

Ceralasertib-induced haematological toxicity modelling to support monotherapy Recommended Phase 2 Dose determination

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Introduction and objectives

Ceralasertib (AZD6738) is an inhibitor of the ATR protein kinase, the apical kinase in the replication stress response DNA-damage induced checkpoint pathway [1], currently in clinical development in patients with solid malignancies as orally daily single (OD) or twice a day (BID) administration.

The main dose limiting toxicities of ceralasertib are haematological, specially thrombocytopenia.

In order to **support the dose and schedule** for ceralasertib monotherapy RP2D and analyse the **safety and tolerability** of the compound, we utilised emerging phase I clinical data to model the relationship between exposure and platelet/neutrophil cell counts and evaluated the optimal dosing schedule needed for cell recovery. Additionally, the **rebound** from baseline during the off-treatment period was calculated from model predictions.

Methods

- A preliminary population PK (popPK) model was built using emerging phase I data from 230 patients receiving ceralasertib from 20 to 320 mg OD. The inclusion of a nonlinear behaviour into the model was explored in order to account for the less than dose proportional increase in exposure observed in the data.
- For the exposure-safety model, preliminary data from 51 subjects who received ceralasertib + durvalumab in a phase I combination study was used for model building (data included different ceralasertib doses (80-480 mg daily doses) and different treatment durations (7- vs 14-day continuous treatment)). We assumed that the myelosuppressive effects were driven by ceralasertib only based on the mechanism of action. Individual PK profiles were derived using the ceralasertib popPK model as matched PK and platelet/neutrophil observations were generally not available. See a schematic representation of the workflow in Fig. 1.
- Friberg model [2] was used as the structural PD model to describe drug-induced myelosuppression where the individual PK profiles affected the proliferation of the platelet/neutrophil counts. See a representation of the model and data in Fig. 1 part 2.

Methods

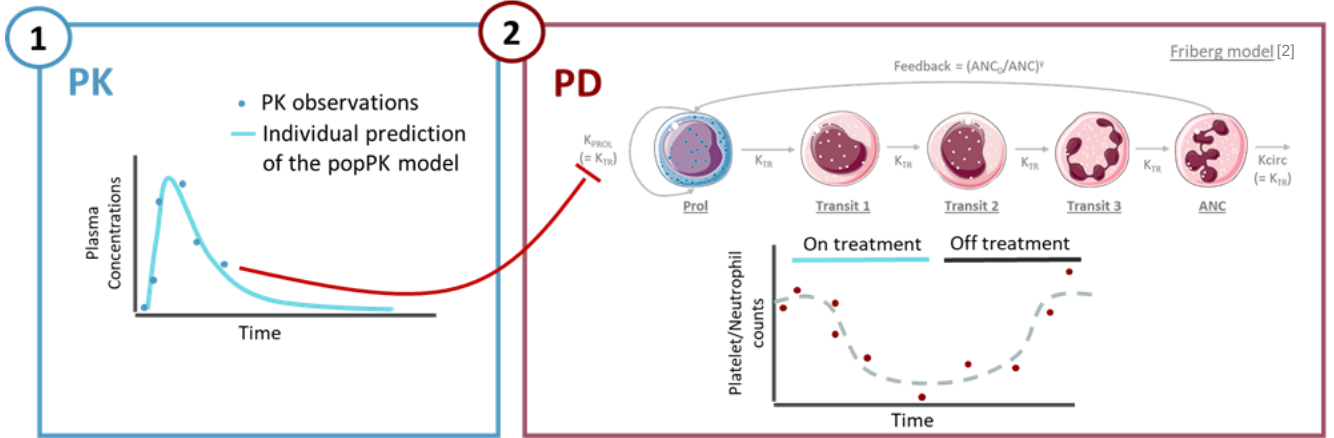


Figure 1. Schematic representation of the workflow and data.

- Modelling procedure was performed using NONMEM 7.3, PsN [3] and NMproject [4]. Simulations of the model in the mrgsolve R package [5] were used to explore different dose and schedule options.

Results

A popPK and a PK-safety models for ceralasertib were developed describing ceralasertib-induced thrombocytopenia and neutropenia.

