Exploration of alternative regorafenib regimens to manage hand–foot skin reaction

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BACKGROUND

- The oral multikinase inhibitor regorafenib is approved for patients with metastatic colorectal cancer (mCRC), advanced gastrointestinal stromal tumors (GIST), and unresectable hepatocellular carcinoma (HCC)[1,2]
- The approved starting dose of regorafenib is 160 mg/day, administered 3 weeks on/1 week off in a 4-week cycle[1,2]
- In four phase 3 studies, regorafenib improved overall survival versus placebo in patients with treatment-refractory mCRC, GIST, and HCC[3–6]
- Most common regorafenib-related toxicities such as diarrhea, fatigue, and hand–foot skin reaction (HFSR) can be managed with dose modifications[3–8]
- In the phase 3 CORRECT trial, regorafenib-related toxicities, including HFSR, were reported in 47% of patients with mCRC (17% grade [Gr] 3), and typically occurred early during treatment[9]
  - In CORRECT, the median time to first occurrence of HFSR was 15 days and the median time to Gr 3 HFSR was 22 days[9]
- Alternative regorafenib dosing regimens during the first cycle might improve tolerability in clinical practice; analysis of exposure–response relationships can help guide dose optimization

OBJECTIVES

- Develop a model to describe the relationship between regorafenib dose, plasma concentration, and time to first occurrence of Gr 3 HFSR, considering the influence of predefined baseline prognostic factors (PFs)
- Analyze the effect of alternative dosing schedules versus regorafenib standard dosing on Gr 3 HFSR in patients with mCRC

METHODS

Model development

- Data from patients who received regorafenib or placebo in four phase 3 trials (Table 1) were used to develop the dose–exposure–response (DER) model
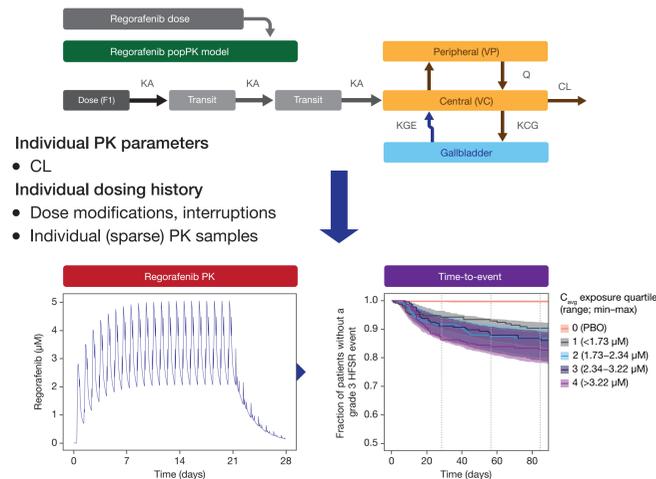
Table 1. Phase 3 regorafenib clinical trials with standard approved dosing

Phase 3 trial	Regorafenib, n*	Placebo, n*	Trial details
All studies	1142	580	
CORRECT[3]	500	253	Efficacy and safety of regorafenib vs placebo in patients with mCRC who progressed after standard therapies
CONCUR[4]	136	68	Efficacy and safety of regorafenib vs placebo in Asian patients with mCRC who progressed after standard therapies
GRID[5]	132	66	Regorafenib vs placebo for patients with metastatic and/or unresectable GIST whose disease had progressed despite prior treatments with at least imatinib and sunitinib
RESORCE[6]	374	193	Regorafenib vs placebo in patients with HCC whose disease had progressed on prior sorafenib treatment

*Safety analysis set.
GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; mCRC, metastatic colorectal cancer.

- Individual regorafenib exposure (plasma concentration) was estimated by population pharmacokinetics (PK) modeling, accounting for the effect of dose modifications
- For the population PK model, the absorption of orally administered regorafenib was described by an absorption rate constant and two transit compartments (Figure 1)
  - Briefly, regorafenib disposition was described by distribution between central and peripheral compartments with linear elimination from the central compartment, including enterohepatic circulation involving the gallbladder (Figure 1)

Figure 1. Population PK and dose–drug exposure time-to-event models

Individual PK parameters
- CL

Individual dosing history
- Dose modifications, interruptions
- Individual (sparse) PK samples

Vertical dashed lines indicate cycles.
Cavg, average concentration; CL, drug clearance; HFSR, hand–foot skin reaction; KA, absorption rate constant; KCG, rate constant for gallbladder accumulation; KGE, rate constant for meal-dependent gastric emptying; PBO, placebo; PK, pharmacokinetic; popPK, population PK; Q, inter-compartmental flow; VC, volume of central compartment; VP, volume of peripheral compartment.

