Clinical trial simulations in oncologic patients using the InSilicoONCO suite: two use cases

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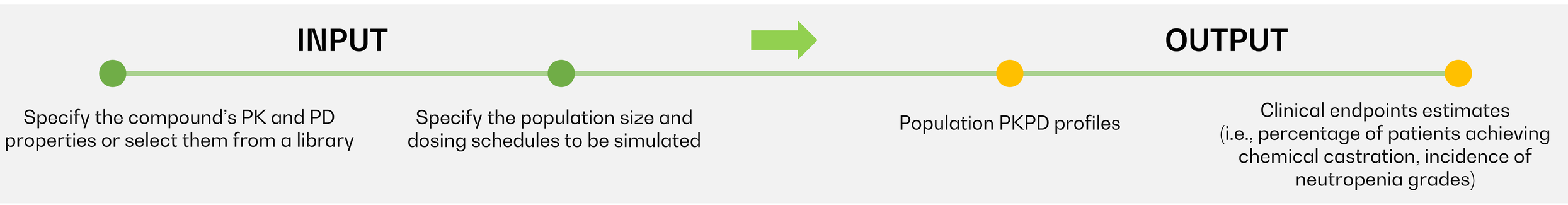
INTRODUCTION

Difficult comparison of new drugs with those already available in the market, clinical trials' high costs and high failure risk are among the major challenges that pharmaceutical companies encounter while setting up their oncology clinical development programs.

To help solve these challenges, InSilicoTrials Technologies has developed *PCa GnRH Agonists Simulator* and *CTx NeutroSim*, two products of InSilicoONCO, a growing suite of cloud-based tools to perform clinical trials simulations in virtual oncologic patients. Specifically, *PCa GnRH Agonists Simulator* simulates testosterone suppression on prostate cancer patients treated with a GnRH agonist; *CTx NeutroSim* simulates neutropenic effects in patients treated with a chemotherapeutic agent.

METHODS

Both *PCa GnRH Agonists Simulator* and *CTx NeutroSim* are based on semi-mechanistic computational pharmacokinetic/pharmacodynamic models [1]–[3]. The simulation workflow for these tools is illustrated in the scheme below. Specifically, *PCa GnRH Agonists Simulator* requires the receptor equilibrium dissociation constant of the GnRH agonist. *CTx NeutroSim* requires the IMP_{drug} parameter that quantifies the drug impact on the hematopoietic stem cells proliferation.



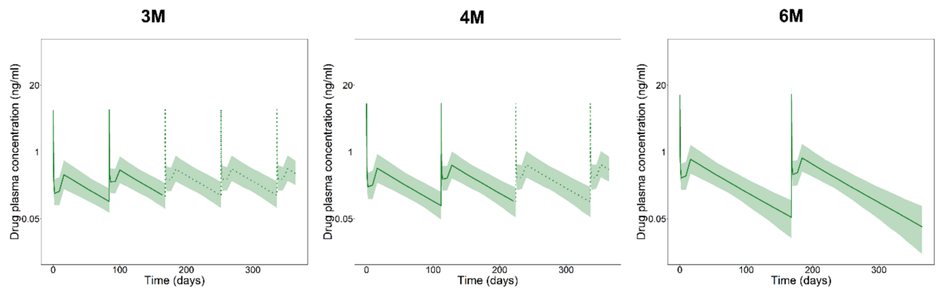
RESULTS

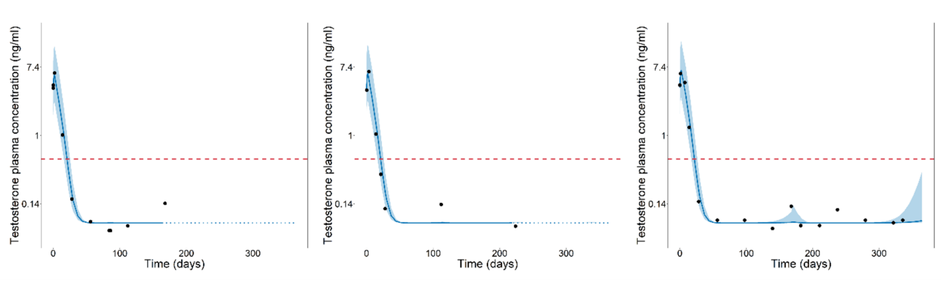
PCa GnRH Agonists Simulator

PCa GnRH Agonists Simulator was applied to replicate real clinical trials of leuprorelin [4,5,6], administered with different sustained release formulations, as provided below.

