Overview of Dose Modifications with STIVARGA® (regorafenib) in the GRID Study

Introduction

- STIVARGA (regorafenib) is an oral multikinase inhibitor approved by the US Food and Drug Administration in February 2013 for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate[3]
- GIST is the most common form of sarcoma of the gastrointestinal (GI) tract and accounts for 1-3% of all malignant GI tumors[1]
- In the US, the incidence of GIST has been estimated at 5,000-6,000 new cases annually[2]
- The approval of STIVARGA was based on data from GRID (GIST – Regorafenib In Progressive Disease), an international, multicenter, randomized, double-blind, placebo-controlled, phase III study, which showed that the addition of STIVARGA to best supportive care (BSC) resulted in a statistically significant increase in progression-free survival (PFS) vs. the addition of placebo to BSC in patients with GIST (Figure 1. GRID: Pivotal Study Design)[4]
- STIVARGA provides an important treatment option for appropriate patients with GIST for whom other approved drugs are no longer effective[3]

Figure 1. Pivotal Study Design[4]

*Radiographic assessments of response were performed every 4 weeks for the first 3 cycles, every 6 weeks for cycles 4-6 and every 8 weeks after cycle 6.

- **Primary endpoint: progression-free survival (PFS)[4]**
  - **Based on disease assessment by independent radiological review using modified RECIST 1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodule within a pre-existing tumor mass was progression**
- **Key secondary endpoint: overall survival (OS)[4]**

Important Safety Information

WARNING: HEPATOTOXICITY

- Severe and sometimes fatal hepatotoxicity has been observed in clinical trials.
- Monitor hepatic function prior to and during treatment.
- Interrupt and then reduce or discontinue STIVARGA for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence.

Objectives

- Review the most frequent adverse events (AEs) associated with STIVARGA from the GRID trial
- Review dose modifications for the management of AEs

Common AEs During Treatment with STIVARGA

- A number of treatment-emergent AEs may occur when on therapy (Table 1. Common Adverse Events)[3]
- It is important that healthcare professionals understand how to recognize and appropriately manage these AEs in patients receiving STIVARGA

Table 1. Common Adverse Events[3]

Adverse drug reactions (≥10%) reported in patients treated with regorafenib and reported more commonly than in patients receiving placebo	Regorafenib (N=132)			Placebo (N=66)		
	All	Gr 3	Gr 4	All	Gr 3	Gr4
Skin and subcutaneous tissue disorders						
HFSR/PPE, %	67	22	0	15	2	0
Rash*, %	30	7	0	3	0	0
Alopecia, %	24	2	0	2	0	0
General disorders and administration site conditions						
Asthenia/fatigue, %	52	4	0	39	2	0
Fever, %	21	0	0	11	2	0
Vascular disorders						
Hypertension, %	59	27	<1	27	5	0
Hemorrhage, %	11	2	2	3	0	0
Gastrointestinal disorders						
Diarrhea, %	47	8	0	9	0	0
Mucositis, %	40	2	0	8	2	0
Nausea, %	20	2	0	12	2	0
Vomiting, %	17	<1	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Dysphonia, %	39	0	0	9	0	0
Infections and infestations						
Infection, %	32	4	<1	5	0	0
Metabolism and nutrition disorders						
Decreased appetite and food intake, %	31	<1	0	21	3	0
Hypothyroidism**, %	18	0	0	6	0	0
Nervous system disorders						
Headache, %	16	0	0	9	0	0
Investigations						
Weight loss, %	14	0	0	8	0	0
Muscuolskeletal and connective tissue disorders						
Musculoskeletal stiffness, %	14	0	0	3	0	0

*The term "rash" represents reports of events of rash, erythematous rash, macular rash, maculopapular rash, papular rash, and pruritic rash.
**Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

Important Safety Information

Hepatotoxicity: Severe drug-induced liver injury with fatal outcome occurred in 0.3% of 1200 STIVARGA-treated patients across all clinical trials. In gastrointestinal stromal tumor (GIST), fatal hepatic failure occurred in 0.8% of patients in the STIVARGA arm.