- The popPK model consisted of a two-compartment model with first-order absorption (modelled with 3 transit compartments) and linear elimination and a relative bioavailability parameter (F_{rel}) that decreased linearly (with a slope parameter: slp) with increasing ceralasertib dose:
$$F_{rel} = 1 - slp \cdot (80 - dose)$$
- The PK-safety model demonstrated that individual PK profiles affected the proliferation of the cells by a linear inhibitory function. See final parameter estimates of the Friberg model and between-subject variability in Table 1.
- Model and simulation results showed that two-week off treatment period is optimal for platelet/neutrophil recovery (Fig. 2 shows platelet count simulation). A shorter off treatment period would lead to an incomplete recovery of the platelets/neutrophils for some patients which would provoke more grade 3, 4 adverse events in subsequent cycles and potential treatment delays. The probability of having $\geq$ grade 3-4 thrombocytopenia and neutropenia are summarized in Table 2.
- Platelet counts showed a higher rebound (increase from baseline values) in the off-treatment period compared to neutrophils (characterized with the feedback parameter γ), specially under the 14 days 240 mg BID dose of ceralasertib (see Table 2).

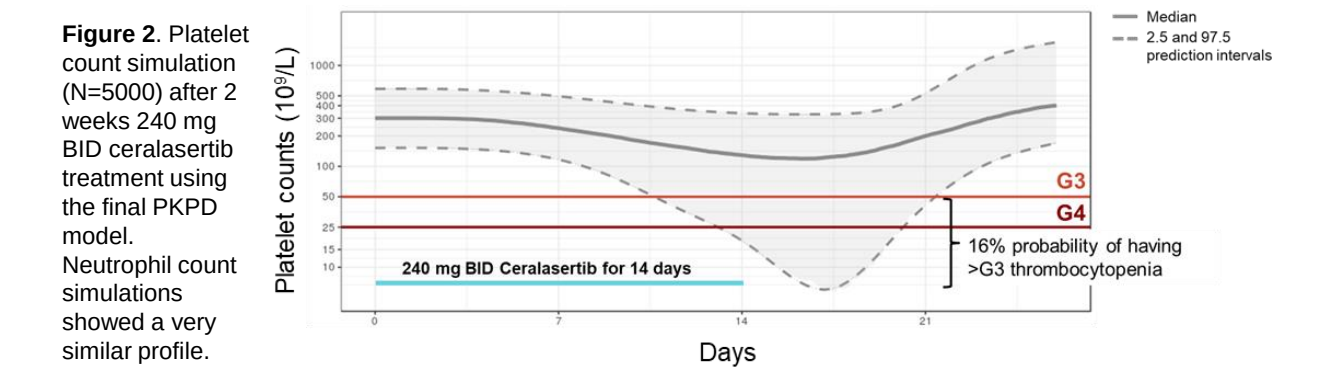


Figure 2. Platelet count simulation (N=5000) after 2 weeks 240 mg BID ceralasertib treatment using the final PKPD model. Neutrophil count simulations showed a very similar profile.

Table 1. Parameter estimates and between-subject variability for the final PKPD models. CV: Coefficient of variation.

	PK-platelet counts model	PK-neutrophil counts model
Parameter name	Estimate (CV%)	Estimate (CV%)
Baseline level (10 ⁹ /L)	296 (36%)	5.39 (35%)
Mean transit time (h,MTT)	130 (-)	116 (26%)
Feedback (γ)	0.314 (16%)	0.164 (15%)
Drug effect: slope (mL/ng)	0.207 (56%)	0.145 (73%)

Table 2. Summary of the probabilities of having $\geq$ grade 3-4 thrombocytopenia or neutropenia for different ceralasertib treatment regimens and the increase from baseline (%) predicted in the off-treatment period.

	240 mg BID for 14d	160 mg BID for 14d	240 mg BID for 7d
$\geq$ Grade 3 Thrombocytopenia	<20%	<15%	<5%
$\geq$ Grade 4 Thrombocytopenia	<10%	<5%	0%
$\geq$ Grade 3 Neutropenia	<20%	<15%	<5%
$\geq$ Grade 4 Neutropenia	<10%	<5%	0%
% rebound in platelets (increase from baseline)	45-50%	35-40%	30-35%
% rebound in neutrophils	<10%	<10%	<10%

Conclusions

These modelling and simulation results suggest that doses of 160mg BID or 240 mg BID ceralasertib for 14 days are safe as platelets and neutrophil counts recover after two weeks off treatment period. A higher rebound is predicted for platelets compared with neutrophils, and is maximal at the 240 mg BID dose for 14 days.

References

- [1] Foote, K.M., et al. J Med Chem. 61:9889-907 (2018).
- [2] Friberg, L. E., et al. J. Clin. Oncol. (2002).
- [3] <http://psn.sourceforge.net>
- [4] <https://github.com/tsahota/NMproject>
- [5] <https://github.com/metrumresearchgroup/mrgsolve>