- The first step in model development was to select the optimal hazard shape and exposure–response relationship simultaneously based on all patients (placebo and regorafenib groups), whereby each shape (i.e. constant, Gompertz, Weibull, or log-logistic model) was fitted with different exposure–response models
- The model with the lowest Akaike information criterion was selected for the formal analysis of PFs
- PFs were selected using a Cox proportional hazard analysis and PF level grouping where needed
- Based on the assumption that regorafenib concentration changes the hazard, the concentration–effect relationship was defined by a parameter for the maximal effect on the hazard (E_{max}), a parameter for the concentration resulting in 50% of the maximal effect (EC_{50}), and a parameter for the steepness of the concentration–effect relationship and a parameter to describe the delay between the concentration–effect relationship

Computation

- Non-linear mixed-effects modeling was used (NONMEM software[10]) combined with PsN (version 4.7.0); GFortran (GCC version 5.4.0) was used as compiler
- Diagnostic graphics, exploratory analyses, and post-processing of NONMEM outputs were performed using R version 3.3.2[11] and RStudio[12]

Model evaluation

- Models were re-run on a data set containing daily records to generate the survival prediction for 1500 days for each patient
- 1000 study replicates were generated by drawing 1000 random numbers per individual from a uniform distribution between 0 and 1, which were used to derive time-to-events (TTE) based on individual survival curves; 1000 Kaplan–Meier curves were generated and 95th percentiles plotted against observed curves
- Visual predictive checks were deemed adequate if observed data (stratified by treatment, PF level, and exposure category) fell within the simulated ribbon
- For the Gr 3 HFSR TTE model, dropouts (due to death, disease progression, adverse events or other reasons) were taken into account for the simulations, using actual HFSR censoring (patient no longer followed up [30 days after the last dose or earlier due to death]) times

Simulations

- Random sampling from a virtual population of patients with mCRC was used to generate 300 virtual clinical trials (300 patients in each study), with six parallel arms for different dosing scenarios (Table 2)
- Dosing scenarios were simulated for 3 cycles, assuming no dose interruptions or modifications (dropouts were taken into account for the simulations, using simulated individual dropout times obtained from separate models)
- The first occurrence of Gr 3 HFSR was simulated for each dosing scenario, and calculated (mean and 95% confidence interval [CI]) as a percentage of patients without Gr 3 HFSR
- For each simulated trial, PK parameters were drawn from a multivariate normal distribution of estimated structural PK parameters
- Similarly, Gr 3 HFSR parameters were drawn from their respective distributions
  - The observation period was 84 days with observation intervals of 7 days

Table 2. Regorafenib dosing regimens and dosing scenarios used for simulations

Dosing regimens												
Standard	160 mg/day, 3 weeks on/1 week off for 3 cycles											
Reduced dose and escalation regimens	80 or 120 mg/day, 3 weeks on/1 week off for 3 cycles											
	80 mg/day in Week 1, escalated to 120 mg/day in Week 2, and to 160 mg/day in Week 3 of Cycle 1, followed by either 120 mg/day or 160 mg/day 3 weeks on/1 week off, in Cycles 2 and 3											

Model dosing simulations												
	Regorafenib dose (mg/day)											
Week	1	2	3	4	5	6	7	8	9	10	11	12
Scenario 1	PBO	PBO	PBO	0	PBO	PBO	PBO	0	PBO	PBO	PBO	0
Scenario 2	160	160	160	0	160	160	160	0	160	160	160	0
Scenario 3	120	120	120	0	120	120	120	0	120	120	120	0
Scenario 4	80	120	160	0	160	160	160	0	160	160	160	0
Scenario 5	80	80	80	0	80	80	80	0	80	80	80	0
Scenario 6	80	120	160	0	120	120	120	0	120	120	120	0

PBO, placebo.

RESULTS

- The distribution of demographic and baseline PFs is provided in Table 3

Table 3. Distribution of demographic and baseline PFs for the exposure–response analysis