Dose Modifications in the GRID Trial

- In the GRID study, the median duration of therapy was 22.9 (range 0.1, 50.9) weeks for patients receiving STIVARGA[3]
- Dose interruptions for AEs were required in 58% of patients receiving STIVARGA and 50% of patients had their dose reduced[3]
- Drug-related AEs that resulted in treatment discontinuation were reported in 2.3% of STIVARGA-treated patients compared to 1.5% of patients who received placebo[3]

Hand-Foot Skin Reaction (HFSR)

- STIVARGA caused an increased incidence of HFSR and severe rash requiring dose modification[3]
- The overall incidence of HFSR (67% vs. 12%) and the incidence of Grade 3 HFSR (22% vs. 0%) were increased with STIVARGA compared to placebo for GIST[3]
- The incidence of Grade 3 rash (7% vs. 0%) was higher in STIVARGA-treated patients in GIST[3]
- Toxic epidermal necrolysis occurred in 0.17% of 1200 STIVARGA-treated patients across all clinical trials[3]
- HFSR is characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or soles of the feet (Figure 2. Grading HFSR)[5]
- Recommended dose modifications and measures for HFSR have been developed (Table 2. Dose Modifications for HFSR)[3]

Figure 2. Grading HFSR[5]

HFSR: A disorder characterized by redness, marked discomfort, swelling and tingling in the palms of the hands or soles of the feet

Grade 1	Grade 2	Grade 3
Minimal skin changes or dermatitis (e.g., erythema, edema or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, edema or hyperkeratosis) with pain; limiting instrumental activities of daily living	Severe skin changes (e.g., peeling, blisters, bleeding, edema or hyperkeratosis) with pain; limiting self-care activities of daily living

Table 2. Dose Modifications for HFSR[3]

Observed HFSR	Occurrence	Recommended Dose Modifications and Measures
Grade 2	1st occurrence	▪ **Decrease dose to 120 mg**
	No improvement within 7 days	▪ **Interrupt therapy** ▪ **If HFSR does not completely resolve, reduce dose to 80 mg**
	2nd occurrence	▪ **Interrupt therapy** ▪ **When resuming treatment, reduce dose to 80 mg**
	3rd occurrence	▪ **If patient failed to tolerate the 80 mg dose, discontinue treatment permanently**
Grade 3	1st occurrence	▪ **Interrupt therapy for ≥7 days** ▪ **When resuming treatment, decrease dose to 120 mg**
	2nd occurrence	▪ **Interrupt therapy for ≥7 days** ▪ **When resuming treatment, decrease dose to 80 mg**
	3rd occurrence	▪ **If patient failed to tolerate the 80 mg dose, discontinue treatment permanently**

Important Safety Information

Liver Function Monitoring: Obtain liver function tests (ALT, AST, and bilirubin) before initiation of STIVARGA and monitor at least every 2 weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the upper limit of normal (ULN) or baseline values. Temporarily hold and then reduce or permanently discontinue STIVARGA, depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis.

Hemorrhage: STIVARGA caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) for GIST was 11% with STIVARGA compared to 3% with placebo. Fatal hemorrhage occurred in 4 of 632 (0.6%) STIVARGA-treated patients and involved the respiratory, gastrointestinal, or genitourinary tracts. Permanently discontinue STIVARGA in patients with severe or life-threatening hemorrhage and monitor INR levels more frequently in patients receiving warfarin.

Dermatological Toxicity: STIVARGA caused an increased incidence of hand-foot skin reaction (HFSR) (also known as palmar-plantar erythrodysesthesia [PPE]) and severe rash, frequently requiring dose modification. The overall incidence of HFSR (67% vs 12%) and the incidence of Grade 3 HFSR (22% vs 0%) were increased with STIVARGA compared to placebo for GIST. The incidence of Grade 3 rash (7% vs 0%) was higher in STIVARGA-treated patients in GIST. Toxic epidermal necrolysis occurred in 0.17% of 1200 STIVARGA-treated patients across all clinical trials. Withhold STIVARGA, reduce the dose, or permanently discontinue depending on the severity and persistence of dermatologic toxicity.

