

Exposure-Response Modeling and Simulation of lucitanib Induced Dose Limiting Toxicities and Response Categories in Patients with Solid Tumors

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OBJECTIVE

Lucitanib is a multikinase inhibitor targeting FGFR1-2, VEGFR1-3 and PDGFRα/β showing a strong antitumor and antiangiogeneic activity in subcutaneous xenograft models. Lucitanib is undergoing a Phase I/IIa trial to determine the maximum tolerated dose and optimal dosing schedule in patients with advanced solid tumors. The drug is given 15 and 12.5 mg once a day (OD) with a reduction of 5 mg when dose limiting toxicities (DLT) occur. The objective of this project is to develop exposure response models for time course of graded (NCI-CTC grade) DLTs (proteinuria, asthenia) and tumor response (RECIST) as function of dosing history to simulate alternative dosing strategies that could help improving safety and efficacy.

METHODS

Models

The endpoints were analyzed independently with proportional odds ratio models. The models describe the transition probabilities of proteinuria asthenia grades and response categories as a function of dose and time. Patient dosing histories are accounted for in a virtual compartment with a first-order elimination rate driving transition probabilities. The probabilities are dependent on the preceding stage through a first-order Markov element (1-3). The model describes the daily probabilities to have grade $\leq n = 0, 1, 2$ for an individual i when previous grade was j

$$\text{logit}\left[P_i(\text{Grade} \leq n | j)\right] = \sum_n \beta_{nj} + f(\text{dose}, t) + \eta_i$$

$$f(\text{dose}, t) = \alpha \cdot A_i(t) \cdot K$$

$$\frac{dA}{dt} = \text{Dose}_i(t) - K \cdot A$$

$$\eta_i \sim N(0, \sigma^2)$$

$$\text{logit}(x) = \log\left[\frac{x}{1-x}\right]$$

Model parameters were estimated in NONMEM 7.2

Simulations

Multiple replications (200) of 200 patients receiving alternative dosing strategies were simulated with either continuous or intermittent dosing with various starting doses. The impact of dose reductions of 2.5 mg instead of 5 mg is also assessed. Mean delivered dose intensities across patients and days and proportion of patients with at least one grade 2 or 3 proteinuria or asthenia and responders are computed at replication level. For each patient

- daily proteinuria and asthenia grades were predicted: Grade 0, 1, 2, or 3
 - If grade 2 or 3, the next day dose was set to 0 (dose interruption) until recovery to grade <2 (grade 0 or 1)
 - If grade 3, all subsequent doses were reduced by 2.5 mg (dose reduction)
- Response categories were predicted at each cycle then response rates were computed across patients

RESULTS

Adverse event models

Asthenia occurs twice faster than proteinuria (half-life of 3 vs. 6 days) and the dynamics of tumor response is slower (half-life ~9 days).

Table I. Proteinuria model parameter estimates

	Estimate	SE	RSE (%)
$\beta_{0 0}$	6.87	0.394	5.74
$\beta_{0 1}$	-1.81	0.545	30.1
$\beta_{0 2}$	-1.92	0.526	27.4
$\beta_{0 3}$	-1.11	0.791	71.1
$\beta_{1 0}$	0.396	0.133	33.7
$\beta_{1 1}$	7.2	0.585	8.12
$\beta_{1 2}$	0.786	0.259	33
$\beta_{1 3}$	0.544	0.258	47.3
$\beta_{2 0}$	2.05	0.474	23.2
$\beta_{2 1}$	1.07	0.45	42
$\beta_{2 2}$	9.13	1.4	15.4
$\beta_{2 3}$	0.649	0.298	46
$K \text{ (day}^{-1}\text{)}$	0.117	0.0216	18.5
$\alpha \text{ (day.mg}^{-1}\text{)}$	-0.0877	0.0203	23.2
σ	1.71	0.738	43

Dose (mg)	5	10	15	20	30
No Patients	3	9	38	17	7

Table II. Asthenia model parameter estimates

	Estimate	SE	RSE (%)
$\beta_{0 0}$	5.51	0.345	6.26
$\beta_{0 1}$	-3.3	0.36	10.9
$\beta_{0 2}$	-2.1	0.363	17.3
$\beta_{1 0}$	1.58	0.294	18.6
$\beta_{1 1}$	9.35	0.372	3.98
$\beta_{1 2}$	0.905	0.243	26.9
$K \text{ (day}^{-1}\text{)}$	0.241	0.0738	30.5
$\alpha \text{ (day.mg}^{-1}\text{)}$	-0.075	0.0178	23.7
σ^2	0.879	0.456	51.9

