HARNESS THE POWER OF STIVARGA® (regorafenib)

Proven efficacy maximizes OS potential for your previously treated patients with mCRC[1]

- In the pivotal CORRECT trial, STIVARGA demonstrated a 6.4-month (95% CI, 5.8-7.3) median OS in previously treated patients with mCRC, compared with 5.0 months (95% CI, 4.4-5.8) for placebo[1]
- 23% reduction in risk of death with STIVARGA (HR, 0.77; 95% CI, 0.64-0.94; *P*=0.0102)[1]
- 41% disease control rate with STIVARGA vs 15% with placebo[2]

CORRECT (COIoRectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy) was a large, international, placebo-controlled, double-blind, randomized (2:1), phase III trial that evaluated the efficacy and safety of STIVARGA in patients with mCRC who had progressed after all approved standard therapies (N=760). OS was the primary endpoint of CORRECT.[1]

Indication

STIVARGA is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy.

Important Safety Information

WARNING: HEPATOTOXICITY

- **Severe and sometimes fatal hepatotoxicity has occurred 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.**

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CI=confidence interval; HR=hazard ratio; mCRC=metastatic colorectal cancer; OS=overall survival.

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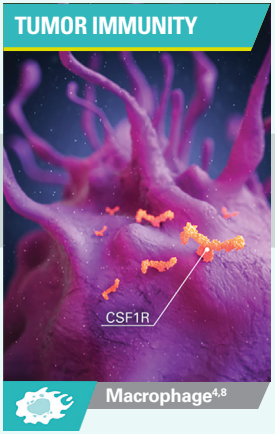
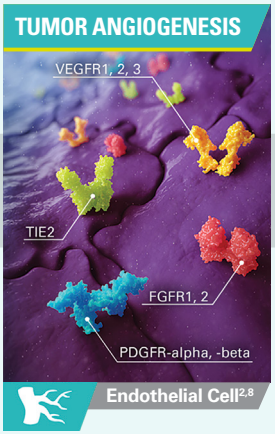
STIVARGA® (regorafenib) is a multikinase inhibitor that targets normal cellular functions and pathological processes such as oncogenesis, tumor angiogenesis, metastasis, and tumor immunity[1]

Target the tumor 4 ways through multikinase inhibition[1]

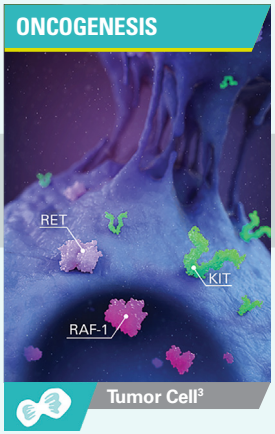
STIVARGA



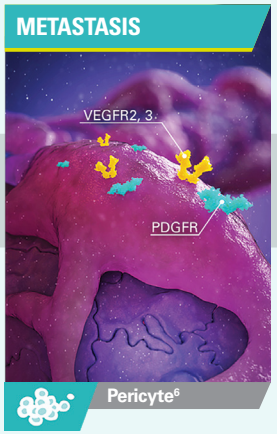
STIVARGA disrupts tumor immunity by inhibiting CSF1R, a receptor important for macrophage proliferation[1,3]



STIVARGA inhibits key angiogenic receptors: VEGFR1, 2, and 3; TIE2; PDGFR-alpha and -beta; and FGFR1 and 2 via kinase inhibition[1,4-6]



STIVARGA potently blocks multiple protein kinases, including KIT, RAF-1, and RET, which are important in oncogenesis[1,4,6]



- STIVARGA inhibits VEGFR2 and 3, important mediators involved in endothelial cell proliferation and migration[1,6,7]
- Blocks PDGFR, believed to play a role in cancer-associated, fibroblast-induced metastasis[1,8]

STIVARGA® (regorafenib) inhibits a large set of tyrosine kinases, resulting in multiple antitumor activities[1,9]

- In in vitro biochemical or cellular assays, STIVARGA or its major human active metabolites, M-2 and M-5, inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl, and CSF1R at concentrations of STIVARGA that have been achieved clinically[1]
- In in vivo models, STIVARGA demonstrated anti-angiogenic activity in a rat tumor model and inhibition of tumor growth in several mouse xenograft models, including some for human colorectal carcinoma. STIVARGA also demonstrated anti-metastatic activity in a mouse xenograft model and 2 mouse orthotopic models of human colorectal carcinoma[1]

