Exploratory analysis of tumor growth rate in patients with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib in the GRID phase 3 trial

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INTRODUCTION

- Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in oncogenesis, tumor angiogenesis, and the tumor microenvironment[1]
- In the phase 3 randomized, double-blind (DB) GRID trial, regorafenib significantly improved progression-free survival (PFS) versus placebo in patients with advanced GIST who had progressed on imatinib and sunitinib (hazard ratio [HR] 0.27; 95% CI 0.19–0.39; one-sided P<0.0001)[2]
- No significant difference in overall survival (OS) was observed at the time of the primary PFS analysis (HR 0.77; 95% CI 0.42–1.41; one-sided P=0.199)[2]
  - This result was likely confounded by the high rate of crossover from placebo to regorafenib (85%) at the time of progression

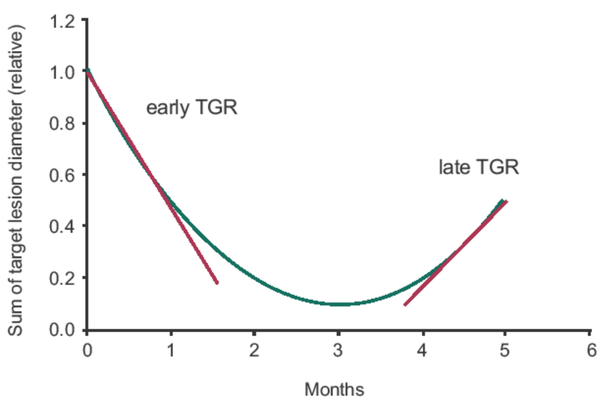
OBJECTIVE

- This exploratory analysis evaluated target lesion size over time to gain insight into tumor growth rate (TGR) during treatment with placebo and/or regorafenib

METHODS

- Progression was assessed by independent blinded central review
- At the time of independently assessed tumor progression during the DB phase:
  - Patients receiving placebo were allowed to cross over to open-label (OL) regorafenib
  - Patients receiving blinded regorafenib were allowed to continue on OL regorafenib
- Changes in sum of target lesion diameters over time were approximated by a parabola-like 3-parametric model separately for the DB and OL periods
  - Target lesions were assessed at baseline, every 4 weeks for the first 3 months, every 6 weeks for the next 3 months, and then every 8 weeks until the end of treatment (DB: centrally assessed; OL: investigator assessed)
- TGR, defined as the percent change from baseline per month in the sum of target lesion diameters, is calculated as the slopes at the earliest and latest time points of the model curve (Figure 1)

***Figure 1:** Lesion growth model fit*



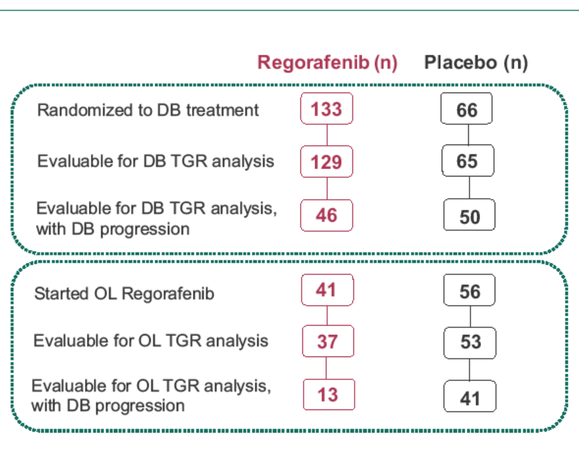
TGR, tumor growth rate.

RESULTS

Patient disposition

- The final patient numbers in the GRID study, indicating how many patients progressed and either switched to or continued with OL regorafenib, are shown in Figure 2

***Figure 2:** Patient disposition[3]*



DB, double-blind; OL, open-label; TGR, tumor growth rate.

Analyses of TGRs

- TGRs showed that when patients first received regorafenib their tumors were stabilized (small early TGR) and then increased in size (positive late TGR) indicating tumor growth (Table 1)
- Tumor sizes generally increased during DB treatment for patients receiving placebo (Table 1; Figure 3)
- Patients receiving placebo who crossed over to receive OL regorafenib after progression had a small early TGR, indicating tumor shrinkage with regorafenib treatment (Table 1; Figure 4)

Exploratory analysis of the prognostic value of TGR for PFS

- Whether early TGR was prognostic for disease progression was examined in patients receiving placebo dichotomized into low and high early TGR groups during DB treatment
- Patients with high early TGR had worse PFS than those with low early TGR, suggesting that early TGR could be prognostic for disease progression (Figure 5a)
- Patients receiving placebo who crossed over to OL regorafenib appeared to derive the same benefit from regorafenib regardless of whether they had high or low early TGR (Figure 5b)

