

Distinguishing myelosuppressive response of a paclitaxel – radium-223 combination using a model-based analysis of an individual cross-over phase-Ib trial in cancer patients with bone lesions

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Introduction

Concomitant treatment with radium-223 and paclitaxel is a potential treatment for cancer patients with bone metastases; the agents have potentially synergistic mechanisms of action, e.g. myelosuppression.

Objective

Evaluate the potential interaction of concomitant paclitaxel and radium-223 treatment on the myelosuppression with a PK/PD modeling approach.

Methods

Neutrophil data were obtained from an open-label, multicenter, nonrandomized phase Ib study in cancer patients with bone metastases, intended to enable the separation of the myelosuppressive effect of the 2 drugs, and allowing a small sample size (Figure 1). The first 12 weeks were the main observation period with neutrophil observations obtained twice per week. There were 12 patients included in the analysis, all of whom completed treatment cycles 1 – 3.

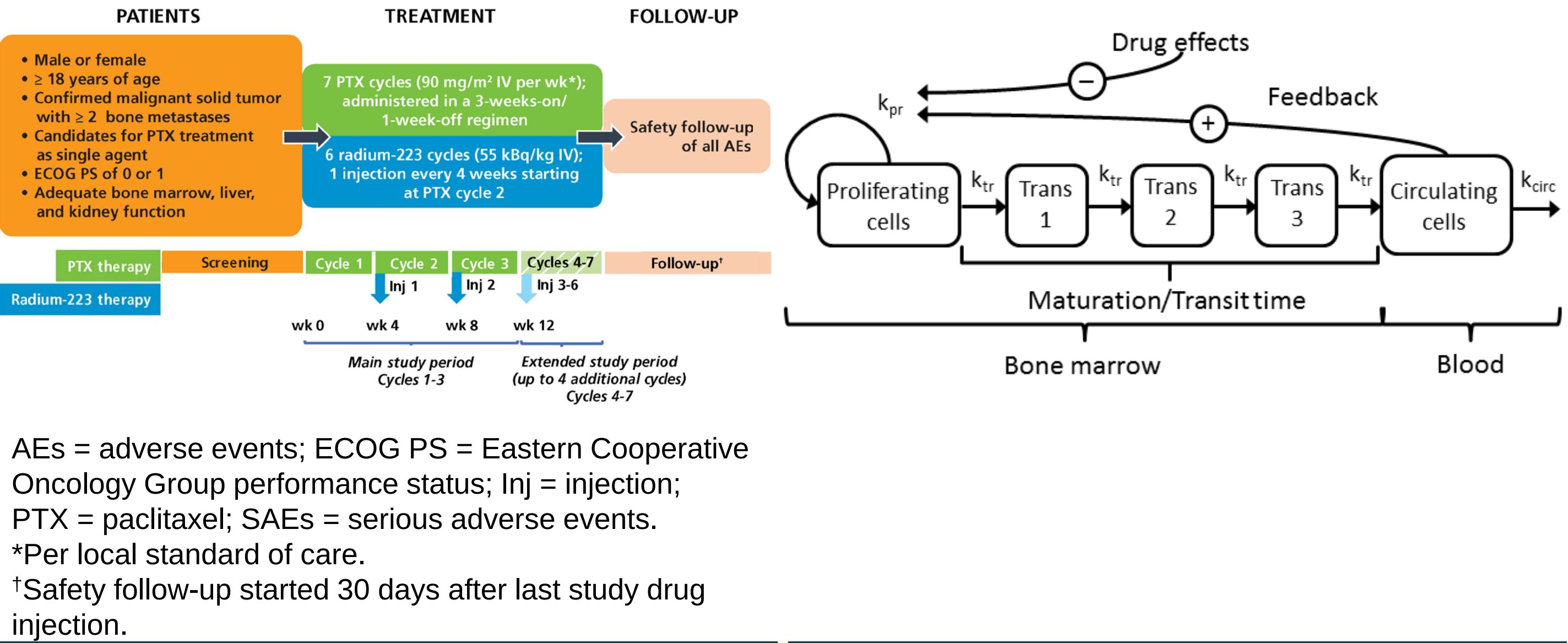


Figure 1: Study Design **Figure 2: Model structure**

A previously developed semimechanistic PK/PD model [1] was used, describing the time course of paclitaxel-induced myelosuppression (Figure 2). This model had been adapted for monotherapy with radium-223. The paclitaxel and radium-223 models were combined to evaluate the myelosuppression under concomitant treatment with radium-223 and paclitaxel in the current phase Ib study. The combined model was used to simulate a typical subject treated with the standard of care for paclitaxel mono, radium-223 mono and concomitant treatment.