Figure 1. Proteinuria model qualification

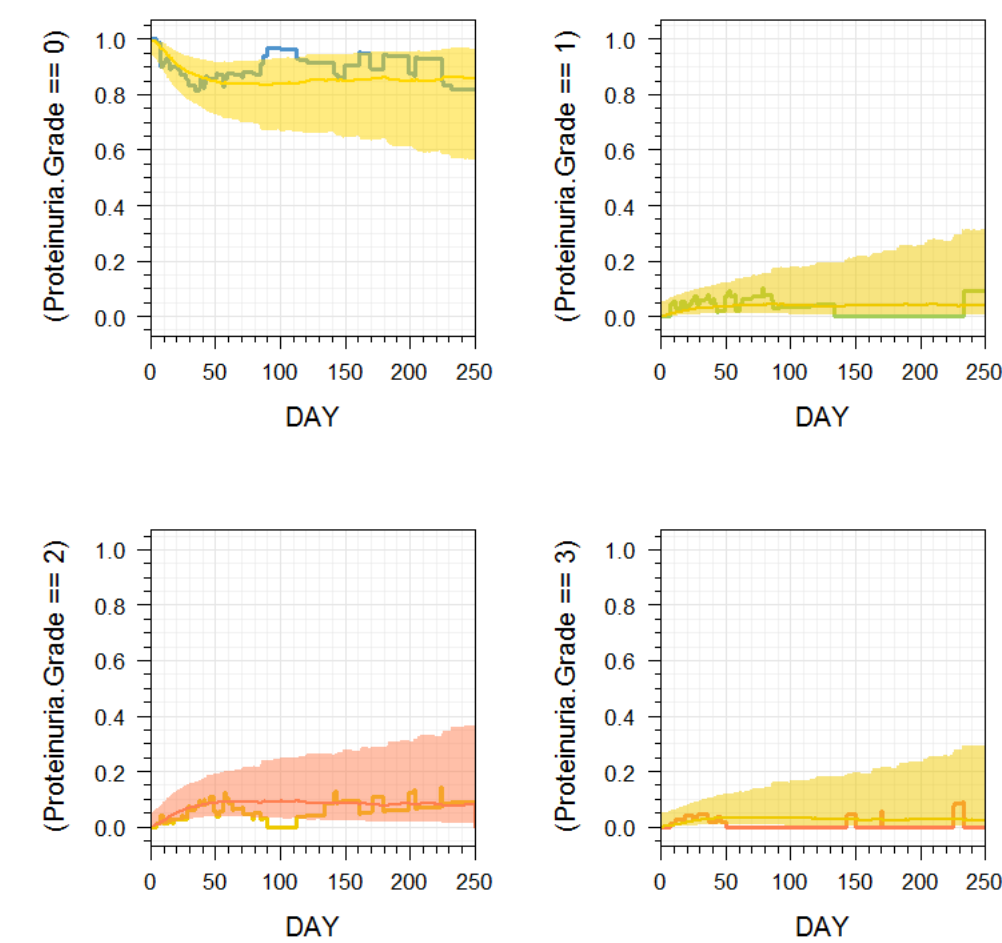
