Additional file 1

Estimation of AUC

For each cycle, AUC was calculated. Concentration of doxorubicin was estimated in plasma immediately after infusion of PLD ($c_0$), prior to onset of apheresis ($c_{\text{aphstart}}$) and after termination of apheresis ($c_{\text{aphend}}$). Elimination of Caelyx was assumed first order and monophasic$^2$ (equ. 3).

$$c(t) = c_0 \cdot \exp\left(-\frac{1}{k}t\right) \quad (3)$$

With

$$k = \frac{t_{1/2}}{0.693} \quad (4)$$

The constant $k$ was estimated by regression analysis using the measured doxorubicin concentrations $c_0$ and $c_{\text{aphstart}}$. Regression was done iterative by slide write curve fitting function (Slide Write 6.0, Advanced graphics software Inc., California, USA).

To calculate the AUC, the respective integrals of equ. 3 were used. To calculate AUC without apheresis ($AUC_{\text{normal}}$), the integral between $t=0$ and $t=504$ (3 weeks = 21 days = 504 h) was estimated.

$$AUC_{\text{normal}} = \int_0^{504} c_0 \cdot -k \cdot \exp\left(-\frac{1}{k}t\right) dt \quad (5)$$

For calculating of the AUC with apheresis ($AUC_A$), the AUC of three distinct phases were summarized:

$$AUC_{\text{aperh}} = AUC_{\text{aperh1}} + AUC_{\text{aperh2}} + AUC_{\text{aperh3}} \quad (6)$$

$AUC_{\text{aperh1}}$ corresponds to the AUC until the onset of apheresis, $AUC_{\text{aperh2}}$ corresponds to the AUC during the time of apheresis, and $AUC_{\text{aperh3}}$ describes the AUC from termination of apheresis until end of cycle.
With $t_{\text{aphstart}}$ being the time in hours until apheresis was initiated, $AUC_{\text{apher1}}$ was calculated in the same way as $AUC_{\text{normal}}$:

$$AUC_{\text{apher1}} = \int_0^{t_{\text{aphstart}}} c_0 \cdot -k \cdot \exp\left(-\frac{1}{k}t\right) dt \quad (7)$$

With $c_{\text{aphstart}}$ being the plasma concentration of doxorubicin at apheresis onset, $c_{\text{aphend}}$ being the respective concentration when apheresis was terminated, and $t_{\text{apher}}$ being the duration of apheresis (~3-4 h), $AUC_{\text{Phase2}}$ was calculated:

$$AUC_{\text{apher2}} = (c_{\text{aphstart}} - c_{\text{aphend}}) \cdot t_{\text{apher}} \quad (8)$$

When apheresis was terminated, elimination was assumed to proceed normal, and $AUC_{\text{apher3}}$ was calculated from $t=t_{\text{aphend}}$ until the end of cycle ($t=504$ h) using $c_{\text{aphend}}$ and $k$.

$$AUC_{\text{Phase3}} = \int_{t_{\text{aphend}}}^{504} c_{\text{aphend}} \cdot -k \cdot \exp\left(-\frac{1}{k}t\right) dt \quad (9)$$

The differences in AUC were calculated as:

$$\Delta AUC = \left(1 - \frac{AUC_{\text{apher}}}{AUC_0}\right) \cdot 100 \ [\%] \quad (10)$$