

# A time-to-event analysis of paclitaxel-related peripheral neuropathy in patients with advanced non-small cell lung cancer receiving first line chemotherapy

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## Background and Objectives

Peripheral neuropathy (PN) is a cumulative, dose-limiting adverse event of paclitaxel (PTX). Over 20% of patients on doses >175 mg/m<sup>2</sup>, 3-weekly, experience clinically important PN (CIPN, grades ≥2) [1]. The risk of CIPN increases with higher PTX doses and exposure (time of plasma concentration >0.05 μM, T<sub>C>0.05 μM</sub>) [2,3]. PK/PD-guided dosing significantly lowers the risk of CIPN compared to the standard BSA-guided dosing [4]. A description of

change in risk of PTX-associated PN with time is missing: hence the underlying biology and cumulative nature of PN not accounted for. The focus of this work was to:

- describe how the risk of PTX-associated PN changes with time,
- identify associated patient- and treatment-related factors to guide treatment and reduce the occurrence of PN.

## Methods

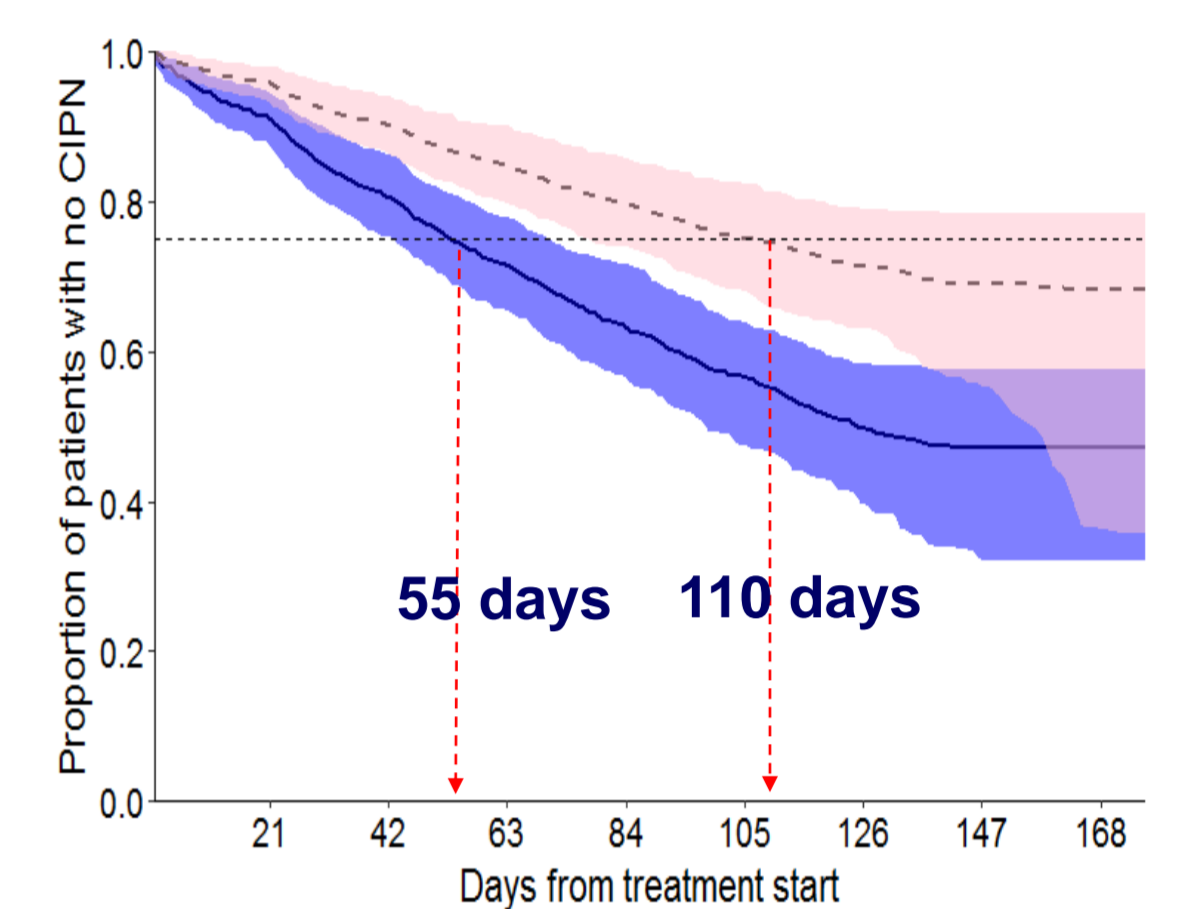
- Patients (n=366) from the CEPAC-TDM trial, treated with PTX plus carboplatin or cisplatin, 3-weekly, ≤6 cycles, were included [4]
- PTX dosing (treatment arms): BSA-guided (n=183) or PK/PD-guided (n=183)
- PN was documented according to the common toxicity criteria (V. 4.0) [5]
- Incidence (1<sup>st</sup> occurrence) of CIPN was considered an event
- Time-to-event analysis was used to describe risk of CIPN with time
  - Models: constant, Weibull, Gompertz, log normal and cycle-varying hazard
- Impact of PTX dose, AUC, T<sub>C>0.05 μM</sub>, treatment arm, age, weight, sex, and smoking status were evaluated:
  - Univariate analysis (all covariates): statistical significance, LRT, α=0.05 (df=1)
  - Full covariate modelling (FCM) [6] (pre-selected covariates).
- CIPN risk was explored at 200 mg/m<sup>2</sup> and 175 mg/m<sup>2</sup> dose levels
- Software: R (3.4.3), RStudio (1.1.447), NONMEM (7.3.0), PsN (4.2.0) and Pirana (2.9.4). NONMEM FO method.