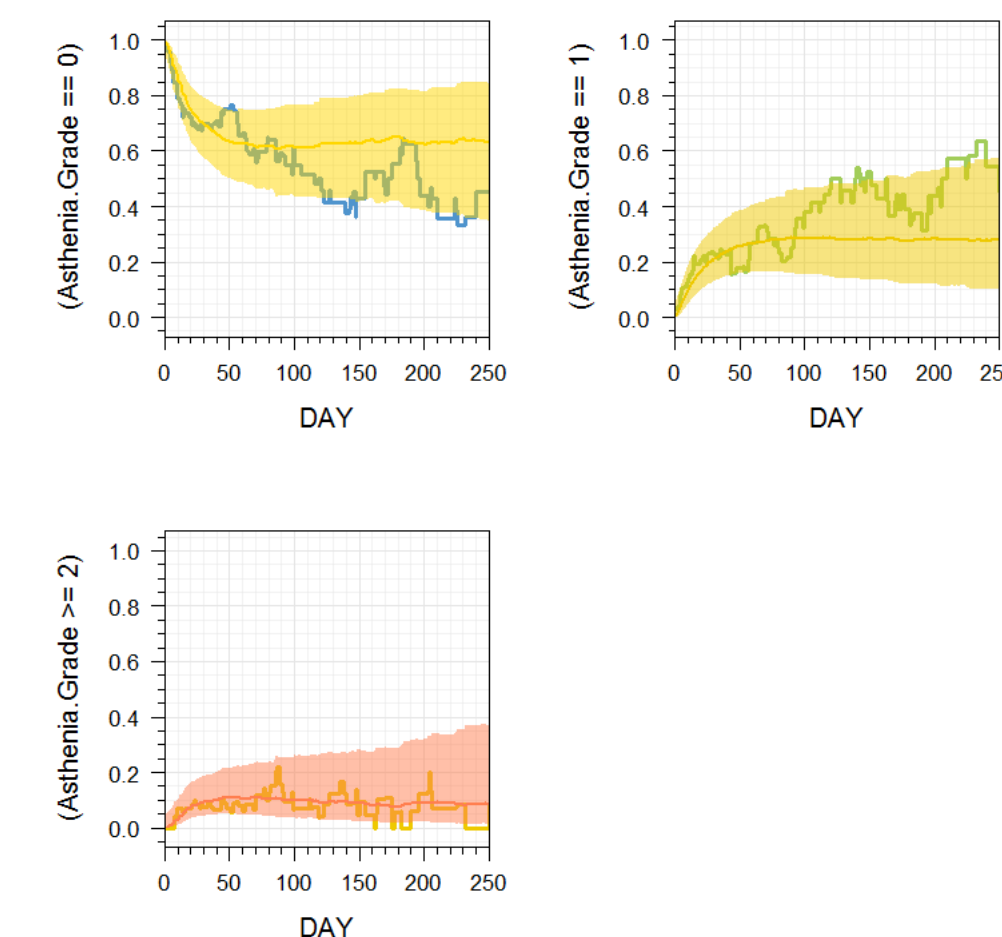