Important Safety Information (continued)

Hepatotoxicity: Severe drug-induced liver injury with fatal outcome occurred in STIVARGA-treated patients across all clinical trials. In most cases, liver dysfunction occurred within the first 2 months of therapy and was characterized by a hepatocellular pattern of injury. In metastatic colorectal cancer (mCRC), fatal hepatic failure occurred in 1.6% of patients in the STIVARGA arm and in 0.4% of patients in the placebo arm.

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.

Infections: STIVARGA caused an increased risk of infections. The overall incidence of infection (Grades 1-5) was higher (32% vs 17%) in 1142 STIVARGA-treated patients as compared to the control arm in randomized placebo-controlled trials. The incidence of grade 3 or greater infections in STIVARGA-treated patients was 9%. The most common infections were urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) and pneumonia (2.6%). Fatal outcomes caused by infection occurred more often in patients treated with STIVARGA (1.0%) as compared to patients receiving placebo (0.3%); the most common fatal infections were respiratory (0.6% vs 0.2%). Withhold STIVARGA for Grade 3 or 4 infections, or worsening infection of any grade. Resume STIVARGA at the same dose following resolution of infection.

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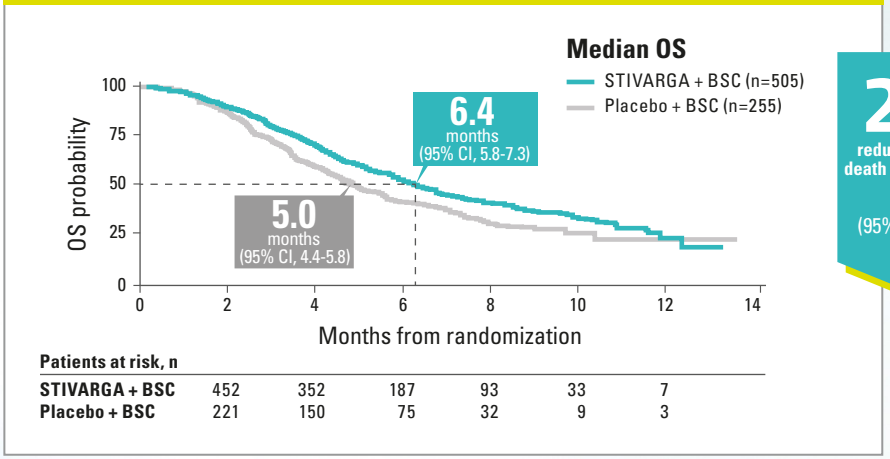
Harness the proven efficacy of STIVARGA® (regorafenib) to maximize OS potential for your previously treated patients with mCRC

Significant improvement in OS[1]*



23%
reduction in risk of death with STIVARGA[1]
HR: 0.77
(95% CI, 0.64-0.94)
P=0.0102

BSC=best supportive care.

*OS was the primary endpoint of CORRECT.[1]

CORRECT (COloRectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy) was a large, international, placebo-controlled, double-blind, randomized (2:1), phase III trial that evaluated the efficacy and safety of STIVARGA in patients with mCRC who had progressed after all approved standard therapies (N=760).[1]

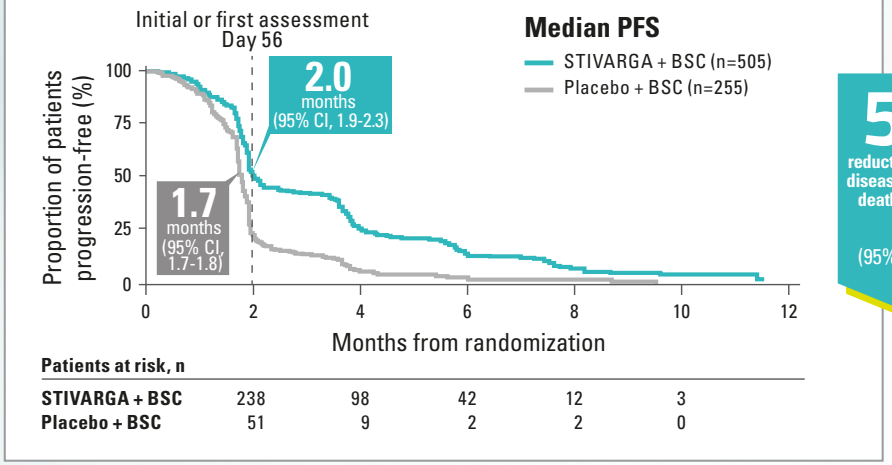
- STIVARGA improved OS in CORRECT, which included patients with historically collected *KRAS* status (N=729)[1]
  - Historical *KRAS* status was assessed (59% mutant, 41% wild-type *KRAS*)
- There were 275 deaths out of 505 patients treated with STIVARGA (55%) vs 157 deaths out of 255 patients treated with placebo (62%)[1]