## Results (cont.)

**Table 1.** Parameters estimates of the cycle-varying hazard model, including statistically significant covariates

Parameters	Models (parameter relations)		
	Base model	Relative dose [mg/m <sup>2</sup> : on F	Treatment arm: on F
OFV	1345.9	1336.9	1333.4
ΔOFV (from base model)	0	-9	-12.5
K [% RSE] [day <sup>-1</sup> ]	0.0564 (42)	0.0480 (50)	0.0556 (42)
F [% RSE] [day <sup>-1</sup> ]	0.00560 (35)	0.00530 (39)	0.0037 (35)
COV [%RSE] [unit <sup>-1</sup> ]	-	0.0118 (39)	0.703 (29)

K: 1<sup>st</sup> order hazard decay rate constant, F: hazard surge scale factor, COV: covariate effect parameter, describing change in F with a unit increase in PTX dose or for PK/PD-guided relative to BSA-guided dosing.



**Fig 3.** Kaplan-Meier plots for risk of CIPN by treatment arm: median proportion for BSA-guided dosing (solid line), blue shade (90% CI) and PK/PD-guided dosing (dashed line), pink shade (90% CI).

- FCM: pre-defined covariates evaluated against F

$$F = TVF \cdot \left( \frac{PTX \text{ Dose}}{Ref \text{ PTX Dose}} \right)^{EDose} \cdot \left( \frac{Age}{Ref \text{ Age}} \right)^{EAge} \cdot \left( \frac{Wt}{Ref \text{ Wt}} \right)^{EWt} \cdot ES_{Sex} \cdot ES_{Smok}^{Smoking \text{ status}}$$

TVF: typical value of F; Ref PTX Dose, Ref Age and Ref Wt are population median values of PTX dose, age and weight respectively; EDose, EAge, EWt, ES<sub>Sex</sub> and ES<sub>Smok</sub> are covariate effect parameters for PTX dose, age, weight, sex and smoking status respectively.

- For each covariate, HR were computed at different covariate levels (Fig 4)
- Model application: comparison of risk of CIPN at 175 mg/m<sup>2</sup> and 200 mg/m<sup>2</sup>

## Results

- 105 events were reported: more frequent at cycle start, and gradual decline across the cycle
- The cycle-varying hazard model best described the data (Fig. 1, Fig. 2):
  - surge in events at cycle start and gradual decline across cycles

