Original Article
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Sorafenib in the Treatment of Early Breast Cancer: Results of the Neoadjuvant Phase II Study – SOFIA

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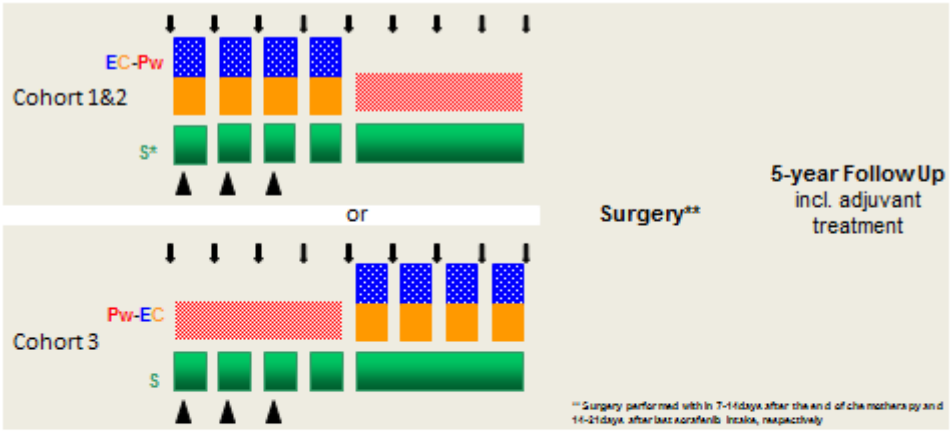
Table S1. Summary of maximum treatment cycles per drug and cohort

Cycles EC	Cohort 1 N = 12	Cohort 2 N = 12	Cohort 3 N = 12	Total
4	12	12	12	36
weeks Paclitaxel				
0	1	0	0	1
6	0	1	0	1
9	1	0	0	1
12	10	11	12	33
weeks Sorafenib				
3	2	.	·	2
5	1	.	·	1
9	1	.	·	1
11	.	2	·	2
12	2	.	·	2
13	1	.	.	1
14	.	.	1	1
15	.	.	2	2
18	1	.	·	1
19	.	.	2	2
21	1	1	·	2
23	2	7	7	16
26	1	1	·	2
unknown	.	1	·	1

Figure S1. Study Design and Dose escalation model.

A



Epirubicin: 90 mg/m² i.v.
Cyclophosphamide: 600 mg/m² i.v. } EC cycle: once every 21days on day 1
Paclitaxel: 80 mg/m² i.v., weekly
*Sorafenib: 800mg orally (cohort 1)
*Sorafenib: Dose escalation 200-800mg during EC (cohort 2)
Sorafenib: Dose escalation 200-800mg during Pw (cohort 3)
Pharmacokinetic analyses EC/Pw cycle 1 and EC/Pw cycle 2 or 3
Sampling for translational research