Important Safety Information (continued)

Hemorrhage: STIVARGA caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 18.2% in 1142 patients treated with STIVARGA vs 9.5% with placebo in randomized, placebo-controlled trials. The incidence of grade 3 or greater hemorrhage in patients treated with STIVARGA was 3.0%. The incidence of fatal hemorrhagic events was 0.7%, involving the central nervous system or 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.

STIVARGA® (regorafenib) significantly improved PFS

Significant improvement in PFS[1,2]*



51%
reduction in the risk of disease progression or death in CORRECT[1,2]
HR: 0.49
(95% CI, 0.42-0.58)
P<0.0001

PFS=progression-free survival.

*PFS, time from randomization to progression or death.[2]

Important Safety Information (continued)

Gastrointestinal Perforation or Fistula: Gastrointestinal perforation occurred in 0.6% of 4518 patients treated with STIVARGA across all clinical trials of STIVARGA administered as a single agent; this included eight fatal events. Gastrointestinal fistula occurred in 0.8% of patients treated with STIVARGA and in 0.2% of patients in the placebo arm across randomized, placebo-controlled trials. Permanently discontinue STIVARGA in patients who develop gastrointestinal perforation or fistula.

Dermatological Toxicity: In randomized, placebo-controlled trials, adverse skin reactions occurred in 71.9% of patients with STIVARGA arm and 25.5% of patients in the placebo arm including hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia syndrome (PPES) and severe rash, requiring dose modification.

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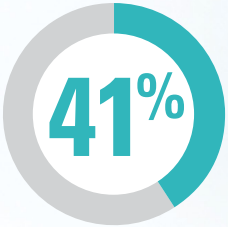
Disease control rates (DCR) from the CORRECT Trial[2]



DCR with STIVARGA included 41% stable disease rate and 1% partial response rate (n=207/505)[2]

DCR with placebo included 15% stable disease rate and 0.4% partial response rate (n=38/255)[2]

- Disease control is defined as a proportion of patients with a best response of complete or partial response or stable disease; assessment of stable disease had to be made at least 6 weeks after randomization[2]

Important Safety Information (continued)

Dermatological Toxicity (continued): In the randomized, placebo-controlled trials, the overall incidence of HFSR was higher in 1142 STIVARGA-treated patients (53% vs 8%) than in the placebo-treated patients. Most cases of HFSR in STIVARGA-treated patients appeared during the first cycle of treatment. The incidences of Grade 3 HFSR (16% vs <1%), Grade 3 rash (3% vs <1%), serious adverse reactions of erythema multiforme (<0.1% vs 0%), and Stevens-Johnson syndrome (<0.1% vs 0%) were higher in STIVARGA-treated patients. Across all trials, a higher incidence of HFSR was observed in Asian patients treated with STIVARGA (all grades: 72%; Grade 3: 18%). Toxic epidermal necrolysis occurred in 0.02% of 4518 STIVARGA-treated patients across all clinical trials of STIVARGA administered as a single agent. Withhold STIVARGA, reduce the dose, or permanently discontinue depending on the severity and persistence of dermatologic toxicity.

Hypertension: Hypertensive crisis occurred in 0.2% in STIVARGA-treated patients and in none of the patients in placebo arm across all randomized, placebo-controlled trials. STIVARGA caused an increased incidence of hypertension (30% vs 8% in mCRC). The onset of hypertension occurred during the first cycle of treatment in most patients who developed hypertension (67% in randomized, placebo controlled 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.