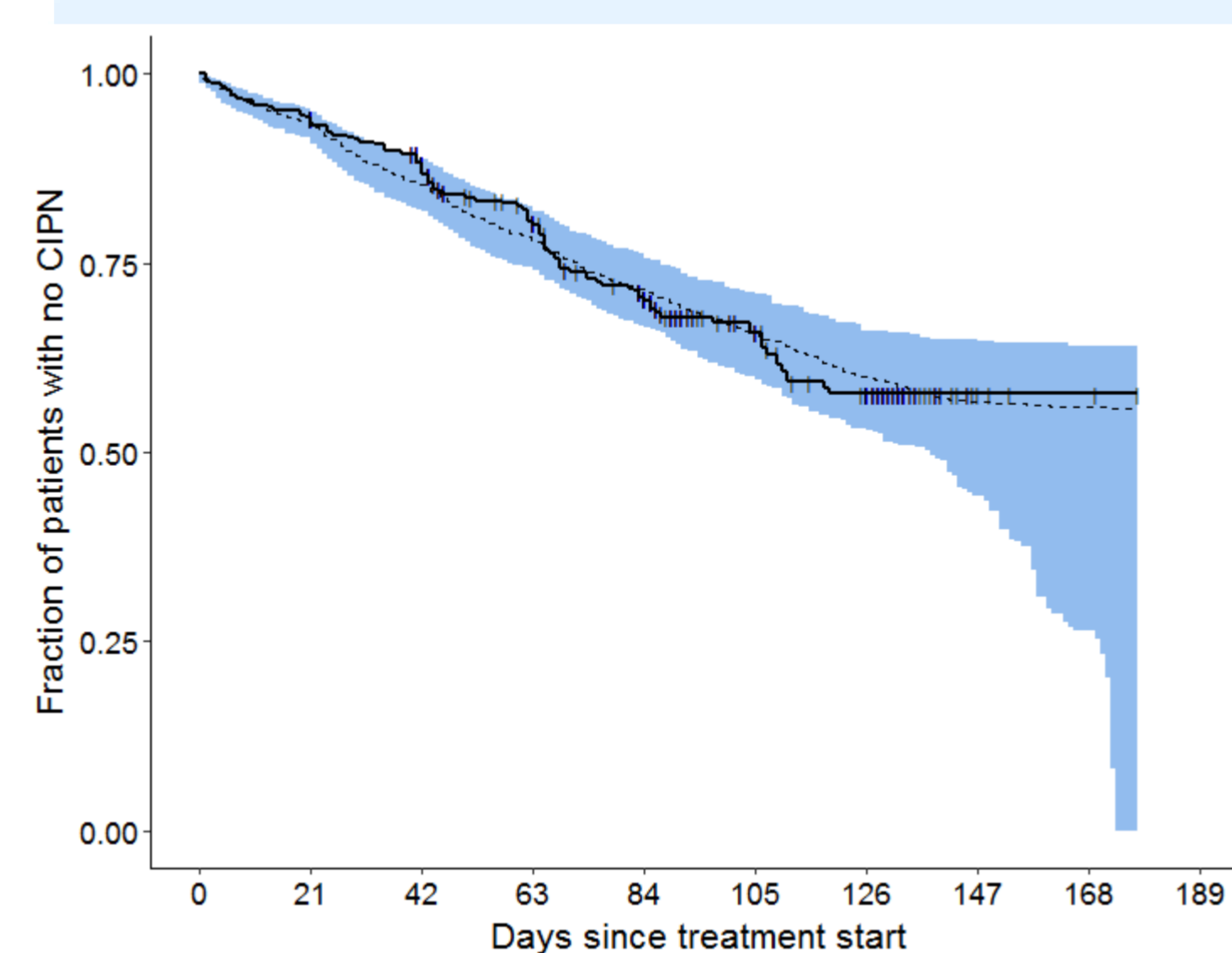
Unit hazard of CIPN at cycle start

↓ F

Hazard (λ) compartment

- Risk increases at cycle start
- Risk decreases across cycle

↓ K



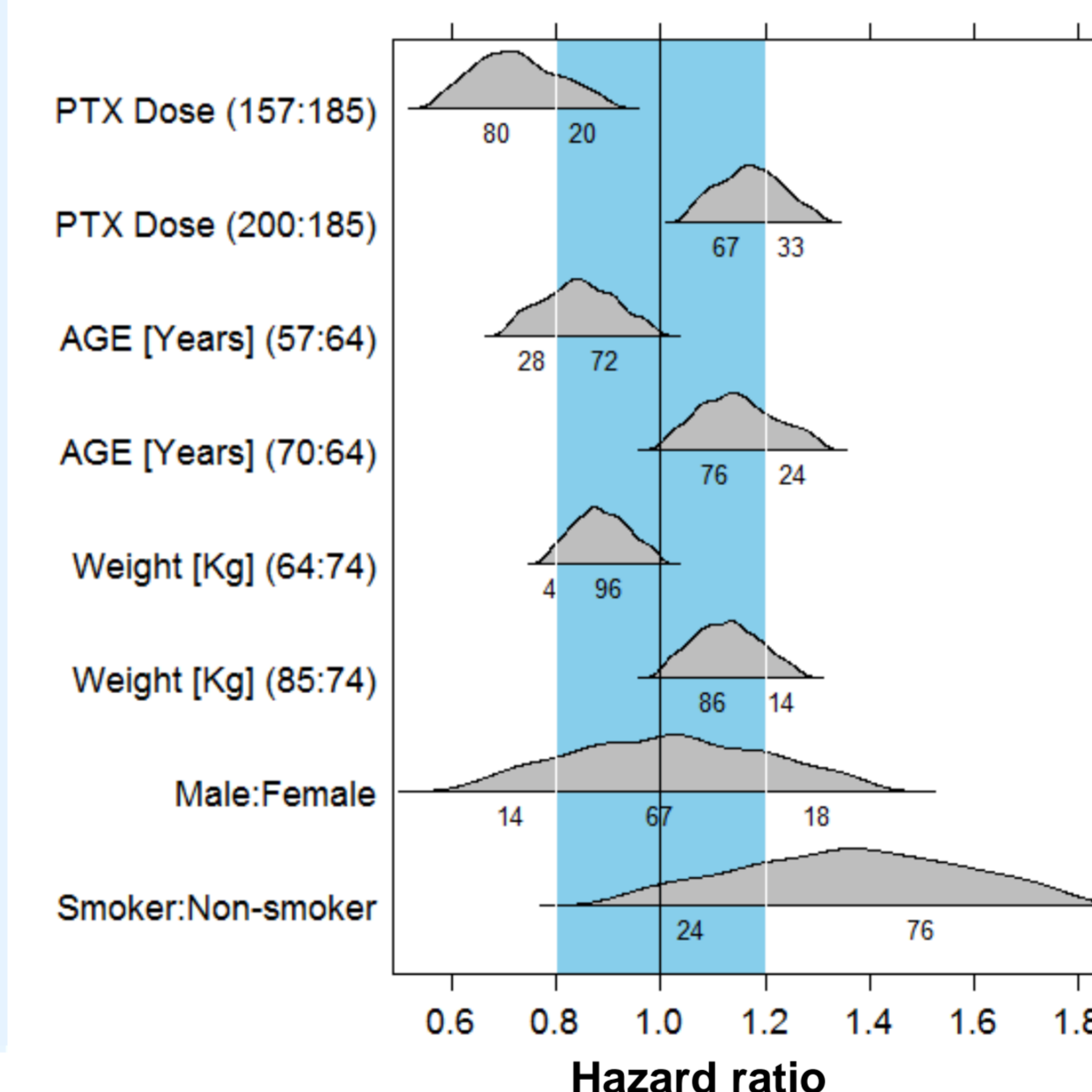
**Fig 2.** Kaplan-Meier VPC for the cycle-varying hazard model. solid line: observed data, vertical lines: censor times, dashed line: median simulated CIPN, blue shade: 95% CI