Prognostic factor	Level	Regorafenib (n=1142) n	%	Placebo (n=580) n	%	Q1 (n=286) n	%	Q2 (n=265) n	%	Q3 (n=285) n	%	Q4 (n=286) n	%
Age	<65 years	686	60.1	383	66.0	159	55.6	172	60.4	167	58.6	188	65.7
	≥65 years	456	39.9	197	34.0	127	44.4	113	39.6	118	41.4	98	34.3
Sex	Male	804	70.4	397	68.4	201	70.3	207	72.6	200	70.2	196	68.5
ECOG PS	0	613	53.7	325	56.0	141	49.3	143	50.2	167	58.6	162	56.6
	1	528	46.2	255	44.0	144	50.3	142	49.8	118	41.4	124	43.4
	>1	1	0.1	0	0	1	0.3	0	0	0	0	0	0
Prior lines of treatment	1	203	17.8	97	16.7	49	17.1	41	14.4	49	17.2	64	22.4
	2–3	444	38.9	221	38.1	122	42.7	114	40.0	108	37.9	100	35.0
	≥4	495	43.3	262	45.2	115	40.2	130	45.6	128	44.9	122	42.7
Metastases	Liver	903	79.1	452	77.9	225	78.7	217	76.1	224	78.6	237	82.9
	Lung	668	58.5	333	57.4	158	55.2	160	56.1	168	58.9	182	63.6
Renal function*	Normal	726	63.6	383	66.0	174	60.8	172	60.4	183	64.2	197	68.9
	Mild	358	31.3	171	29.5	96	33.6	98	34.4	87	30.5	77	26.9
	Moderate	57	5.0	26	4.5	16	5.6	14	4.9	15	5.3	12	4.2
Hepatic function†	A	663	58.1	321	55.3	161	56.3	187	65.6	169	59.3	146	51.0
	B1	317	27.8	167	28.8	78	27.3	71	24.9	80	28.1	88	30.8
	B2	128	11.2	72	12.4	37	12.9	23	8.1	25	8.8	43	15.0
	C	34	3.0	19	3.3	10	3.5	4	1.4	11	3.9	9	3.1
Serum albumin	<2.8 g/dL	12	1.1	7	1.2	5	1.7	5	1.8	2	0.7	0	0
	2.8–3.5 g/dL	199	17.4	103	17.8	60	21.0	57	20.0	42	14.7	40	14.0
	>3.5 g/dL	931	81.5	470	81.0	221	77.3	223	78.2	241	84.6	246	86.0
WBC count‡	≤5.5×10⁹/L	384	33.6	207	35.7	104	36.4	80	28.1	96	33.7	104	36.4
	>5.5×10⁹/L	757	66.3	371	64.0	182	63.6	205	71.9	189	66.3	181	63.3

Renal function – Normal: eGFR (mL/min/1.73m²) ≥90; Mild: eGFR 60–89; Moderate: eGFR 30–59. Hepatic function – Normal (category A): Total bilirubin ≤1.0 mg/dL, AST/ALT ≤40 U/L; Mild (category B1): Total bilirubin ≤1.0 mg/dL, AST/ALT >40 U/L; Mild (category B2): Total bilirubin >1.0–1.5 mg/dL, AST/ALT Any level; Moderate (category C): Total bilirubin >1.5–3.0 mg/dL, AST/ALT Any level.
*1 patient missing in the regorafenib and Q2 groups; †1 patient in the placebo group had severe (category D) hepatic dysfunction (total bilirubin >3.0 mg/dL, AST/ALT any level); ‡1 patient missing in the regorafenib and Q4 groups and 2 missing in the placebo group.
ALT, alanine transaminase; AST, aspartate transaminase; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; PF, prognostic factor; Q, quartile; WBC, white blood cell.

Model evaluation: Exposure–response analysis

- Gr 3 HFSR was observed in 2/580 patients (0.34%) in the placebo group and 184/1142 patients (16.1%) in the regorafenib group
- The probability of Gr 3 HFSR tended to be greater in higher exposure categories (Figure 2)
- Multivariate analysis identified baseline hepatic function to be significantly associated with Gr 3 HFSR (P<0.01), with a hazard ratio of 0.56 (95% CI 0.38, 0.74) for patients with abnormal hepatic function (category B1–D) versus normal hepatic function
- The prediction of Gr 3 HFSR was improved when the change in individual regorafenib concentration was taken into account; the exposure–response relationship was steep, with a small change in regorafenib concentration resulting in a considerable change in the occurrence of Gr 3 HFSR. A delay between change in regorafenib concentration and Gr 3 HFSR hazard was quantified with a half-life of 9.3 days (95% CI 6.09, 19.90). The regorafenib concentration in most patients was greater than the estimated EC_{50} (1.09 μM; 95% CI 0.45, 1.73)

Simulation results

- Simulations of 3 cycles of regorafenib showed a reduced probability of Gr 3 HFSR for all alternative dosing schedules versus standard dosing (Figure 3)
- A 33% lower incidence of Gr 3 HFSR was found for the 80 mg/day 3 weeks on/1 week off regimen (10%) versus the standard dose (15%) after 84 days of treatment (Figure 4)
- The simulated Gr 3 HFSR incidences for Scenario 4 (13%) and the standard dose (15%) (Figure 4) closely resembled the actual incidences observed in ReDOS of 14.8% for the escalating dose and 16.1% for the standard dose[7]

