning as early as 24-72 hours after administration of paclitaxel (Scripture et al., 2006; Boyette-Davis et al., 2013).

The risk of PN has been shown to increase with higher paclitaxel doses, by comparing proportions of PN in patients receiving different paclitaxel doses (Green et al., 2005; Seidman et al., 2008), and higher systemic exposure i.e. time of paclitaxel plasma concentration above 0.05 μM ($T_{C>0.05\ \mu M}$) and area under the concentration time curve based on Kaplan-Meier analysis and logistic regression analysis (Mielke et al., 2005; Kraff et al., 2015). Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is currently the only recommended treatment option for chemotherapy-induced PN symptoms (Hershman et al., 2014). However, up to 44% of the patients with paclitaxel-induced PN treated with duloxetine experience no relief (Otake et al., 2015), further emphasizing the limited treatment options.

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Chemotherapy-induced PN is commonly measured using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (NCI, 2009). Symptoms of PN are graded in order of increasing severity from grades 0 (normal) to 4 (severe) or 5 (death). NCI-CTCAE PN grades≥2 are considered clinically relevant as the inflicted patient may require anticancer treatment delay or dose reductions (Park et al., 2017). To identify factors associated with increased risk of PN, the odds of occurrence of PN have been compared for different patient characteristics including age or treatment-related factors such as paclitaxel exposure (Kraff et al., 2015; Tanabe et al., 2017; Abraham et al., 2014). These statistical analyses, however, ignore the influence of the time of onset of PN in describing the risk of PN, and potentially conceal the underlying time-related pathophysiological or pharmacological processes, e.g. change in drug exposure over time, required to accurately characterize the occurrence of PN.

Time-to-event analysis (TTE) (Holford, 2013) provides a framework to integrate the impact of time of occurrence of PN while describing the occurrence of PN. In parametric TTE analysis, the time-course in probability of PN is described using parameters of a TTE model. Prior knowledge of biological and pharmacological processes associated with the occurrence of PN can be integrated in the model, hence providing mechanistically plausible and more accurate description of observed PN data. Parametric TTE models can further be used to simulate and predict the risk of events such as PN at specific time points for patients with specific covariate characteristics or dosing regimens (Lu et al., 2017; Svensson et al., 2018).

This work aimed at (i) describing the time-course in risk of 1st occurrence of clinically relevant paclitaxel-associated PN using parametric TTE analysis, (ii) evaluating the impact of paclitaxel exposure and relevant patient characteristics on the risk of

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clinically relevant PN and (iii) generating inference on the risk of clinically relevant PN for different paclitaxel dosing schedules in order to manage the risk of PN.

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Methods

Demographic and clinical data

We analyzed clinical data from the CEPAC-TDM study, an open-label, randomized phase III, multi-center study, ClinicalTrials.gov identifier NCT01326767 (Joerger et al., 2016). Briefly, 365 patients with newly diagnosed advanced non-small cell lung cancer (NSCLC) received paclitaxel (3-hour intravenous infusion) plus carboplatin (target AUC=6 mg·min/mL) or cisplatin (80 mg/m^2) every 3 weeks (q3w) for a maximum of six cycles. In the conventional, body surface area (BSA)-guided dosing arm, 182 patients (734 treatment cycles) received the standard paclitaxel doses of 200 mg/m^2 while in the experimental pharmacokinetic (PK)-guided dosing arm, 183 patients (720 treatment cycles) received PK-guided dosing of paclitaxel according to an algorithm based on paclitaxel exposure ($T_{C>0.05\ \mu M}$) from the previous cycle (Joerger et al., 2012). PK sampling was performed only in the PK-guided dosing arm and $T_{C>0.05\ \mu M}$ determined by posthoc estimation based on a paclitaxel PK model (Joerger et al., 2012). Median patient age was 64 years (range 41-78), and the proportion of females and current smokers was 33% and 37%, respectively. A detailed summary of the dosing algorithm and patient demographic and clinical characteristics has been published (Joerger et al., 2016). PN symptoms, severity, date of onset and date of resolution were documented during study visits and graded according to NCI-CTCAE version 4.0 (NCI, 2009).

Time-to-event model of paclitaxel-associated PN

Based on clinical judgement and literature (Park et al., 2017), PN data was dichotomized, with grade 1 categorized as clinically non-relevant and grades≥2 (PN2+) as clinically relevant. The 1st occurrence of PN2+ (incidence) within each patient was considered an event. Parametric time-to-event analysis was employed to

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describe the risk of PN2+ over time. In this setting, the actual time of 1st occurrence of PN2+ in an individual, t, was regarded as the value of a random variable T. A hazard-based approach was used, in which the distribution of T was specified through a parametric hazard function, h(t), obtained from the probability that a patient experienced 1st occurrence of PN2+ at time t. Based on h(t), the probability density function (pdf) of T can be derived as well as the so-called survivor function (S(t)) which described the probability that an individual had not experienced the event before a given time t. Whenever a patient experienced an incidence of PN2+, the likelihood of the event at that time was calculated using the pdf of T, whereas if a patient never experienced PN2+, the survivor function corresponding to the final day of the last treatment cycle (censoring time) was calculated. The mathematical formulas linking h(t), S(t) and the pdf of T at time t are given as follows:

$$h(t) = \lim_{\delta t \to 0} \left\{ \frac{P(t \le T < t + \delta t)}{\delta t} \right\} \qquad \text{equation 1}$$

$$S(t) = \exp\left(- \int_0^t h(u) \cdot du \right) \qquad \text{equation 2}$$

$$pdf(t) = S(t) \cdot h(t) \qquad \text{equation 3}$$

in which u is a variable for integration by substitution and standard notation for integration.

Different baseline hazard functions (constant, Weibull and Gompertz) were investigated for their ability to describe the risk of 1st occurrence of PN2+ over time. All these functions describe a monotonic change in hazard over time. Given the knowledge on PN pathophysiology i.e. substantial damage of the neurons 1-3 days after exposure to clinically relevant concentrations of paclitaxel (Gornstein and Schwarz, 2017) and observations in the CEPAC-TDM study i.e. a higher proportion of patients experiencing PN2+ within the first few days after paclitaxel administration,

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we considered in addition a “cycle-varying hazard model” to allow for a cycle-specific change in hazard over time. In this model, a surge in hazard was linked to the administration of paclitaxel and estimated as a hazard surge term *F*. In this analysis, *F* was estimated by scaling a unit hazard introduced into the hazard compartment at the time of paclitaxel administration (Supplementary Figure 1). Across a cycle, from the first to the last day, the hazard declined following a 1st-order process described by the rate constant *K*. Equations 4 and 5 below show the cycle-varying hazard model:

$$h(t_{Dose}) = h_{Previous} + F; \quad \text{at the cycle start,} \quad \text{equation 4}$$

$$\frac{dh(t)}{dt} = -K h(t) \quad \text{within cycle,} \quad \text{equation 5}$$

in which $h(t_{Dose})$ and $h_{Previous}$ (both in day^{-1}) are the hazards of 1st occurrence of PN2+ at the begining of a cycle (cycle day 1) and the end of the previous cycle, respectively (for cycle 1, $h_{Previous} = 0$); h(t) (in day^{-1}) is the hazard of 1st occurrence of PN2+ at any cycle time t; *F* the hazard surge term describing the increase in hazard of 1st occurrence of PN2+ at the start of a cycle, and *K* the 1st-order hazard decay rate constant describing the decline in hazard of 1st occurrence of PN2+ over time within each cycle.

