A systems pharmacology modeling approach for assessing the clinical haematoxicity of anti-cancer agent combinations
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**Objectives**: The use of anticancer agents in combinations can bring about improved efficacy but also increase the risk for myelosuppression. The ability to explain and predict the degree and duration of combination haematological toxicity of anti-cancer agents can be of great value in the clinical context.

**Methods**: A mathematical model of cell cycle was built to recapitulate in-vitro experiments assessing the impact of vistusertib on cell cycle progression of human bone marrow CD34+ progenitor cells [1]. In particular, the measured fraction of cells in G1, S/G2/M and G0 phases under 24hr treatment with various doses of vistusertib [1] were used to calibrate cell cycle parameters and infer drug effects. A systems pharmacology model was obtained by contextualizing the cell cycle model within the Friberg model of neutrophil dynamics in response to vistusertib blood concentrations as predicted from a previously developed population PK model using clinical data.
**Results:** The model shows that vistusertib delays the rate of G1 to S transition, as well as having a small effect upon cell cycle arrest by increasing the transition rate from G1 to G0 phase. The systems pharmacology model was used to simulate the effect of vistusertib, prospectively predicting a small reduction in neutrophil count. The prediction is consistent with clinical data of vistusertib in combination with hormonal therapy (fulvestrant), see Figure 1. Despite vistusertib having only a small impact on neutrophil proliferation, population simulations suggest that there may be a potentiation of myelosuppressive effects of other agents when given in combination.

**Conclusions:** Systems pharmacology modeling based on *in-vitro* bone marrow cell suppression data can help investigate neutrophil time course of multiple drug combinations in a manner that is impractical clinically, thereby informing the choice of optimal dose regimen.