Figure 2. Observed and predicted probability of grade 3 HFSR over time (0–84 days), taking into consideration observed dropout and regorafenib dose modifications by C_{avg} exposure quartile
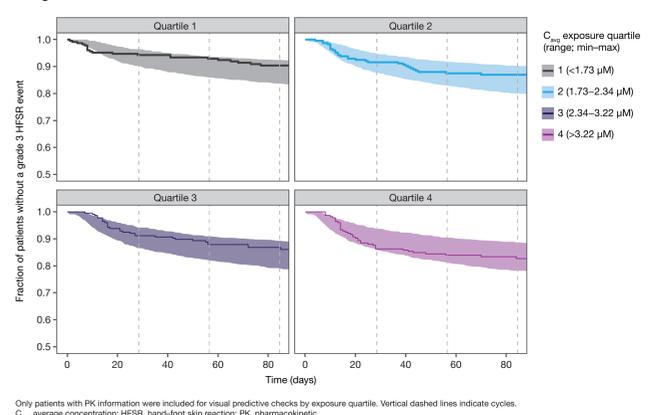

Only patients with PK information were included for visual predictive checks by exposure quartile. Vertical dashed lines indicate cycles.
C_{avg}, average concentration; HFSR, hand–foot skin reaction; PK, pharmacokinetic.

Figure 3. Simulated fraction of patients without grade 3 HFSR over 3 (28-day) treatment cycles for different regorafenib treatment scenarios versus standard dosing
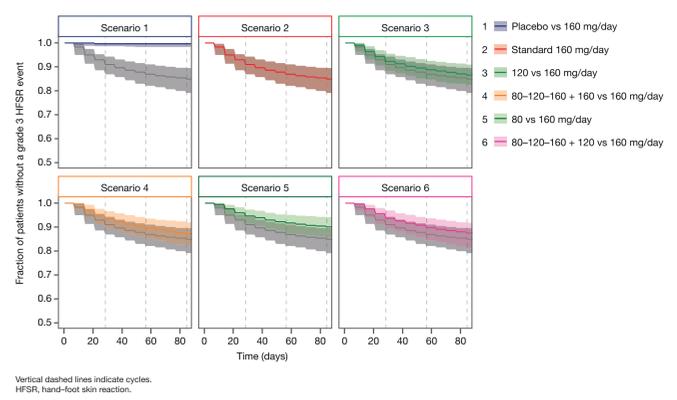
Vertical dashed lines indicate cycles.
HFSR, hand–foot skin reaction.

Figure 4. Simulated fraction of patients without grade 3 HFSR for 3 cycles for different regorafenib treatment scenarios
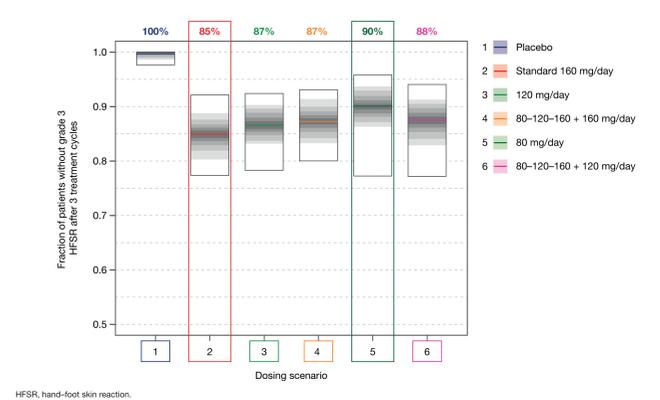
HFSR, hand–foot skin reaction.

CONCLUSIONS

- DER modeling and simulation of the time to first Gr 3 HFSR event, based on data from four phase 3 studies of regorafenib monotherapy at a standard dose of 160 mg/day, suggests that the incidence of HFSR was decreased for all alternative dosing scenarios
  - A dose of 120 mg/day or a starting dose of 80 mg followed by 120 or 160 mg may be alternative dosing scenarios based on a numerical trend toward reduced Gr 3 HFSR
  - A numerically lower incidence of Gr 3 HFSR was observed for the lower regorafenib starting dose of 80 mg/day
- Since a lower starting dose of regorafenib may be associated with reduced efficacy if it is not escalated to the standard dose, an analysis of DER for overall survival, taking into consideration the influence of predefined baseline PFs in patients with mCRC based on available phase 3 data, is ongoing

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