Schedule name	Clinical trial reference	Number of patients	Schedule (dose / interval)	Study duration (days)
3M leuprolide	NCT01415960 [4]	163	22.5 mg / 3 months	168
4M leuprolide	M93-013 [5]	45	30 mg / 4 months	224
6M leuprolide	NCT00626431 [6]	148	45 mg / 6 months	336

The compound's pharmacokinetic and pharmacodynamic properties were selected from the GnRH agonists library available in the simulator. Predicted population distributions of testosterone concentrations in plasma well contained the mean testosterone levels measured in actual patients.





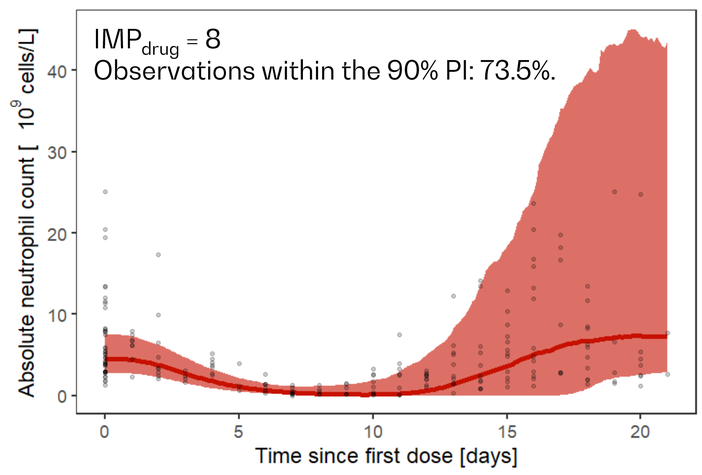
Percentages of virtual patients achieving and maintaining chemical castration resulted in agreement with clinical findings.

Schedule	Estimate of the virtual population (95% CI)	Estimate of the real population	Relative error
3M leuprolide	99.8% (99.5%, 100%)	96.8%	3%
4M leuprolide	99.6% (99.2%, 100%)	94%	5.9%
6M leuprolide	98.3% (97.5%, 99.1%)	93.4%	4.9%

CTx NeutroSim

CTx NeutroSim was applied to simulate the neutropenic effects of docetaxel administered as 1h infusion of 100 mg/m^2 on day 1 of a 3-week cycle.

The value 8 for the drug-related parameter IMP_{drug} was obtained by comparing simulation results across different IMP_{drug} values against synthetic data generated from a published PK/PD model of docetaxel [7] (see Figure below) and was implemented in the model.



Simulation results well reproduced the neutropenia incidence, time to nadir and absolute neutrophil count at nadir observed in a real phase II clinical study of docetaxel [8].

Neutropenia incidence (%)	In silico trial	Radvin *et al.*, 1995
Grade 0	0	0
Grade 1	0	0
Grade 2	0	2.44
Grade 3	4.76	2.44
Grade 4	95.2	95.1
Neutrophil nadir (10^9 cells/L)*	0.093 (0.0, 0.83)	0.2 (0.0, 1.2)
Time to nadir (days)*	9.8 (7.1, 21)	7 (6, 13)

*median (min, max)

CONCLUSION

PCa GnRH Agonists Simulator and *CTx NeutroSim* enable the setup and run of in silico clinical trials in a user-friendly way by a step-by-step integrated workflow. Both tools can be used to explore different clinical trial scenarios, allowing to optimize phase I and II clinical trial design, cutting time and costs of a drug development program for pharmaceutical companies and CROs.

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