Impact of covariates on hazard of 1st occurence of PN2+

Paclitaxel PK data was only available in the PK-guided dosing arm, however we aimed to evaluate the impact of paclitaxel PK on PN for the entire dataset. As such, individual patient paclitaxel exposure metrics i.e. time of plasma concentrations above thresholds, 0.01 μM, 0.05 μM, and 0.1 μM ($T_{C>0.01\ \mu M}$, $T_{C>0.05\ \mu M}$, and $T_{C>0.1\ \mu M}$, respectively) and area under the plasma concentration-time curve between the start

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and end of a cycle (AUC_{cycle}) were derived by imputation (single and multiple), based on a PK model developed from the PK-guided dosing arm data and individual patient data (supplementary data). The imputation strategy was validated by comparing distributions of imputed and estimated exposure in the PK-guided dosing arm, both at individual and population level.

Covariate analysis was performed in two steps: first, covariates were univariately evaluated with respect to *F* and *K,* based on paclitaxel exposure from single imputation, to independently determine the paclitaxel exposure metric most predictive of PN2+. Parameter-covariate relations were evaluated using the linear, proportional and exponential models. Secondly, paclitaxel exposure, age, sex, and smoking status were jointly evaluated in a full covariate model (FCM) (Gastonguay, 2011) based on their known mechanistic pharmacological link to peripheral neuropathy. Age-related changes in nerve fibres such as axonal atrophy and electrophysiological changes such as impaired nerve regeneration after injury have been described (Verdú et al., 2000). Estrogen-mediated increase in proinflammatory cytokines and testosterone-mediated production of anti-inflammatory cytokines are linked to stronger immune response and higher sensitivity to neuropathic pain in females compared to males (Rosen et al., 2017). Smoking was found to impair functional recovery subsequent to peripheral nerve injury (Rinker et al., 2010). These covariates were also significantly associated with peripheral neuropathy in the clinical setting (de Graan et al., 2013; Kanbayashi et al., 2013; Kawakami et al., 2012). The final FCM parameters were derived after multiple imputation (50 replicates) of paclitaxel exposure (Johansson and Karlsson 2013; Svensson et al., 2018). Subsequently, the dependency of covariate effects of paclitaxel exposure, age, sex and smoking status on treatment arm (BSA-guided or PK-guided dosing) was assessed by estimating the

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FCM parameters with and without treatment arm as a covariate. Subsequently, based on the estimated FCM parameters, 250 virtual clinical trials were simulated for a standard paclitaxel dosing schedule, varying the level of a specific covariate while keeping other covariates at reference value, and cumulative proportions of PN2+ computed at the end of treatment.

Time-to-event model evaluation

To compare the different baseline hazard models and evaluate the FCM, Kaplan-Meier visual predictive checks were used: 250 datasets were generated by simulation from the developed models, followed by graphical comparison of the simulated and observed data. In univariate covariate analysis, the likelihood ratio test (LRT) was used to assess statistical significance of covariates. For any two nested models e.g. the baseline TTE model (with no covariates) and a covariate model, a change in objective function value of ≥3.84 points as numeric quality criterion for covariate inclusion showed statistical significance of the covariate effect, corresponding to an asymptotic type 1 error of α=0.05 (chi-squared distribution with one degree of freedom, corresponding to one additional model parameter).

Risk of PN2+ with different paclitaxel dosing schedules

Exploiting the developed TTE full covariate model, simulations were performed to evaluate the risk of 1st occurrence of PN2+ in 3 clinically relevant paclitaxel dosing schedules for NSCLC, summarised in Table 1. A virtual population of 1000 NSCLC patients was generated by sampling with replacement from the distribution of patient characteristics in the CEPAC-TDM database: sex and smoking status were sampled empirically (i.e. without consideration for the distribution of other patient characteristics), whereas age was sampled based on the distribution within the respective sex. All three dosing schedules were administered to each patient, one at

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a time, and typical paclitaxel PK exposure derived using the paclitaxel PK model. Parameters (250 sets) of the FCM without treatment arm effect were sampled from their uncertainty distributions and for each set a clinical trial was simulated based on the virtual populations. Hence, model parameter uncertainty and randomness of the time-to-event model were the two levels of variability included during the simulations. As outcome, (i) the simulated proportion of patients who experienced PN2+ was compared between the different dosing schedules across time during treatment and (ii) risk ratios between the different dosing schedules were computed based on simulated proportions of PN2+ at the end of treatment for each trial.

Software

Dataset preparation and statistical evaluation were performed in R 3.4.3 (R Development Core Team, 2018) and TTE analysis performed with the first-order method in NONMEM 7.3.0 with assistance of PsN 4.2.0 (Lindbom et al., 2005) and Pirana 2.9.4 (Keizer et al., 2011).

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Results

Exploratory PN data analysis

In total, 105 patients (28.8%) experienced 1st occurrence of PN2+ during any treatment cycle. Generally, a higher number of events was observed in the first few days subsequent to paclitaxel treatment administration (cycle start), with the numbers gradually declining across the cycle in all observed cycles (Figure 1, solid line). The number of events recorded on day 1 of a cycle increased across cycles; no event was recorded on day 1 of the first cycle. No specific trend in proportion of incidence of PN2+ across treatment cycles was apparent, however cycle 1 had the lowest proportion of PN2+ (5.6%), with cycle 4 having the highest proportion of PN2+ (14.6%).

Of the 260 patients who did not experience PN2+, 75 received 6 cycles of treatment (meaning they did not dropout but were censored at the end of the study period), whereas the remaining 185 patients were considered dropouts (censored at dropout) with regards to PN2+ analysis. The reasons for dropout included tumour progression (43.0%), patient death (13.0%) and amongst others cessation of treatment at physician's discretion, withdrawal of consent and intolerable non-neurological toxicities. Therefore dropouts were assumed random with regards to PN2+ and not explicitly accounted for in developing this time-to-event model of peripheral neuropathy.