B

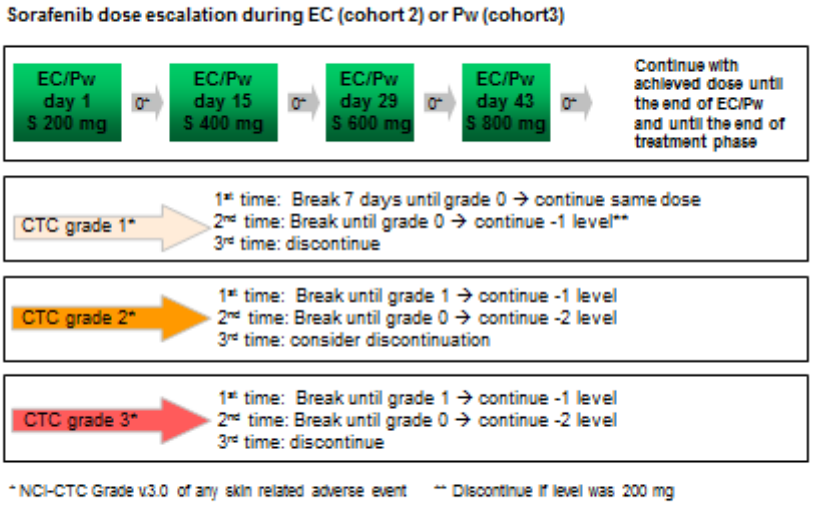
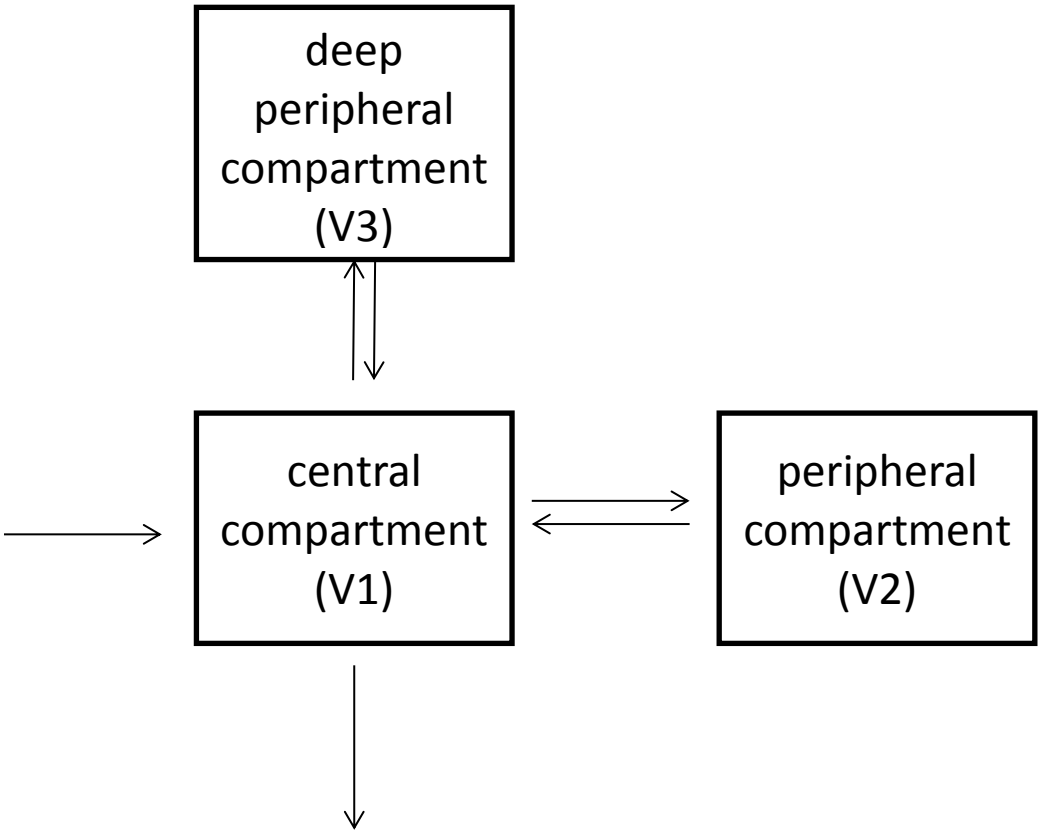


Figure S2. Pharmacokinetic model for the prediction of epirubicin plasma concentrations after infusion.



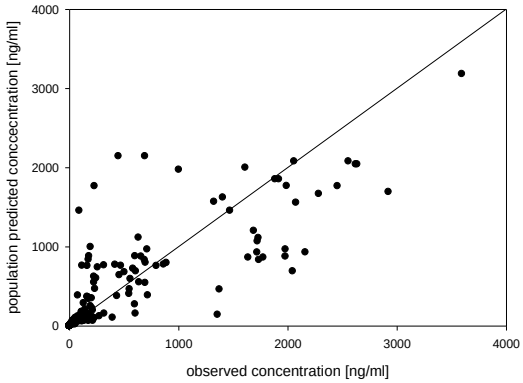


Figure S3. Population predicted epirubicin concentrations versus observed concentrations.