STIVARGA® (regorafenib) safety profile

AEs reported in ≥10% of mCRC patients treated with STIVARGA and reported more commonly than in patients receiving placebo[1]*

AEs		**STIVARGA** (n=500)		**Placebo** (n=253)	
		All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
General disorders and administration site conditions	Asthenia/fatigue	64%	15%	46%	9%
	Pain	59%	9%	48%	7%
	Fever	28%	2%	15%	0%
Metabolism and nutrition disorders	Decreased appetite and food intake	47%	5%	28%	4%
Skin and subcutaneous tissue disorders	HFSR/PPES	45%	17%	7%	0%
	Rash†	26%	6%	4%	<1%
Gastrointestinal disorders	Diarrhea	43%	8%	17%	2%
	Mucositis	33%	4%	5%	0%
Investigations	Weight loss	32%	<1%	10%	0%
Infections and infestations	Infection‡	31%	9%	17%	6%
Vascular disorders	Hypertension	30%	8%	8%	<1%
	Hemorrhage‡	21%	2%	8%	<1%
Respiratory, thoracic, and mediastinal disorders	Dysphonia	30%	0%	6%	0%
Nervous system disorders	Headache	10%	<1%	7%	0%

AEs=adverse events; HFSR/PPES= hand-foot skin reaction/palmar-plantar erythrodysesthesia syndrome.

*Adverse reactions graded according to National Cancer Institute Common Toxicity for Adverse Events version 3.0 (NCI CTCAE v3.0).

†The term "rash" represents reports of events of drug eruption, rash, erythematous rash, generalized rash, macular rash, maculopapular rash, papular rash, and pruritic rash.

‡Fatal outcomes observed.

Important Safety Information (continued)

Cardiac Ischemia and Infarction: STIVARGA increased the incidence of myocardial ischemia and infarction (0.9% with STIVARGA vs 0.2% with placebo) in randomized placebo-controlled trials. 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.

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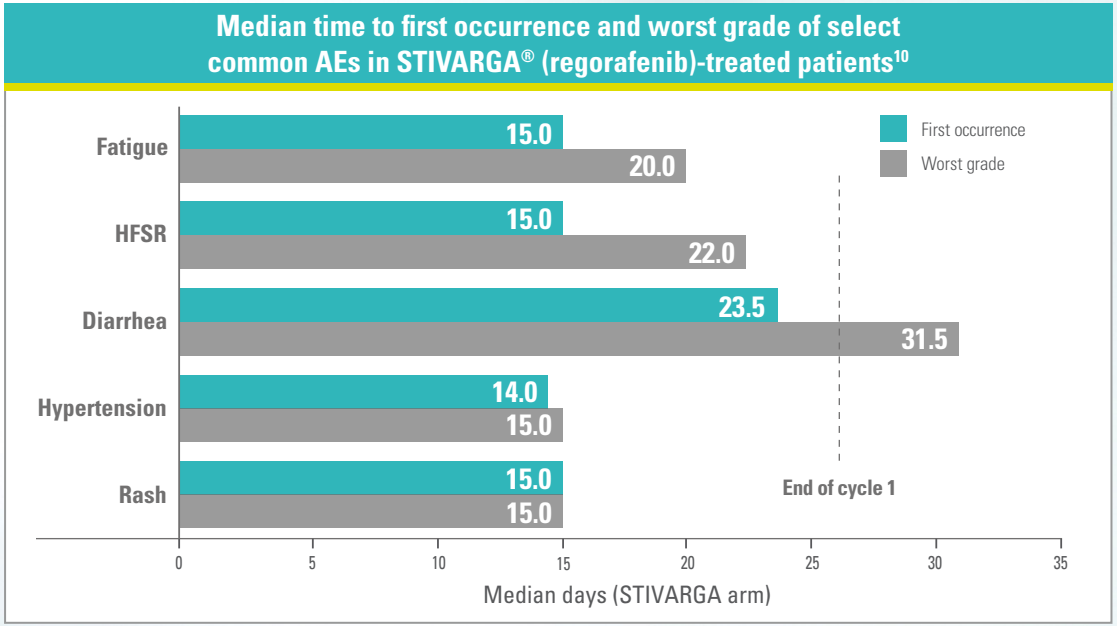
Median time to select treatment-related AEs ≥Grade 3 occurring in ≥5% of patients in either arm of the CORRECT trial[2,10]*