Exploratory analysis correcting for the impact of crossover on OS

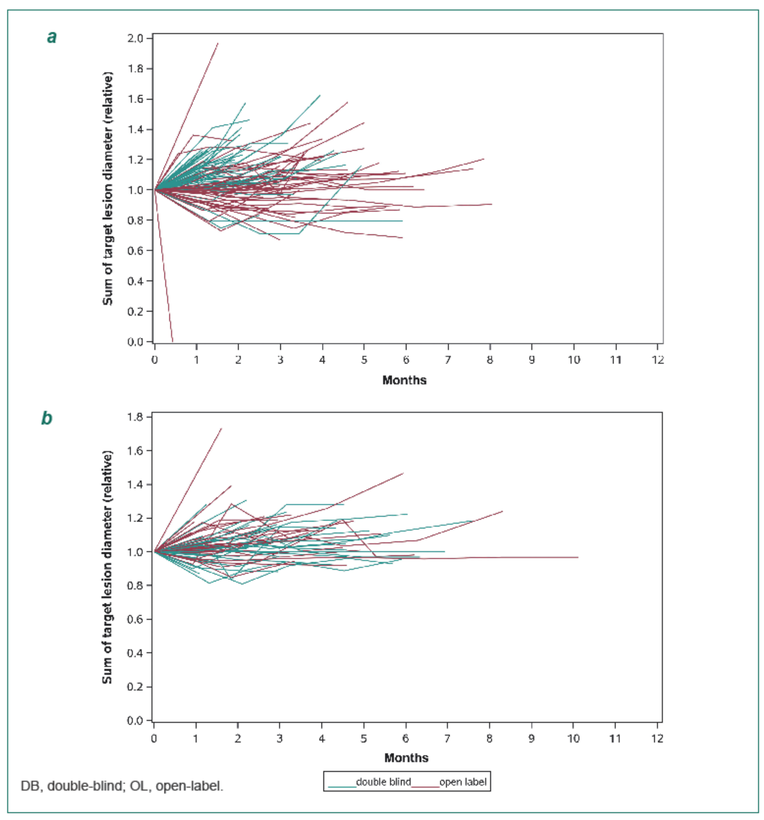
- Exploratory analyses correcting for the impact of crossover on OS (by iterative parameter estimation method) suggest that regorafenib has a positive impact on OS[3]
- Correction method assumes that the effect of regorafenib on OS is similar for initial DB and OL after disease progression
- TGR analysis provides some evidence supporting this assumption
  - Early DB regorafenib TGR: 0.2 (-2.2, 2.6)
  - Early OL regorafenib TGR for patients receiving placebo: -2.6 (-12.2, 6.9)

***Table 1:** TGRs for evaluable patients during DB or OL treatment*

Group	Received DB treatment, n	Received OL regorafenib, n	Early TGR % change/ month (95% CI)	Late TGR % change/ month (95% CI)
Early and late TGRs during DB and OL treatment				
DB regorafenib (all)	129	–	0.1 (-2.7–2.9)	3.8 (-0.6–8.2)
DB placebo (all)	65	–	6.8 (2.1–11.5)	11.6 (7.0–16.1)
DB regorafenib subset	37	–	0.2 (-2.2–2.6)	4.0 (1.5–6.4)
DB placebo subset	53	–	8.6 (5.1–12.1)	13.6 (10.5–16.7)
Regorafenib—regorafenib	–	37	5.2 (1.9–8.5)	4.6 (1.6–7.6)
Placebo–regorafenib	–	53	-2.6 (-12.2–6.9)	-0.6 (-10.1–9.0)
Early and late TGR: Patients with progression during DB treatment				
DB regorafenib (all)	46	–	3.3 (-0.7–7.3)	11.8 (7.0–16.6)
DB placebo (all)	50	–	9.4 (3.8–14.9)	12.6 (6.8–18.4)
DB regorafenib subset	13	–	2.8 (-2.4–8.0)	6.2 (1.1–11.3)
DB placebo subset	41	–	11.4 (8.1–14.8)	14.7 (10.9–18.4)
Regorafenib–regorafenib	–	13	6.9 (2.0–11.8)	2.9 (-0.9–6.7)
Placebo–regorafenib	–	41	-2.9 (-15.2–9.3)	-1.6 (-13.8–10.6)