Time-to-event model of paclitaxel-associated PN2+

Based on the LRT, no statistically significant difference in model fit was found between the constant, Weibull and Gompertz hazard models (change in OFV <3.84 points between the 3 models, but 24.4 higher than cycle-varying hazard model, Supplementary Table 1). However, as the cycle-varying hazard and constant hazard

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models were not nested these models were compared using visual predictive checks (Supplementary Figure 2 (A-D)), rather than the LRT. The cycle-varying hazard model best characterized the observed profile of 1st occurrence PN2+ across time. In contrast to the constant, Weibull and Gompertz hazard models (Supplementary Figure 3 (A-C)), the cycle-varying hazard model (Supplementary Figure 3 (D)) described an increase in hazard of PN2+ at cycle start, followed by the gradual decrease within the cycle. As such the cycle-varying hazard model was adopted for subsequent analyses.

Impact of covariates on the hazard of 1st occurence of PN2+

Paclitaxel exposure from single imputation closely matched the exposure estimated based on paclitaxel PK, and both fell largely within the interquartile range of paclitaxel exposure from multiple imputation, by comparison at both individual and population levels (Supplementary Figures 4 and 5), demonstrating reliability of the imputation procedure. Hence individual imputed paclitaxel exposure was adopted in both the BSA-guided and PK-guided dosing arms for further covariate evaluation. Generally, paclitaxel exposure (paclitaxel AUC_{cycle}, $T_{C>0.01\ \mu M}$, $T_{C>0.05\ \mu M}$ and $T_{C>0.1\ \mu M}$) was not constant, mainly as result of dose adaptations in the PK-guided dosing arm, but gradually declined across treatment cycles with increase in variability between patients (AUC_{cycle} and $T_{C>0.05\ \mu M}$ shown in Figure 2).

Paclitaxel AUC_{cycle}, $T_{C>0.01\ \mu M}$, $T_{C>0.05\ \mu M}$ and $T_{C>0.1\ \mu M}$ all had statistically significant impact on the hazard of 1st occurrence of PN2+ (Table 2) from univariate analysis, whereas trends of increase in hazard of PN2+ were observed with older patients, males compared to females and current smokers compared to current non-smokers. Higher paclitaxel exposure was associated with a higher surge in hazard or a lower rate of decline in hazard across time when evaluated against *F* or *K* respectively,

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resulting in a higher risk of PN2+ within a cycle. Based on the LRT, paclitaxel AUC_{cycle} on *F* was associated with the greatest improvement in model fit compared to the base model with no covariates (16.1 point drop in OFV, Table 2). The impact of paclitaxel AUC_{cycle} on PN2+ was less significant when evaluated with respect to K, reduction in OFV of 12.1. Joint evaluation of the impact paclitaxel AUC_{cycle} with respect to F and K did not further improve model fit compared to F alone i.e. change in OFV of 17.3, though reduced the precision of parameter estimates. This could be attributed to the strong correlation between F and K. Furthermore, the condition number for the model with the impact of paclitaxel AUC_{cycle} on F was 84.3 excluding ill-conditioning. As such we retained the impact of paclitaxel AUC_{cycle} only on F for subsequent full covariate modelling.

Joint evaluation of the impact of covariates using a full covariate model

Based on mechanistic pharmacologic plausibility of covariates on PN and prior clinical knowledge (de Graan et al., 2014; Kanbayashi et al., 2013; Kawakami et al., 2012), age, sex and smoking status were included for joint evaluation in a full covariate model (FCM). The relationship between covariates and the hazard surge term (*F*) in the FCM was parameterized as shown in equations 6 and 7, for the models without and with treatment arm as covariate, respectively:

$$F = TVF \cdot \exp(E_{AUC} \cdot (\mathrm{AUC_{cycle}} - \mathrm{AUC_{(cycle,\ med)}})) \cdot \exp(E_{Age} \cdot (\mathrm{Age} - \mathrm{Age_{med}})) \cdot (E_{Sex})^{\mathrm{Sex}} \cdot (E_{Smok})^{\mathrm{Smoker}} \quad \text{equation 6}$$

$$F = TVF \cdot exp(E_{ARM} \cdot \mathrm{ARM}) \cdot \exp(E_{AUC} \cdot (\mathrm{AUC_{cycle}} - \mathrm{AUC_{(cycle,\ med)}})) \cdot \exp(E_{Age} \cdot (\mathrm{Age} - \mathrm{Age_{med}})) \cdot (E_{Sex})^{\mathrm{Sex}} \cdot (E_{Smok})^{\mathrm{Smoker}} \quad \text{equation 7}$$

in which *TVF* is the typical value of *F* for a male (Sex = 0, Sex = 1 for females), current non-smokers (Smoker = 0, Smoker = 1 for current smokers), of median age (Age_{med} = 64 years) and median paclitaxel AUC_{cycle} ($AUC_{(cycle,\ med)}$); ARM (BSA-

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guided dosing = 0, PK-guided dosing = 1) is covariate for treatment arm; E_{AUC}, E_{Age}, E_{Sex}, E_{Smok} and E_{Arm} are covariate effect coefficients for paclitaxel AUC_{cycle}, age, sex, smoking status and treatment arm, respectively.

Based on parameter estimates of the FCM with no treatment arm effect (equation 6), an *F* of 0.00487 day^{-1} (Table 3) was estimated as the hazard on the 1st day of treatment for a typical patient population (males, current non-smokers with median age (64 years) and paclitaxel AUC_{cycle}) which translated into on average 4.87 in 1000 patients experiencing PN2+. This hazard declined with a 1st-order rate constant (K = 0.0518 day^{-1}) to 0.00164 day^{-1} on day 21 (last day of a cycle 1) i.e. 1.64 in 1000 patients experiencing PN2+. For cycle 6, the hazards on days 1 and 21 were 0.00733 and 0.00247 respectively, translating into 7.33 in 1000 and 2.47 in 1000 patients experiencing PN2+ on days 1 and 21, respectively.

Covariate impact assessment, by varying a specific covariate while keeping the rest at typical values, revealed a 20% increase in *F* (1.00/1000 increase in proportions of PN2+) and 43% increase in F (2.10/1000 increase in proportions of PN2+) for a 5 μmol·h/L and 10 μmol·h/L increase in paclitaxel AUC_{cycle}, respectively; a 9% increase in *F* (0.429/1000 increase in proportions of PN2+) and 18.5% increase in F (0.900/1000 increase in proportions of PN2+) for a 5-year and 10-year increase in age, respectively; a 27% higher *F* (1.31/1000 increase in proportions of PN2+) in smokers compared to non-smokers and a 14% lower F (0.670/1000 decrease in proportions of PN2+) in females compared to males. Of note, for the continuous covariates AUC_{cycle} and age due to the exponential function of the relation on F, a higher exposure and higher age led to a more pronounced effect on F, i.e. increase in hazard of 1st occurrence of PN2+ at the start of a cycle. Visualization of covariate impact in terms of proportions of patients experiencing PN2+ across time on

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treatment is shown in Supplementary Figure 6. Based on the 250 virtual clinical trial simulations, the estimated percentage increase in risk of PN2+, comparing the 97.5th and 2.5th percentiles of covariate distributions, was 22.0% and 62.0% for paclitaxel AUC_{cycle} with and without treatment arm effect respectively, in contrast to 39.0% and 44.0% for age with and without treatment arm effect respectively (Figure 3), revealing a much stronger dependency of the covariate effect of paclitaxel AUC_{cycle} on treatment arm compared to that of age on treatment arm.