- AEs can occur at any time during the course of treatment and monitoring is critical during the first cycle and throughout therapy[2,11]
- 8.2% of STIVARGA patients discontinued treatment because of drug-related AEs vs 1.2% of placebo patients[1]

Important Safety Information (continued)

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristics finding on MRI, occurred in one of 4800 STIVARGA-treated patients across all clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, severe headache, visual disturbances, confusion, or altered mental function. Discontinue STIVARGA in patients who develop RPLS.

Important Safety Information (continued)

Wound Healing Complications: Impaired wound healing complications can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, STIVARGA has the potential to adversely affect wound healing. Withhold STIVARGA for at least 2 weeks prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of STIVARGA after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity: STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose.

Nursing Mothers: Because of the potential for serious adverse reactions in breastfed infants from STIVARGA, do not breastfeed during treatment with STIVARGA and for 2 weeks after the final dose.

Most Frequently Observed Adverse Drug Reactions in mCRC (≥30%): The most frequently observed adverse drug reactions (≥30%) in STIVARGA-treated patients vs placebo-treated patients in mCRC, respectively, were: asthenia/fatigue (64% vs 46%), pain (59% vs 48%), decreased appetite and food intake (47% vs 28%), HFSR/PPE (45% vs 7%), diarrhea (43% vs 17%), mucositis (33% vs 5%), weight loss (32% vs 10%), infection (31% vs 17%), hypertension (30% vs 8%), and dysphonia (30% vs 6%).

References: 1. STIVARGA [prescribing Information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc; February 2020. **2.** Grothey A, Van Cutsem E, Sobrero A, et al; for the CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):303-312. **3.** Matsushime H, Roussel MF, Ashmun RA, Sherr CJ. Colony-stimulating factor 1 regulates novel cyclins during the G1 phase of the cell cycle. *Cell.* 1991;65(4):701-713. **4.** Zopf D, Fitchner I, Bhargava A, et al. Pharmacologic activity and pharmacokinetics of metabolites of regorafenib in preclinical models. *Cancer Med.* 2016;5(11):3176-3185. **5.** Zhao Y, Adjei A. Targeting angiogenesis in cancer therapy: moving beyond vascular endothelial growth factor. *Oncologist.* 2015; 20(6):660-673. **6.** Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer.* 2011;129(1):245-255. **7.** Schmieder R, Hoffmann J, Becker M, et al. Regorafenib (BAY 73-4506): antitumor and antimetastatic activities in preclinical models of colorectal cancer. *Int J Cancer.* 2014; 135(6):1487-1496. **8.** Takigawa H, Kitadai Y, Shinagawa K, et al. Multikinase inhibitor regorafenib inhibits the growth and metastasis of colon cancer with abundant stroma. *Cancer Sci.* 2016;107(5):601-608. **9.** Rey JB, Launay-Vaucher V, Tournigand C. Regorafenib as a single-agent in the treatment of patients with gastrointestinal tumors: an overview for pharmacists. *Target Oncol.* 2015;10(2):199-213. **10.** Grothey A, Sobrero A, Falcone A, et al. Time profile of adverse events from regorafenib treatment for metastatic colorectal cancer in phase III CORRECT study. Poster presented at: American Society of Clinical Oncology 2013 Gastrointestinal Cancers Symposium; January 24-26, 2013; San Francisco, CA. Poster 3637. **11.** Grothey A, George S, van Cutsem E, Blay JY, Sobrero A, Demetri GD. Optimizing treatment outcomes with regorafenib: personalized dosing and other strategies to support patient care. *Oncologist.* 2014;19(6):669-680.

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Stivarga® (regorafenib) tablets

For your appropriate patients with mCRC who have been previously treated with 2 chemo-based therapies

HARNESS THE CLINICALLY PROVEN POWER OF STIVARGA® (regorafenib)

Maximize potential OS with the proven efficacy of STIVARGA

23%

REDUCTION IN RISK OF DEATH WITH STIVARGA

(HR, 0.77; 95% CI, 0.64-0.94; *P*=0.0102)[1]

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