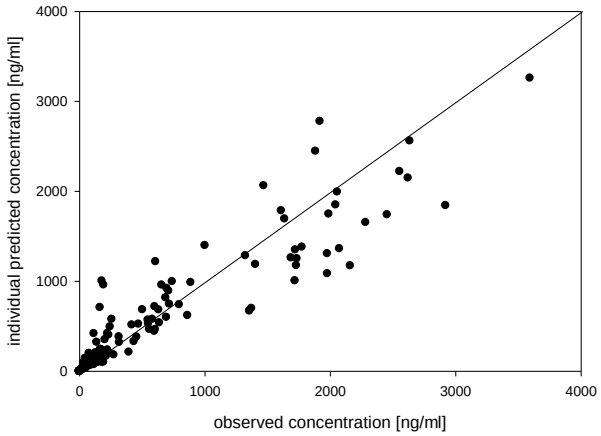


Figure S4. Individual predicted epirubicin concentrations versus observed concentrations.

Supplementary Material and Methods

Tumour assessment

Haematology was assessed weekly and biochemistry every three weeks. The target lesion and lymph nodes were measured every 6 weeks and prior to surgery by palpation and ultrasound. Mammography was done after 12 weeks and prior to surgery. All other examinations were performed as clinically indicated.
Pathologic response was assessed by the local pathologist and centrally reviewed at GBG headquarters. Response was staged according to the TNM classification [1]. Pathological complete response (pCR) was defined as no residual invasive disease in the breast irrespective of lymph node involvement (ypT0/Tis, ypN0/ypN+). In addition, other pCR definitions were reported. Clinical complete response was defined as the absence of evidence of disease in the breast on palpation or ultrasonographic examination. A partial response was defined as a reduction in the product of the two largest perpendicular diameters of the primary tumour by 50% or more; progressive disease was defined as an increase in tumour size by 25% or more or the presence of a new lesion. All remaining scenarios were categorized as no change. Patients were considered to have had breast conserving surgery if the final surgical procedure was tumorectomy, segmentectomy, or quadrantectomy. Toxic effects were graded with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTC v3). After the initial 12 weeks (4 cycles EC or 12 weeks P) of therapy, an additional tumour core biopsy had to be performed.

Model building procedures

Data analysis was performed using the nonlinear mixed-effect software in ® 7.2.0 (ICON Development Solutions, Ellicott City, MD, USA) with a GNU Fortran 4.6 compiler (Free Software Foundation, Inc., Boston, MA, USA). The toolkit PLT Tools (PLTsoft, San Francisco, CA, USA) served as an application programming interface to NONMEM to aid model development and evaluation. Graphical data visualization was performed using R (R Foundation for Statistical Computing, Vienna, Austria).
Model derivation and justification was guided through a difference in the objective function value (ΔOFV) generated via NONMEM to carry out comparisons between any two models. A ΔOFV of 3.84 point (approximate χ^2-distribution) for an additional parameter was used for determining statistical significance ($P < 0.05$) of the difference between two models, visual inspection of goodness-of-fit plots, physiological plausibility of parameter estimates, and statistical precision of model parameter estimates. The 95% confidence intervals for the parameter estimates should not include zero or unity (whatever applicable). Each model was specified as a set of differential equations that were solved by using subroutine ADVAN6 using the PRED routine and the first-order conditional estimation method with interactions [2].
The model building started with a one-compartment-model by which the data were poorly described. (fig. S2) A two compartment-model described the data better, but still with clear misspecifications. The three-compartment model (fig. 2) described the data much better than the two-compartment model, and was therefore used as the basic model for further analyses. Stepwise inclusion of covariates such as weight, sex and age did not lead to a significant ΔOFV, and therefore no covariates were included in the final model.
In this model the elimination clearance and the clearance (CL1) between central and deep peripheral compartment (CL3) was considered as varying interindividually. Additionally, between occasional variability (BOV) was estimated between the first drug intake (period 1) and the later drug intake (period 2 or 3).

1. American Joint Committee on Cancer: AJCC cancer staging manual. 7th ed. New York: Springer, 2010.
2. Beal SL, Sheiner LB. NONMEM Users Guides, (1989–2006) (Icon Development Solutions, Ellicott City, MD, 2008).