Risk of PN2+ with different paclitaxel dosing schedules

The percentage cumulative risk of PN2+ at the end of treatment with 200 mg/m^2 3-weekly dosing was 44.2% (90% CI: 32.4, 54.8) and 64.1% (90% CI: 45.0, 78.3) for the 80 mg/m^2 weekly dosing schedule, i.e. the 80 mg/m^2 weekly dosing schedule was associated with significantly higher cumulative risk of PN2+ compared to the 200 mg/m^2 3-weekly dosing with a risk ratio of 42.0% (90% CI: 9.00%, 90.0%) (Table 4), after accounting for randomness of the time-to-event model and parameter uncertainty. Though the 200 mg/m^2 3-weekly dosing was associated with more profound increase in risk of PN2+ with each paclitaxel administration compared to 80 mg/m^2 weekly dosing, the higher dosing frequency in weekly dosing led to a gradual increase in risk of PN2+ with higher minimum risk of PN2+ after each paclitaxel administration, hence a higher overall cumulative risk of PN2+ (Supplementary Figure 7). However, a large overlap in proportions of patients experiencing PN2+ was predicted across time between the two dosing schedules (Figure 4A). For the 175 compared to 200 mg/m^2 3-weekly dosing, an 11.0% lower risk of PN2+ (90% CI: 20.5% decrease, 1.00% increase) was predicted (Table 4, Figure 4B), though not statistically significant.

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Discussion and conclusions

A parametric cycle-varying hazard TTE model, based on knowledge of pathophysiology and trends of occurrence of clinically relevant peripheral neuropathy (PN2+), was developed to characterize the time-course of the risk of 1st occurrence of PN2+ in paclitaxel-treated advanced NSCLC patients: the risk of PN2+ significantly increased with higher paclitaxel $AUC_{cycle,}$ and the most vulnerable population was identified as the older, male and current smokers, from joint evaluation of covariate impacts. The established model enables improved prediction of individual patient's risk of PN2+ with different clinically relevant paclitaxel dosing schedules for dose selection during treatment.

TTE analysis offers marked improvements over common approaches used for analysing PN data: traditionally, odds of PN are compared across different patient subpopulations to ascertain associated risk factors (Scripture et al., 2006; Tanabe et al., 2017; Kanbayashi et al., 2013). These approaches only account for the occurrence of the event without consideration for the time of occurrence, as such conceal knowledge on time-dependent pathophysiological or pharmacological processes required to adequately characterize and predict the occurrence of PN. In the CEPAC-TDM study, a Kaplan-Meier-based non-parametric TTE analysis was used to compare the risk of PN between BSA-guided and PK-guided dosing strategies (Joerger et al., 2016). As an extension, parametric TTE analysis was adopted in this work, that allowed (i) basing on prior knowledge on the pathophysiology of PN to better describe the baseline hazard of first occurrence of PN2+ (ii) a mechanistic evaluation of the impact of non-stratified time-varying covariates e.g. paclitaxel AUC_{cycle} and (iii) simulation of the occurrence of PN for

JPET Fast Forward. Published on October 2, 2020 as DOI: 10.1124/jpet.120.000053
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different paclitaxel exposure levels (dosing regimens) and patient characteristics based on the developed parametric hazard function (TTE model).

The cycle-varying hazard model best described the observed PN2+ data: a surge in incidence of PN2+ at cycle start was linked to the administration of paclitaxel with the magnitude estimated using the hazard surge term (*F*). The gradual decline in hazard across time within a cycle was best described as a 1st-order process, using the hazard decline rate constant (*K*). Variability in parameters *F* and *K* between different patients was linked to differences in patient-specific covariate characteristics. This model structure is supported by in vitro data showing that adult dorsal root ganglion neurons, the cell type inflicted by paclitaxel-associated neurotoxicity, undergo substantial damage 1-3 days after exposure to clinically relevant concentrations of paclitaxel (Gornstein and Schwarz, 2017). This was also consistent with observations from the CEPAC-TDM study i.e. a higher proportion of patients experienced PN2+ within the first few days after paclitaxel administration.

The effect of paclitaxel exposure could be estimated separately on *F* and *K*, however this was not possible on both *F* and *K* simultaneously in the same model. Paclitaxel exposure had a stronger effect on *F* compared to *K*, with AUC_{cycle} showing a stronger effect than $T_{C>0.01\ \mu M}$, $T_{C>0.05\ \mu M}$ and $T_{C>0.1\ \mu M}$. Previous studies also showed statistically significant increase in the risk of PN with higher AUC and $T_{C>0.05\ \mu M}$ (Zhang et al., 2016, Mielke et al., 2005; de Graan et al., 2014). Unlike these studies, we accounted for cycle-specific changes in exposure, allowing the hazard in an individual to change across cycles, resulting into a more accurate description of the risk of PN2+ across time with changing paclitaxel exposure. The increase in risk of PN2+ with higher paclitaxel exposure suggests the need for prophylactic management or closer monitoring of symptoms of PN2+, early on within cycles,

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especially in subpopulations at higher risk of PN2+ (elderly, male, current smokers) to enable early treatment e.g. with duloxetine (Otake et al., 2015).

Inclusion of treatment arm effect (BSA-guided versus PK-guided) as a covariate on *F* was associated with a 65% reduction in the covariate effect of paclitaxel AUC_{cycle}. This trend was expected since protocol dose adaptations in the CEPAC-TDM study led to lower paclitaxel AUC_{cycle} in the PK-guided compared to BSA-guided dosing arm, hence the observed relationship between treatment arm and PN2+ is attributed to the difference in paclitaxel AUC_{cycle} between the two dosing arms. Treatment arm only partly reduced the covariate effect of paclitaxel AUC_{cycle} meaning that paclitaxel AUC_{cycle} was a stronger predictor of PN2+ compared to treatment arm.