Liver Function Test Abnormalities

- Severe drug induced liver injury with fatal outcomes occurred in 0.8% of patients with GIST in the STIVARGA arm[3]
- Among STIVARGA- and placebo-treated patients, respectively, increased AST was observed in 58% and 47% of patients, while increased ALT was observed in 39% and 39% of patients[3]
- Hyperbilirubinemia was observed in 33% vs. 12% of STIVARGA- and placebo-treated patients, respectively[3]
- Elevations in ALT, AST, and bilirubin are graded according to an objective comparison to the established upper limit of normal (Figure 3. Grading Liver Function Test Abnormalities)[5]
- Recommended dose modifications and measures for LFT abnormalities have been developed (Table 3. Dose Modifications for Liver Function Test Abnormalities)[3]

Figure 3. Grading Liver Function Test Abnormalities[5]

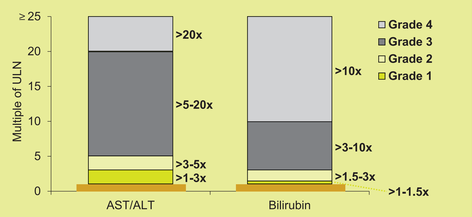

Table 3. Dose Modifications for Liver Function Test Abnormalities[3]

Observed Elevations in ALT and/or AST	Occurrence	Recommended Dose Modifications and Measures
≤5x ULN	Any occurrence	▪ **Monitor liver function tests weekly until return to <3x ULN (grade 1) or baseline**
>5x ULN to ≤20x ULN (grade 3)	1st occurrence	▪ **Interrupt therapy** ▪ **Monitor liver function tests until return to <3x ULN or baseline** ▪ **Only restart therapy if the potential benefit outweighs the risk of hepatotoxicity** ▪ **When restarting therapy, reduce the dose to 120 mg**
	Reoccurrence	▪ **Discontinue treatment permanently**
>20x ULN (grade 4)	Any occurrence	▪ **Discontinue treatment permanently**
>3x ULN (grade ≥2) with concurrent bilirubin >2x ULN	Any occurrence	▪ **Discontinue treatment permanently** ▪ **Monitor liver function tests until resolution or return to baseline**

Dose Modification Procedures for Other AEs

- In addition to HFSR and LFTs, additional dose modifications and measures for other AEs have been developed (Table 4. Dose Modifications for Other Adverse Events)[3]

Table 4. Dose Modifications for Other AEs

- Interrupt regorafenib for symptomatic grade 2 hypertension or any NCI CTCAE grade 3 or 4 adverse reaction
- Reduce the dose of regorafenib to 120 mg after recovery of any grade 3 or 4 adverse reaction
- Reduce the dose of regorafenib to 80 mg after recovery of any grade 3 or 4 adverse reaction at the 120 mg dose, except hepatotoxicity
- Discontinue regorafenib permanently for the failure to tolerate the 80 mg dose or for any grade 4 adverse reaction
  - Only resume regorafenib after a grade 4 adverse reaction if the potential benefit outweighs the risks

Important Safety Information

Hypertension: STIVARGA caused an increased incidence of hypertension (59% with STIVARGA vs 27% with placebo in GIST). Hypertensive crisis occurred in 0.25% of 1200 STIVARGA-treated patients across all clinical trials. Do not initiate STIVARGA until blood pressure is adequately controlled. Monitor blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Temporarily or permanently withhold STIVARGA for severe or uncontrolled hypertension.