**Fig 1.** A schematic of the cycle-varying hazard model. F: hazard surge scale factor K: hazard decay rate constant

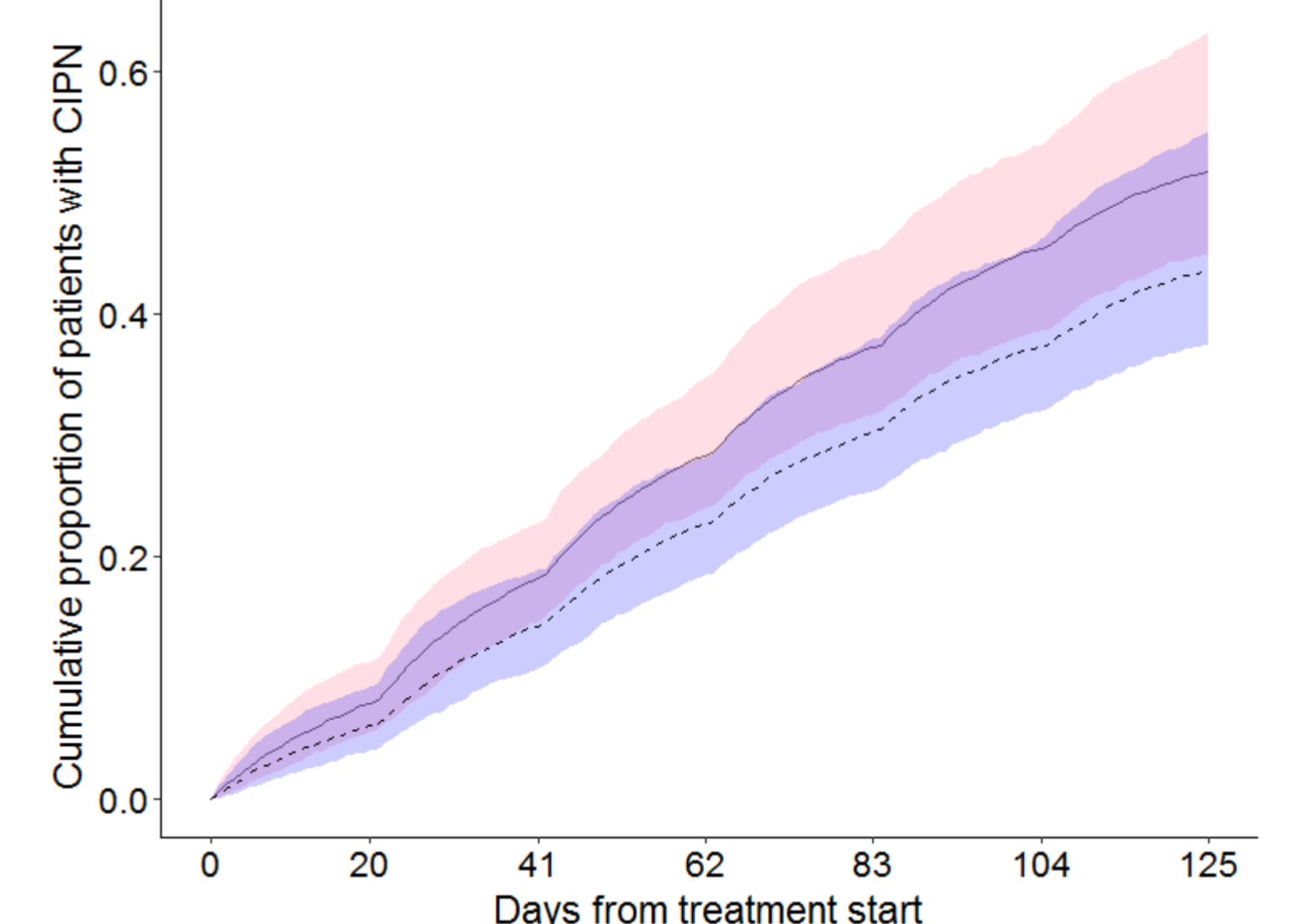
$$\begin{aligned} \text{At cycle time, } t=0 \text{ d, } & \lambda_t = \lambda_{t-1} + F, \\ \text{At cycle time, } t>0 \text{ d, } & \lambda_t = -K \lambda_t \end{aligned}$$

- λ<sub>t-1</sub>: hazard of CIPN on last day of previous cycle, for cycle 1, λ<sub>t-1</sub> = 0
- λ<sub>t</sub>: hazard of CIPN at cycle time, t
- F: hazard surge scale factor, describes hazard increase at cycle start
- K: hazard decay rate constant, describes hazard decrease with time across cycle

- Univariate analysis: only PTX dose and treatment arm were statistically significant
  - CIPN risk increased by 12.5% per 10 mg/m<sup>2</sup> PTX dose increase (Table 1)
  - BSA-guided dosing was associated with 50% risk increase (Fig 3)



**Fig 4.** 1000 bootstrap parameter sets generated from the FCM parameters (with uncertainty). HR computed at two covariate levels. Blue shade: +/-20% of null value (HR=1.0), region of clinical irrelevance



**Fig 5.** Model-predicted incidence of CIPN for 3-weekly dosing, ≤6 cycles. 250 trials simulated (1050 patients each). Median proportions, dashed line: 200 mg/m<sup>2</sup>, pink shade (90% CI); solid line: 175 mg/m<sup>2</sup>, blue shade (90% CI).

- Age (Fig. 4) and PTX dose (Fig. 4, Fig. 5). were clinically relevant on CIPN
  - 15% higher risk, 70:64 year old patients: HR (90% CI), 1.15 ( 1.01, 1.31)
  - Higher risk with 200 mg/m<sup>2</sup> across all treatment times
  - 19% higher risk for 200 mg/m<sup>2</sup>:175 mg/m<sup>2</sup>, HR (90% CI), 1.19 (1.06, 1.33)

## Discussion and Conclusions

- Change in risk of PN with time was described using time-to-event analysis: further accounting for the cumulative nature of PN
- PK/PD-guided dosing reduced the risk of PN
- PTX dose and age were clinically important whereas weight, sex and smoking status were not
- The model will be used to improve our understanding of the impact of different PTX dosing strategies and patient characteristics on the risk of PN

## References

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