Our findings suggest a higher cumulative risk of PN2+ with 80 mg/m^2 weekly compared to 200 mg/m^2 3-weekly paclitaxel dosing. Weekly dosing was associated with a lower surge in risk of PN2+ for a single paclitaxel administration, however a higher cumulative risk of PN2+ was predicted due to the higher dosing frequency. Previous comparisons of neuropathy risk between weekly and 3-weekly paclitaxel dosing yielded mixed findings (Schuette et al., 2006; Sparano et al., 2008; Seidman et al., 2008; Green et al., 2008; Belani et al., 2008; Fountzilas et al., 2009). Lower paclitaxel $T_{C>0.01\ \mu M}$ with weekly compared to 3-weekly dosing was associated with a reduced toxicities, especially haematological toxicities (Marchetti et al., 2002). For the 3-weekly dosing, the cumulative risk of PN2+ increased with higher paclitaxel doses i.e. higher in 200 mg/m^2 compared to 175 mg/m^2. Ultimately, our results suggest a reduction in risk of PN2+ with paclitaxel dose reduction rather than dose fractionation (same overall paclitaxel dose administered multiple times within a cycle). Given similar efficacy (progression free- and overall survival) in the 175-200 mg/m^2 dose range (Joerger et al., 2016), the lower risk of PN2+ with 175 mg/m^2 3-

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weekly paclitaxel dosing suggests an improved therapeutic benefit compared to 200 mg/m^2 3-weekly paclitaxel dosing.

Alternative time-to-event models that describe a symmetric phase of increase and decrease in hazard of events at predefined times have been employed before for characterizing different events (Plan et al., 2011; Tarning et al., 2014). However, this model structure inadequately described observed PN2+ profiles in this study. Proportions of observed PN2+ peaked a few days after paclitaxel administration, and gradually declined over time across the cycle, a profile not consistent with the symmetric model. Alternatively, the hazard of 1st occurrence of PN2+ could be described using an indirect response model (Upton and Mould, 2014). The paclitaxel concentration-time profiles may be used to drive either the rate of development of the hazard or inhibit the rate of decline of the hazard. The differences in time scale of measurement of paclitaxel concentration and PN2+ events (i.e. hours versus days) would require fixing PN2+ incidence to a specific clock time, hence introducing a bias in the concentration-PN2+ relationship, as such we opted for the cycle-varying hazard model and evaluated the time-course of incidence of PN2+ on a time scale of days.

In previous characterization of the time-course of chemotherapy-induced PN (CIPN) during paclitaxel treatment, Mehrotra et al., 2017 used a kinetic-pharmacodynamic (K-PD) indirect response model. CIPN scores (0-16) were derived from PN grades from the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity grading system and treated as a continuous variable; a score of 4.00 could represent mild experience of each of the four items (score=1). Our database contained NCI-CTCAE PN grades 1–3 (only 3 categories) hence cannot be modelled as a continuous variable. Our model predicted proportions of PN2+ after 6 cycles of

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weekly 80 mg/m^2 paclitaxel dosing was 64.1% (90% CI: 45.0, 78.3%) whereas the K-PD model-predicted CIPN scores ≥ 4.00 was 45.6% for a patient with BSA of 1.87 m^2.

As possible limitation, our model did not account for the impact of the potentially neurotoxic co-administered platinum drugs. Cisplatin is more neurotoxic than carboplatin, with neuropathy incidences of 28%-100% compared to 6%-42% with carboplatin (Stubblefield et al., 2009). Our database contained only PK for paclitaxel. In univariate covariate evaluation with respect to F or K, platinum drug type had no statistically significant impact, with covariate impacts estimated with unreliably wide confidence intervals. The most probable reason was the low proportion of patients i.e. 17% (63 out of 365) co-treated with cisplatin in cycle 1, 14% (9 out of 63) of whom changed to carboplatin in later cycles. This introduces a bias in discriminating the covariate impact of platinum drug type. Though only paclitaxel impact was evaluated, the underlying hazard may partly be attributed to co-administered drugs, suggesting an overestimated impact of paclitaxel exposure in this clinically used drug combination treatment protocol in NSCLC.

In conclusion, we successfully developed a parametric cycle-varying hazard TTE model characterizing the time-course of risk of 1st occurrence of clinically relevant paclitaxel-associated PN. Parametrically describing the baseline hazard of PN2+ enabled basing on mechanistic pharmacologic knowledge e.g. time-dependent change in risk of PN2+ with change in paclitaxel exposure, improving the characterization of observed PN2+ and enabling better prediction of future incidences. FCM evaluation of covariate effects enabled better characterization of the impact of clinically-relevant risk factors of PN2+, revealing older, male, current smokers with high paclitaxel AUC_{cycle} as the highest risk subpopulation and offering

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opportunity for prophylactic intervention or closer monitoring of symptoms for timely treatment. Model-based comparisons suggested that reduction in risk of PN2+ was attainable through dose reduction rather than dose fractionation. The model enables prediction and comparison of individual patient's risks of PN2+ for different clinically-relevant paclitaxel dosing schedules, facilitating dose selection to spare patients the disabling PN2+ and improve paclitaxel combination therapy.

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Acknowledgments

The authors thank the Central European Society of Anticancer Drug Research for providing the study data and the High-performance Computing Services of ZEDAT (Zentraleinrichtung für Datenverarbeitung) at Freie Universitaet Berlin (https://www.zedat.fu-berlin.de/HPC/EN/Home) for the computational time.

Authorship Contributions

Participated in research design: Ojara, Henrich, Huisinga, Hartung, Joerger, Kloft

Performed data analysis: Ojara

Wrote or contributed to writing of the manuscript: Ojara, Henrich, Frances, Huisinga, Hartung, Joerger, Kloft

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JPET Fast Forward. Published on October 2, 2020 as DOI: 10.1124/jpet.120.000053
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Footnote

There was no outside funding for this paper.

CK and WH report grants from an industry consortium (AbbVie Deutschland GmbH & Co. KG, Boehringer Ingelheim Pharma GmbH & Co. KG, Grünenthal GmbH, F. Hoffmann-La Roche Ltd, Merck KGaA, AstraZenaca UK Limited and Sanofi) for the PharMetrX program. CK reports grant for the Innovative Medicines Initiative-Joint Undertaking (‘DDMoRe, Drug Disease Modelling Resources) and the Federal Ministry of Education and Research within the Joint Programming Initiative on Antimicrobial Resistance Initiative (JPIAMR), all outside the submitted work.

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Captions for figures associated with main text

Figure 1: Kaplan-Meier visual predictive check for the cycle-varying hazard baseline time-to-event model showing observed and model prediction of 1st occurrence of peripheral neuropathy grades≥2 (PN2+). Proportion of patients without 1st occurence of PN2+ is plotted across time with observations censored at the last protocol treatment time, solid line: observed data (vertical lines: censor times due to dropout from various reasons); dashed line: median model-predicted profile, 90% CI (blue shade); n: number of patients at specific observation times; arrows: day of planned paclitaxel administration as specified in the study protocol.