Cardiac Ischemia and Infarction: STIVARGA increased the incidence of myocardial ischemia and infarction (1.2% with STIVARGA vs 0.4% with placebo). Withhold STIVARGA in patients who develop new or acute cardiac ischemia or infarction, and resume only after resolution of acute cardiac ischemic events if the potential benefits outweigh the risks of further cardiac ischemia.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS occurred in 1 of 1200 STIVARGA-treated patients across all clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Confirm the diagnosis of RPLS with MRI and discontinue STIVARGA in patients who develop RPLS.

Gastrointestinal Perforation or Fistula: Gastrointestinal perforation or fistula occurred in 0.6% of 1200 patients treated with STIVARGA across all clinical trials; this included 4 fatal events. In GIST, 2.1% (4/188) of STIVARGA-treated patients developed gastrointestinal fistula or perforation; of these, 2 cases of gastrointestinal perforation were fatal. Permanently discontinue STIVARGA in patients who develop gastrointestinal perforation or fistula.

Wound Healing Complications: Treatment with STIVARGA should be stopped at least 2 weeks prior to scheduled surgery. Resuming treatment after surgery should be based on clinical judgment of adequate wound healing. STIVARGA should be discontinued in patients with wound dehiscence.

Dose Modifications in Clinical Practice

Case 1

Table 5. Hypothetical Patient 1

- Patient characteristics
  - Age and sex: 60-year-old male
  - Diagnosis: metastatic GIST
  - Eastern Cooperative Oncology Group (ECOG) performance status (PS): 1
  - Baseline BP: 117/74
- Treatment history
  - Progressed on imatinib
  - Progressed on sunitinib
- Initiated treatment with regorafenib 160 mg/day
- BP monitoring during second week of the first cycle revealed an increase in DBP of 22 mm Hg (a grade 2 event), which was associated with headaches and dizziness
  - Regorafenib was interrupted for 2 weeks until symptoms resolved
  - Treatment was then continued at the 160 mg/day dose
  - The addition of an anti-hypertensive medication to the patient's treatment regimen was discussed
- During the first week of the third cycle, the patient experienced grade 3 diarrhea
  - Regorafenib was temporarily interrupted for 1 week until symptoms resolved
  - Treatment was then continued at a reduced dose of 120 mg/day

Case 2

Table 6. Hypothetical Patient 2

- Patient characteristics
  - Age and sex: 61-year-old female
  - Diagnosis: metastatic GIST
  - ECOG PS: 0
- Treatment history
  - Progressed on imatinib
  - Discontinued sunitinib due to poor tolerability
- Initiated treatment with regorafenib 160 mg/day
- During a physician visit to evaluate LFTs 2 weeks into the first cycle, the patient noted painful blistering and peeling of the skin on her hands, which limited her ability to prepare meals (grade 2 HFSR); diminished energy, and decreased interest in daily activities was also noted (grade 1 fatigue)
  - Treatment was continued without interruption at a reduced dose (120 mg/day)
  - Increased rest was discussed as a potential means to lessen fatigue
- During the second cycle, her grade 2 HFSR reoccurred
  - Regorafenib was temporarily interrupted until symptoms resolved
  - Treatment was then continued at a reduced dose of 80 mg/day

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Important Safety Information

Embryo-Fetal Toxicity: STIVARGA can cause fetal harm when administered to a pregnant woman. Use effective contraception during treatment and up to 2 months after completion of therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers: Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from STIVARGA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Most Frequently Observed Adverse Drug Reactions in GIST (≥30%): The most frequently observed adverse drug reactions (≥30%) in STIVARGA-treated patients vs placebo-treated patients in GIST, respectively, were: HFSR/PPE (67% vs 15%), hypertension (59% vs 27%), asthenia/fatigue (52% vs 39%), diarrhea (47% vs 9%), mucositis (40% vs 8%), dysphonia (39% vs 9%), infection (32% vs 5%), decreased appetite and food intake (31% vs 21%), and rash (30% vs 3%).

References

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Supported by Bayer HealthCare Pharmaceuticals Inc, Whippany, New Jersey, USA.

Stivarga® (regorafenib) tablets

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