Figure 2. Asthenia model qualification



RESULTS

Tumor response model

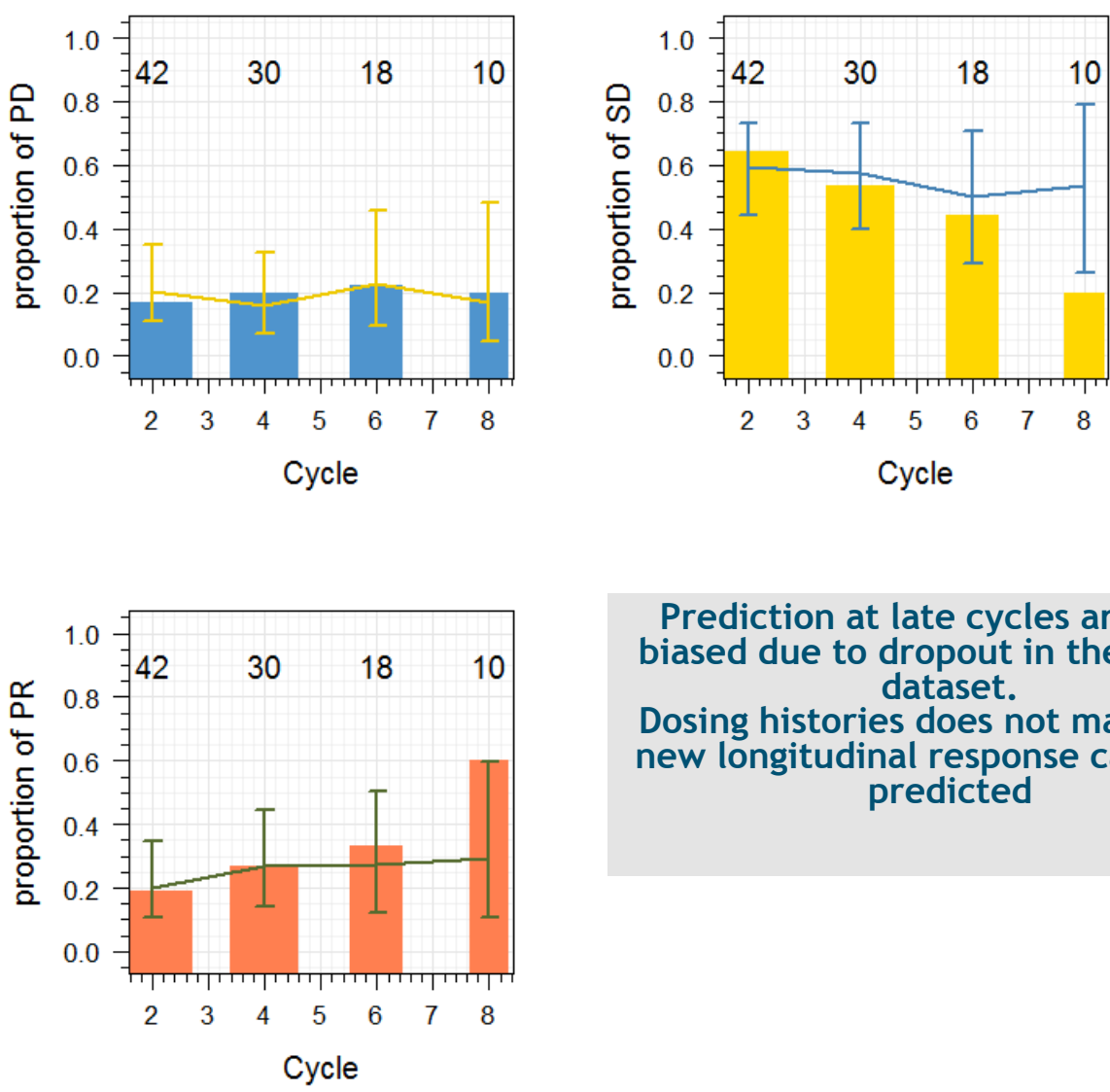
- 3 levels of ordered responses are observed
- Progressive Disease (PD) coded 0
 - Stable Disease (SD), coded 1
 - Partial Response (PR), coded 2
 - For the Markov assumption patients are assumed to be SD before treatment start

Table III. Response model parameter estimates

	Estimate	SE	RSE (%)
$\beta_{SD PD}$	14	2.41	17.3
$\beta_{PR PD}$	-12.5	1.39	11.1
$\beta_{SD SD}$	5.38	1.73	32.2
$\beta_{PR SD}$	-6.66	2.42	36.3
$\beta_{SD PR}$	1.66	0.911	55
$\beta_{PR PR}$	-2.72	2.34	85.9
K	0.0784	0.0293	37.4
α	0.368	0.156	42.4
σ^2	4.91	5.77	118

N = 60 patients

Figure 3. model qualification



Tumor response in breast cancer patients seems to be superior compared to other tumor types (p=0.004).