Models were implemented in NONMEM 7.3.

Results

Following refinement of parameter values, the paclitaxel mono model adequately described the time course of paclitaxel-induced myelosuppression in cycle 1 (Figure 3 & 4).

In the combined radium-223 and paclitaxel model, the drug effect was implemented as Bliss Independence model [2]. The model adequately described the drug-induced myelosuppression in cycles with concomitant treatment (Figure 5 & 6). Model parameter estimates of the final model were consistent with previously reported results [1] (Table 1). For model development the radium-223 effect had been fixed to the estimate from the radium-223 mono model. Supplementary, the radium-223 effect could be estimated in the final model (0.0243, 95% CI: 0.0127, 0.0360) with very similar value and widely overlapping confidence intervals.

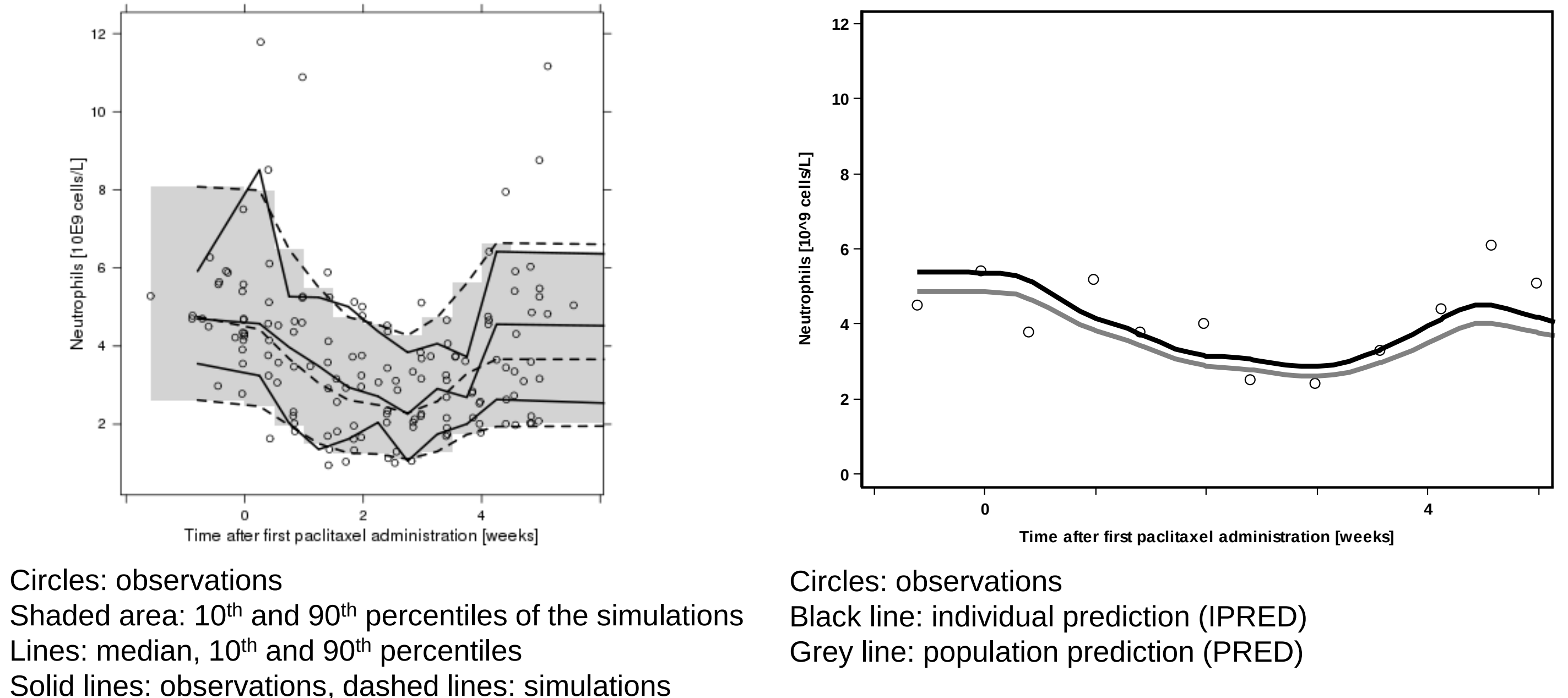


Figure 3: Visual predictive check for paclitaxel mono **Figure 4: Observed and predicted neutrophils of a typical subject for paclitaxel mono**