Figure 2: Distribution of imputed paclitaxel exposure across treatment cycles for the BSA-guided and PK-guided dosing arms combined. Left: area under the plasma concentration-time curve between the start and end of a cycle (AUC_{cycle}); right: time of plasma concentrations above the threshold of 0.05 µM ($T_{C>0.05\ \mu M}$). Boxes: interquartile range (IQR), including median; whiskers (vertical lines): range from box hinge, values within ±1.5•IQR; n: number of patients receiving paclitaxel for a given cycle.

Figure 3: Increase in risk of 1st occurrence of peripheral neuropathy grades≥2 (PN2+) with change in covariate level. Proportions of 1st occurrence of PN2+ were simulated at 2.5th percentile ($P_{0.025}$) and 97.5th percentile ($P_{0.975}$) covariate levels using the cycle-varying hazard full covariate models with (orange) and without (blue) treatment arm as a covariate and percentage change in risk of PN2+ calculated. In each case the covariate of interest was set to the specified percentile while maintaining the remaining covariates at their reference values. AUC_{cycle}: area under the plasma concentration-time curve between the start and end of a cycle.

Figure 4: Cumulative risk of 1st occurrence of peripheral neuropathy grades≥2 (PN2+) across time on treatment. A: 80 mg/m^2 weekly dosing versus 200 mg/m^2 3-weekly dosing, B: 200 mg/m^2 3-weekly dosing versus 175 mg/m^2 3-weekly dosing. Shades represent 90% CI of simulated proportion of patients experiencing 1st occurrence of PN2+ across time on treatment, pink: 80 mg/m^2 weekly dosing, blue: 200 mg/m^2 3-weekly dosing, orange: 175 mg/m^2 weekly dosing.

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Tables associated with the main text

Table 1. Selected clinically relevant paclitaxel dosing schedules

Schedule	Dosing frequency
200 mg/m^2 q3w	day 1 of a 21-day cycle, 6 cycles
175 mg/m^2 q3w	day 1 of a 21-day cycle, 6 cycles
80 mg/m^2 qw	days 1, 8, 15 of a 28-day cycle, 6 cycles

q3w: once every 3 weeks; qw: once every week

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Table 2. Parameter estimates (relative standard errors, %) of the cycle-varying hazard base model and covariate models implementing different imputed paclitaxel PK metrics

Parameter	Base model: no covariate	Covariate model with $T_{C>0.01\ \mu M}$	Covariate model with $T_{C>0.05\ \mu M}$	Covariate model with $T_{C>0.1\ \mu M}$	Covariate model with AUC_{cycle}
OFV	1344.323	1337.249	1334.563	1332.735	1328.224
F, day^{-1}	0.00568 (35)	0.00500 (40)	0.00480 (41)	0.00460 (41)	0.00460 (42)
K, day^{-1}	0.0568 (42)	0.0504 (49)	0.0480 (52)	0.0477 (51)	0.0448 (55)
E_{COV}, $covariate\ unit^{-1}$	-	0.0329 (43)	0.0456 (38)	0.0652 (33)	0.0989 (29)

F: hazard surge scale factor; K: 1st-order hazard decay rate constant; E_{COV}: covariate effect parameter describing change in F with a unit change in paclitaxel exposure relative to the median exposure; OFV: objective function value; $T_{C>0.01\ \mu M,\ 0.05\ \mu M,\ 0.1\ \mu M}$: time of paclitaxel plasma concentrations above thresholds of 0.01 µM, 0.05 µM and 0.1 µM, respectively; AUC_{cycle}; area under the plasma concentration-time curve between the start and end of a cycle.

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Table 3. Pooled parameter estimates, (relative standard errors, %), (95% confidence intervals) of the cycle-varying hazard full covariate model after multiple imputation

Parameter	Parameter description	Model with no arm effect	Model with arm effect
F, day^{-1}	Hazard surge scale factor	0.00487 (42.6), (0.000852, 0.00880)	0.00659 (43.5), (0.000974, 0.0122)
K, day^{-1}	Hazard decay rate constant	0.0518 (47.9), (0.00311, 0.100)	0.0531 (47.2), (0.00486, 0.103)
E_{Arm}	Treatment arm effect on F	NA	-0.621 (41.6), (-1.13, -0.114)
E_{AUC}, 1/(μmol·h/L)	Paclitaxel AUC_{cycle} effect on F	0.0359 (51.1), (0.0000320, 0.0718)	0.00154 (151.5), (-0.0308, 0.0611)
E_{Age}, year^{-1}	Age effect on F	0.0169 (84.1), (-0.0107, 0.0445)	0.0154 (91.4), (-0.0122, 0.0429)
E_{Sex}	Sex effect on F	0.864 (22.2), (0.488, 1.23)	0.841 (22.0), (0.478, 1.20)
E_{Smok}	Smoking status effect on F	1.27 (20.4), (0.761, 1.78)	1.33 (20.2), (0.804, 1.85)

Covariate-parameter relations were implemented using an exponential model for paclitaxel AUC_{cycle}, age, and treatment arm (BSA-guided dosing=0, PK-guided dosing=1) and a power model for sex (male=0, female=1) and smoking status (current non-smokers=0, current smokers=1). The 95% CI of each parameter was derived from standard errors of estimated parameters by transformation of the variance-covariance matrices.