Simulations of asthenia and proteinuria

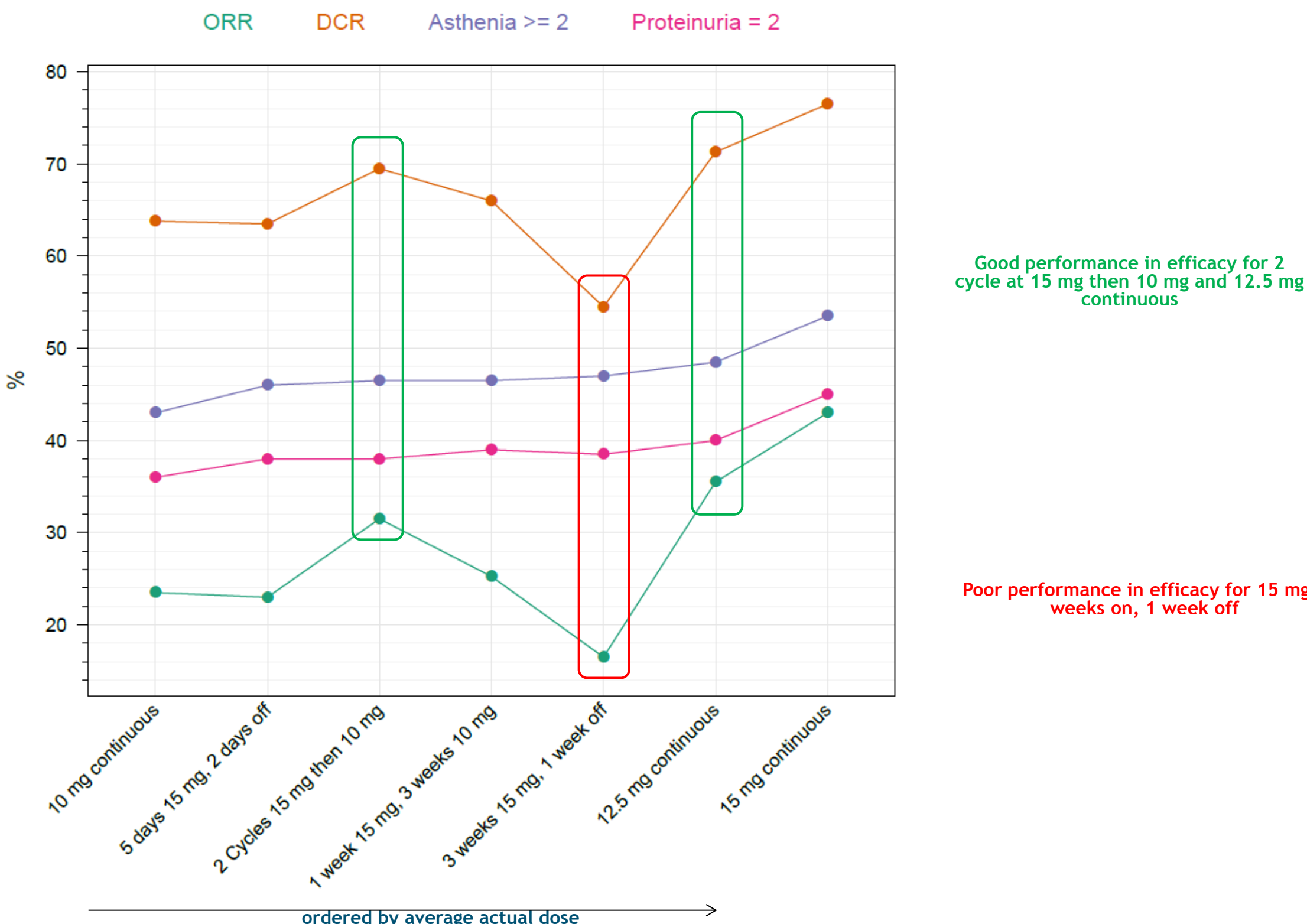
Table IV. Asthenia and proteinuria model simulation

Scenarios	Average nominal dose (mg) (% of reference)	Average actual dose (mg) (% of nominal)	Patients with grade ≥ 2 asthenia (%)	Patients with grade 2 proteinuria (%)	Patients with grade 3 proteinuria (%)
1 Reference: 15 mg continuous	15 (100)	12.8 (85)	53.5	45	20
2 12.5 continuous	12.5 (83)	10.9 (87)	48.5	40	17
3 10 mg continuous	10 (67)	8.87 (89)	43	36	15
4 2 cycles 15 mg then 10 mg	11.3 (75)	9.84 (87)	46.5	38	16
5 3 weeks 15 mg, 1 week off	11.3 (75)	9.92 (88)	47	38.5	16
6 1 week 15 mg, 3 weeks 10 mg	11.3 (75)	9.91 (88)	46.5	39	16
7 5 days 15 mg, 2 days off	10.7 (71)	9.47 (89)	46	38	15

- Scenario 2 (12.5 mg) is intermediate to 10 mg and 15 mg continuous
- Scenarios 4, 5, and 6 got about the same proportions of events than 10 mg with an about 12 % increase in dose intensity
- Scenario 5 and 6 may be better than 4 as the nominal dose intensity is potentially larger after 8 cycles (scenario 4 stays at 10 mg up to end of treatment)
- Scenario 7 is lower in dose intensity with about same proportion of events than 4, 5, and 6

Simulations summary of adverse events and response rates

Figure 4. Summary model simulations



CONCLUSIONS

The simulations of untested strategies in the ongoing phase I/II showed good performance of continuous schedules and poor performance of the 1 week off scenario. The results will guide the choice of the dose and administration schedule in future studies.

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