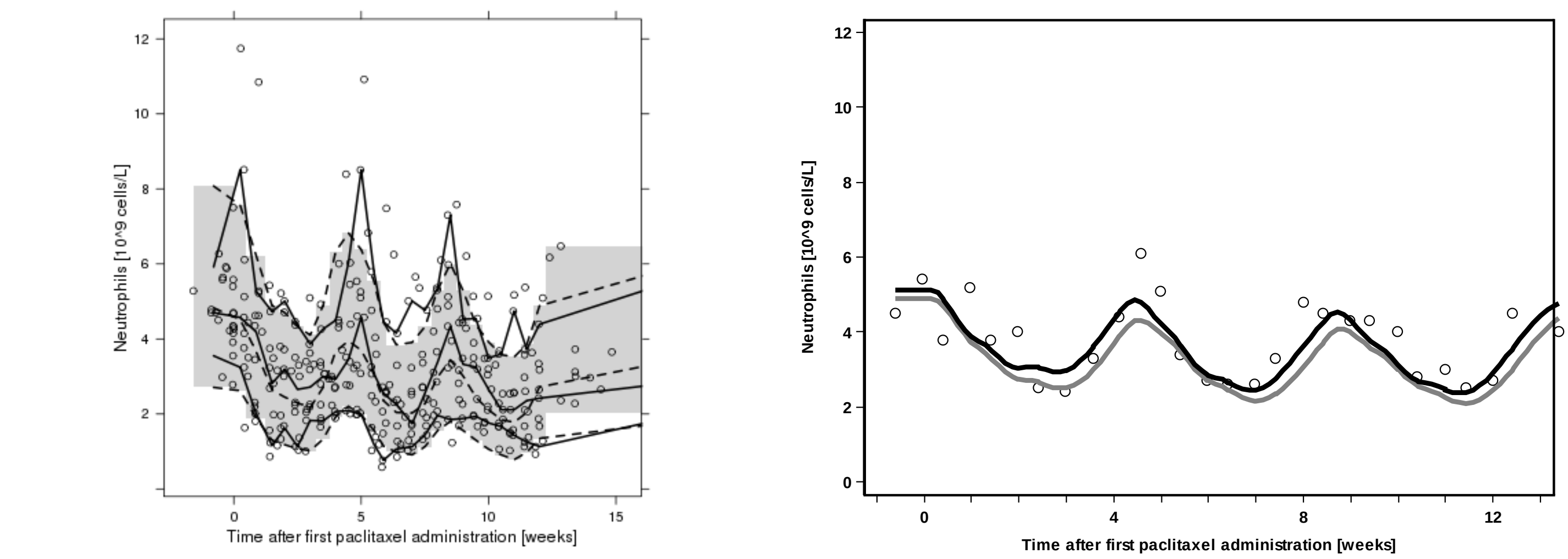


Figure 5: Visual predictive check for concomitant treatment **Figure 6: Observed and predicted neutrophils of a typical subject for concomitant treatment**

Table 1: Parameter estimates of models with paclitaxel and radium-223 mono and concomitant treatment or treatment with other chemotherapies
(f) = fixed

Parameter	Unit	Estimate (95% CI)				
		Fixed effects (THETA)				
		Combined	Paclitaxel mono	Radium-223 mono[3]	Paclitaxel mono Friberg[1]	5 drugs Friberg[1]
Neutrophil cell count at baseline	10 ⁹ cells/L	4.90 (4.12, 5.68)	4.85 (4.20, 5.50)	4.43 (4.18, 4.69)	5.2	4.72 – 5.51
Mean maturation time of neutrophils	h	140 (123, 157)	139 (82.0, 196)	78.7 (56.0, 101)	127	88.7 – 135
Regulating the neutrophil proliferation stimulation	–	0.167 (0.131, 0.203)	0.145 (0.0448, 0.245)	0.165 (0.096, 0.234)	0.23	0.132 – 0.174
Paclitaxel effect	–	31.1 (24.2, 38.0)	26.9 (16.3, 37.5)	–	44.2	–
Radium-223 effect	–	0.0251(f)	–	0.0251 (0.018, 0.038)	–	–
Surrogate half life of radium-223 exposure for neutrophils	h	177(f)	–	177 (150, 203)	–	–
Random effects – Inter-individual variability (OMEGA)						
Neutrophil cell count at baseline	%	35.1(f)	35.1(f)	38.3	35	29 – 42
Mean maturation time of neutrophils	%	18.0(f)	18.0(f)	–	18	14 – 49
Paclitaxel effect	%	43.0(f)	43.0(f)	–	43	–
Radium-223 effect	%	55.2(f)	–	55.2	–	–
Residual error of neutrophils (SIGMA)						
Proportional	%	24.9	26.0	19.8	39.9	34.1 – 48.9
Additive	10 ⁹ cells/L	–	–	2.0	–	–