JPET Fast Forward. Published on October 2, 2020 as DOI: 10.1124/jpet.120.000053
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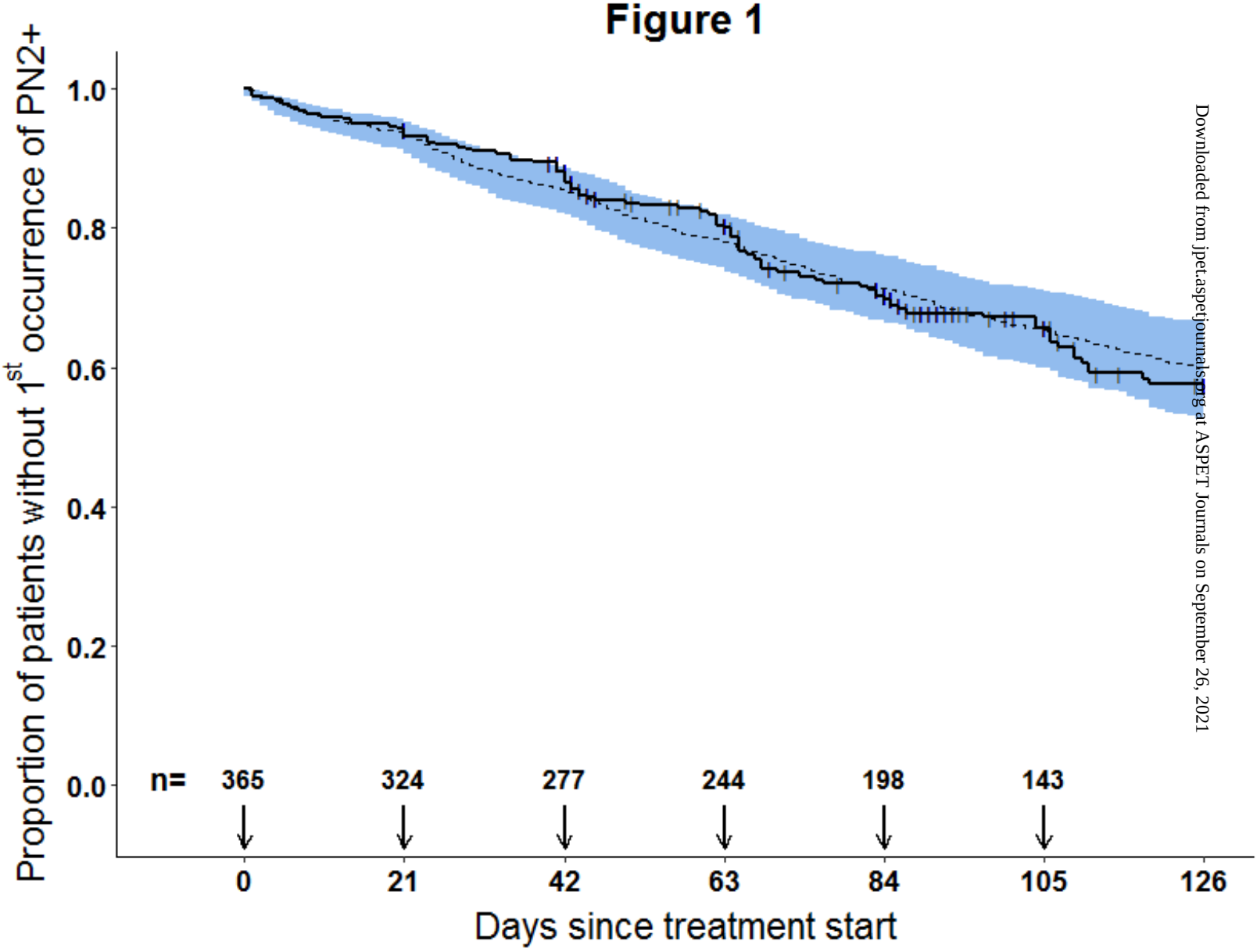
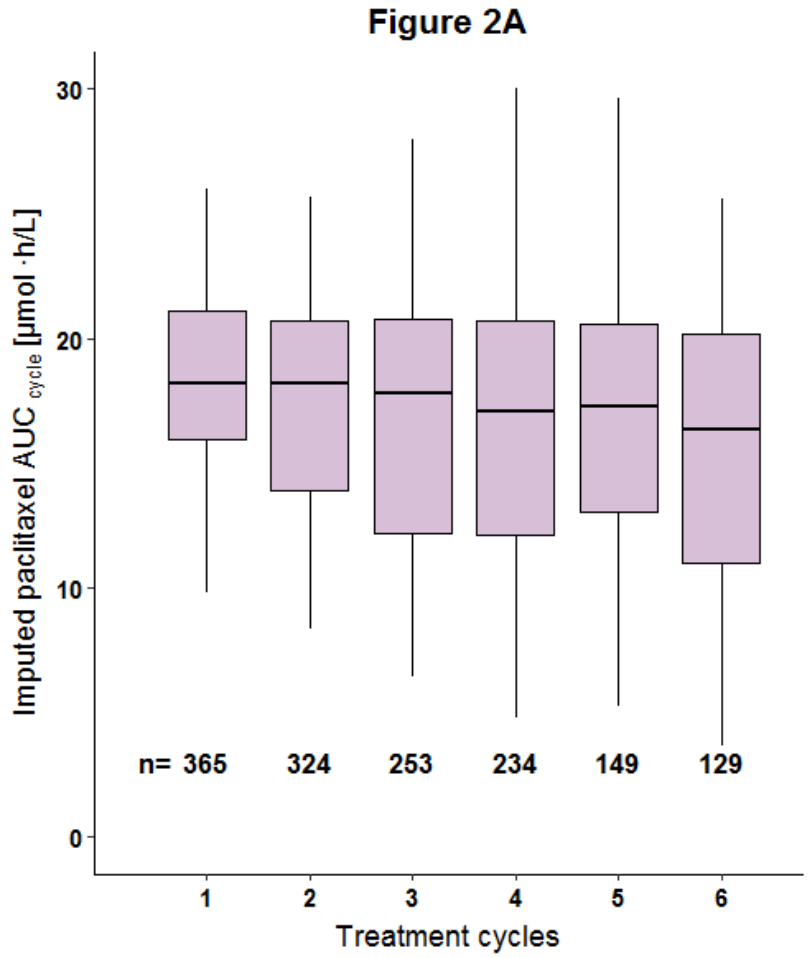
Table 4. Comparison of risk of 1st occurrence of PN2+ (90% confidence intervals) between different clinically relevant paclitaxel dosing schedules

Schedule	**Percentage of PN2+**	**Risk ratio**	
		175 mg/m^2 q3w: 200 mg/m^2 q3w	**80 mg/m^2 qw: 200 mg/m^2 q3w**
200 mg/m^2 q3w	44.2 (32.4, 54.8)	-	-
175 mg/m^2 q3w	39.6 (29.4, 49.3)	0.891 (0.795, 1.01)	-
80 mg/m^2 qw	64.1 (45.0, 78.3)	-	1.42 (1.09, 1.90)

PN2+: peripheral neuropathy grades≥2; q3w: once every 3 weeks; qw: once every week