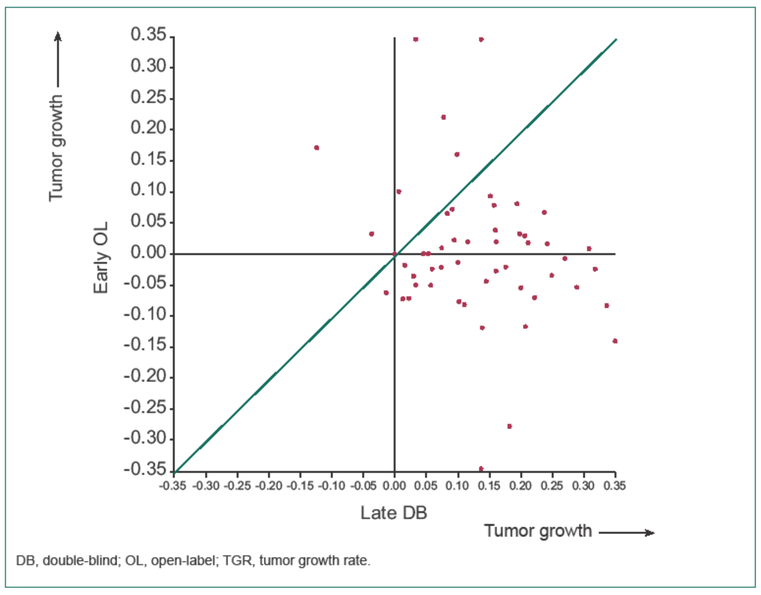
CI, confidence interval; DB, double-blind; OL, open-label; TGR, tumor growth rate.

***Figure 3:** (a) Tumor growth for individual patients receiving DB placebo and OL regorafenib; (b) tumor growth for individual patients receiving DB and OL regorafenib*



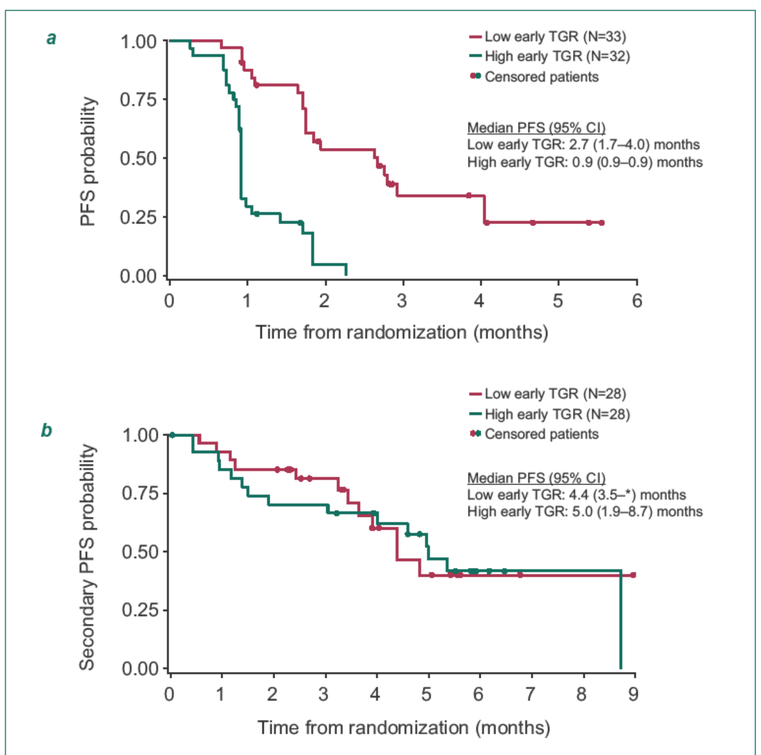
DB, double-blind; OL, open-label.

***Figure 4:** TGRs for individual patients receiving placebo who crossed over to OL regorafenib*



DB, double-blind; OL, open-label; TGR, tumor growth rate.

***Figure 5:** (a) PFS for patients receiving placebo during DB treatment; (b) secondary PFS for patients receiving placebo during OL treatment*



*Value cannot be estimated due to censored data.

DB, double-blind; OL, open-label; PFS, progression-free survival; TGR, tumor growth rate.

CONCLUSIONS

- TGR is an objective measure of tumor growth over time and may provide insight into inherent disease characteristics and treatment effects
- Early TGR during regorafenib treatment was stabilized to a similar extent both for patients randomized to regorafenib and those randomized to placebo who crossed over to receive OL regorafenib after disease progression
- Late TGR around the time of progression during DB treatment was generally less for patients receiving regorafenib than for those receiving placebo
  - This suggests that despite reaching progression, there was still partial suppression of tumor growth in patients receiving regorafenib
- These exploratory results on TGR support the validity of the structural failure time OS crossover correction methods
- TGR may be an additional efficacy parameter to consider when monitoring patients treated with regorafenib
- The exploratory analyses presented here are hypotheses-generating in nature

References

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