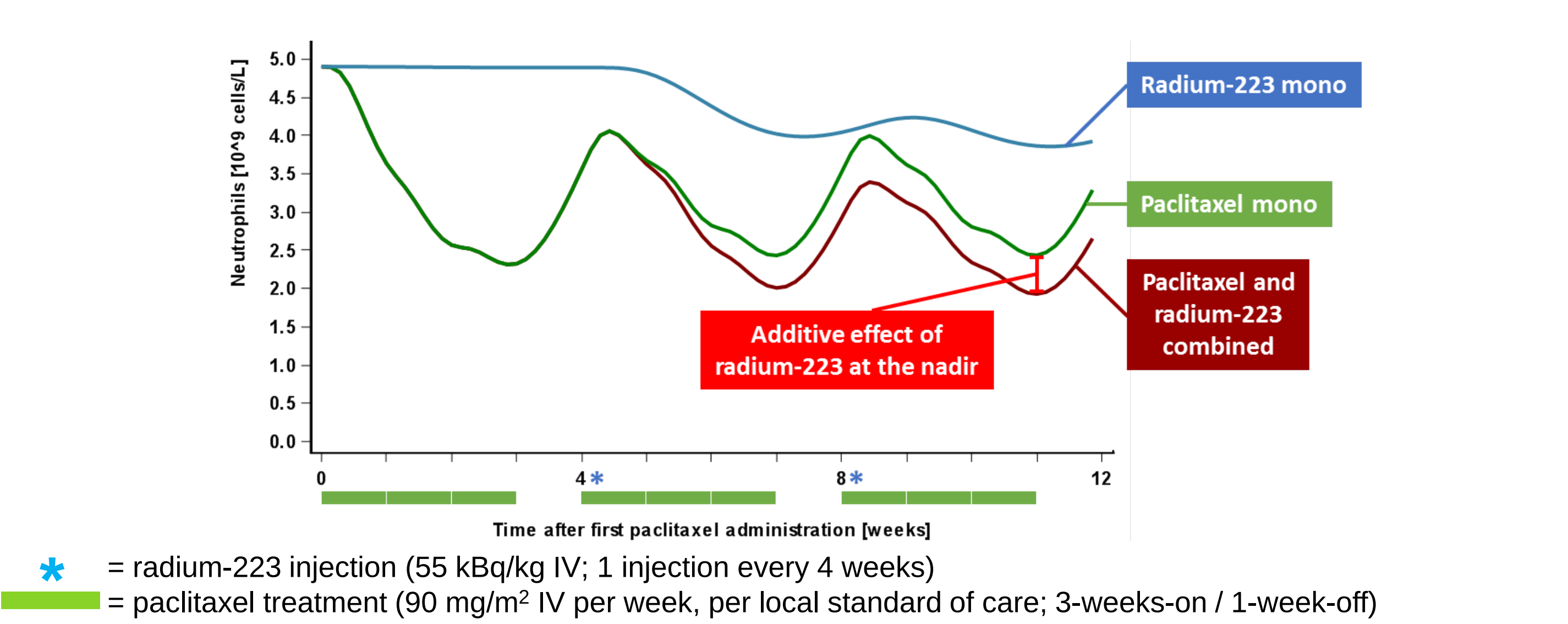


Figure 7: Simulation of a typical subject treated with paclitaxel mono, radium-223 mono and concomitant treatment

Conclusions

A combined radium-223 and paclitaxel myelosuppression model – with the drug effect implemented as Bliss Independence model – described the neutrophil time course adequately well in cancer patients with bone lesions.

The study design proved to be suitable for the separation of the myelo-suppressive effect of the 2 drugs with a small number of subjects.

Simulations of a typical patient, treated according to the analyzed study design, showed that after cycle 3 of treatment, the additional effect of radium-223 results in an additional decrease of the absolute neutrophil count at the nadir by ~10% of the baseline value when co-administered with paclitaxel, versus paclitaxel alone.

References

[1] Friberg et al. J Clin Oncol. 2002; 20: 4713-4721
[2] Foucquier J & Guedj M. 2015; 3(3): 1-11
[3] Solms et al., in preparation: Combination of modeling and clinical data to investigate myelosuppression caused by the combination treatment of paclitaxel with radium-223 dichloride in cancer patients with bone lesions