Figure 1





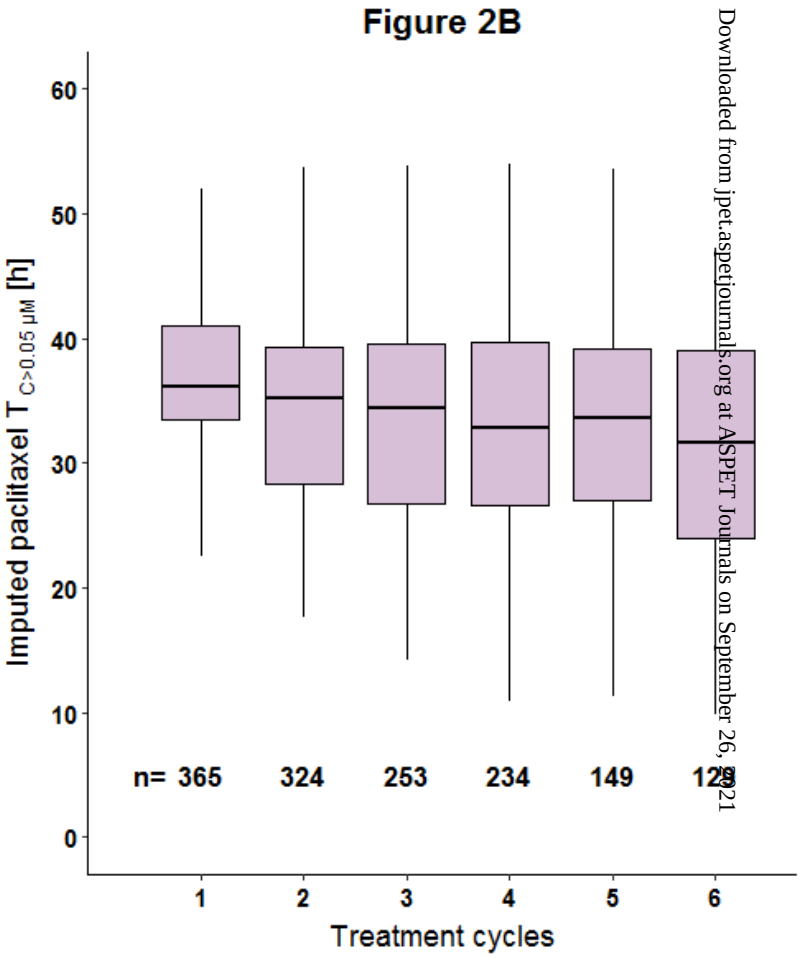


Figure 3

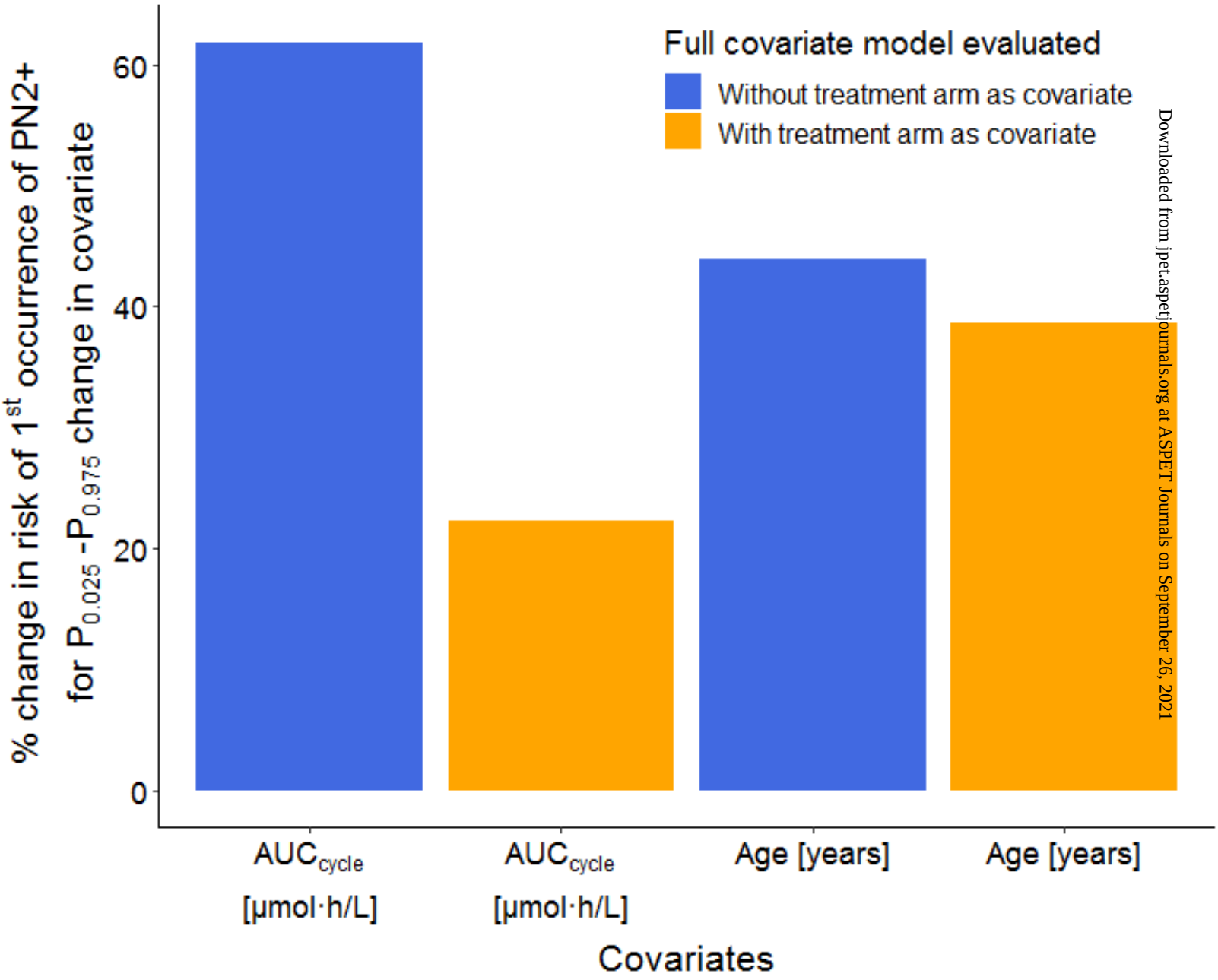


Figure 4A

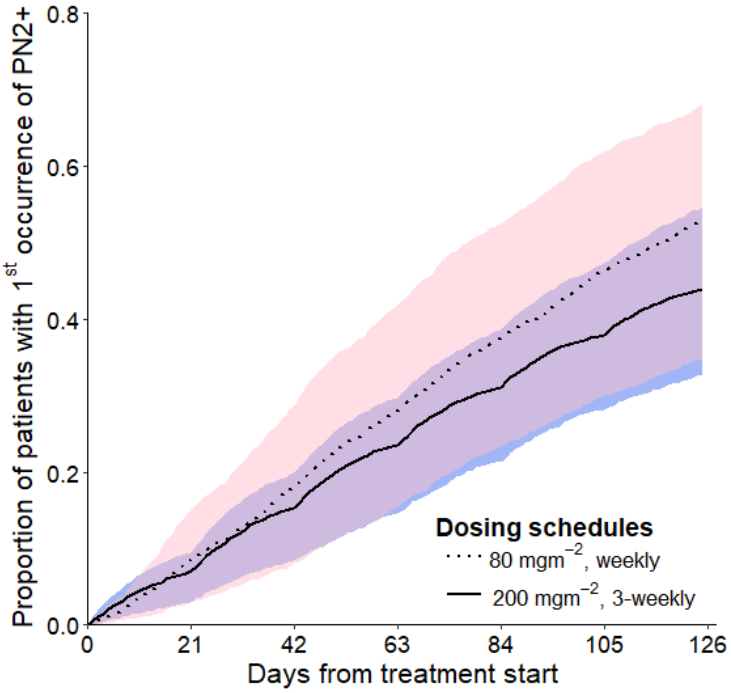


Figure 4B