HARNESS THE POWER OF STIVARGA® (regorafenib)

Proven efficacy maximizes overall survival (OS) potential for your previously treated patients with metastatic colorectal cancer (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]

CI=confidence interval; HR=hazard ratio.

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.**

NEXT

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Stivarga® (regorafenib) tablets

Right patient, right time

PROGRESSION ON (OR INTOLERANCE TO) UPFRONT STANDARD CHEMOTHERAPY REGIMENS[1]

- Fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy
- Anti-VEGF therapy
- Anti-EGFR therapy (if *KRAS* wild-type)

LIFE EXPECTANCY OF AT LEAST 3 MONTHS[2]

- Part of the inclusion criteria in STIVARGA® (regorafenib) clinical trials

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.

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Patient 1

PERSONAL CHARACTERISTICS
- 60-year-old female

INITIAL DIAGNOSIS
- Rectal cancer (T2, N0, M0)
  - ECOG PS=0
  - *RAS* mutant, MSS

15 MONTHS AFTER DIAGNOSIS
- Recurrent disease with liver metastases detected
  - Liver resection, followed by treatment with FOLFOX + bevacizumab

4 MONTHS AFTER LIVER METASTASES
- Recurrent disease with lung metastases
  - Treated with FOLFIRI + bevacizumab

CLINICAL CHARACTERISTICS TODAY
- CT scan showed tumor no longer responding
- Slight rise in CEA levels (≤5 ng/mL)
- ECOG PS=1

Patient 2

PERSONAL CHARACTERISTICS
- 66-year-old male

INITIAL DIAGNOSIS
- Colon cancer (T2, N0, M0)
  - ECOG PS=0
  - *KRAS* WT, MSS
  - Treated with resection

19 MONTHS AFTER DIAGNOSIS
- Liver metastases discovered
  - Treated with FOLFIRI + cetuximab

3 MONTHS AFTER LIVER METASTASES
- Liver tumor growth >15%, with metastases to the diaphragm
  - Treated with FOLFOX + bevacizumab

CLINICAL CHARACTERISTICS TODAY
- Stable disease
- No longer able to tolerate cytotoxic therapy
- ECOG PS=1

Not actual patient cases.

ECOG PS=Eastern Cooperative Oncology Group Performance Status; FOLFIRI=folinic acid, fluorouracil, and irinotecan; FOLFOX=folinic acid, fluorouracil, and oxaliplatin; MSS=microsatellite stable; WT=wild-type.

Important Safety Information (continued)

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.

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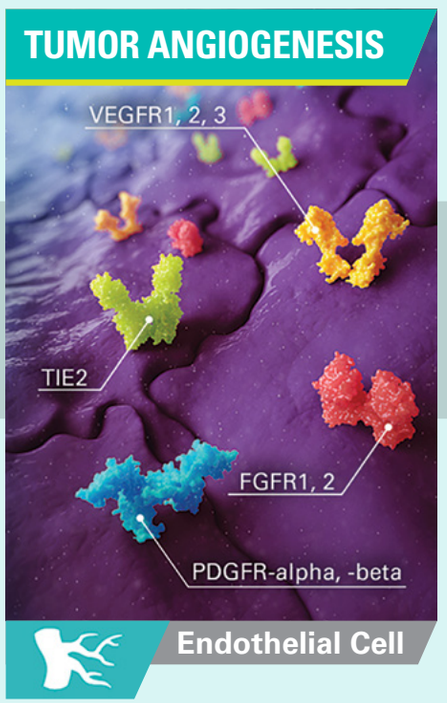
Stivarga® (regorafenib) tablets

STIVARGA® (regorafenib) is the only TKI approved in later-line CRC[1]

STIVARGA 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



Important Safety Information (continued)

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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Stivarga® (regorafenib) tablets

STIVARGA® (regorafenib) inhibits a large set of tyrosine kinases, resulting in multiple antitumor activities[1,17]

- 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]

METASTASIS

Metastasis

- Similar to cancer growth, cancer cell metastasis and invasion depend on the growth of the surrounding cells that make up the tumor microenvironment[18]

How STIVARGA works

- STIVARGA inhibits VEGFR2 and 3, important mediators involved in endothelial cell proliferation and migration[1,12,19]
- Blocks PDGFR, believed to play a role in cancer-associated, fibroblast-induced metastasis[1,20]

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.

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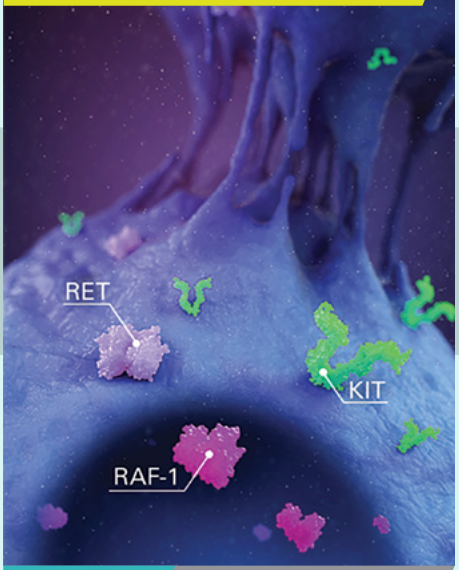
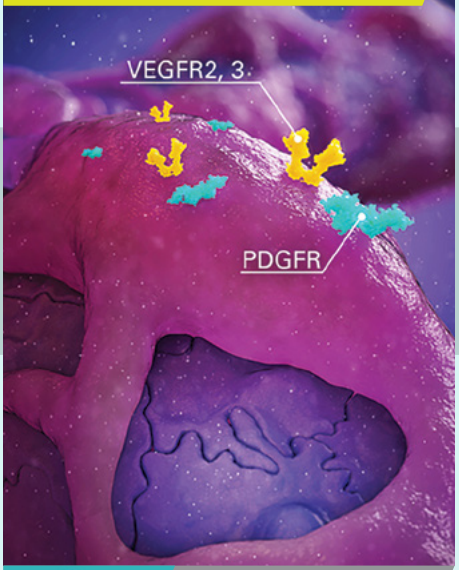
Stivarga® (regorafenib) tablets

ONCOGENESIS



Tumor Cell

METASTASIS



Pericyte

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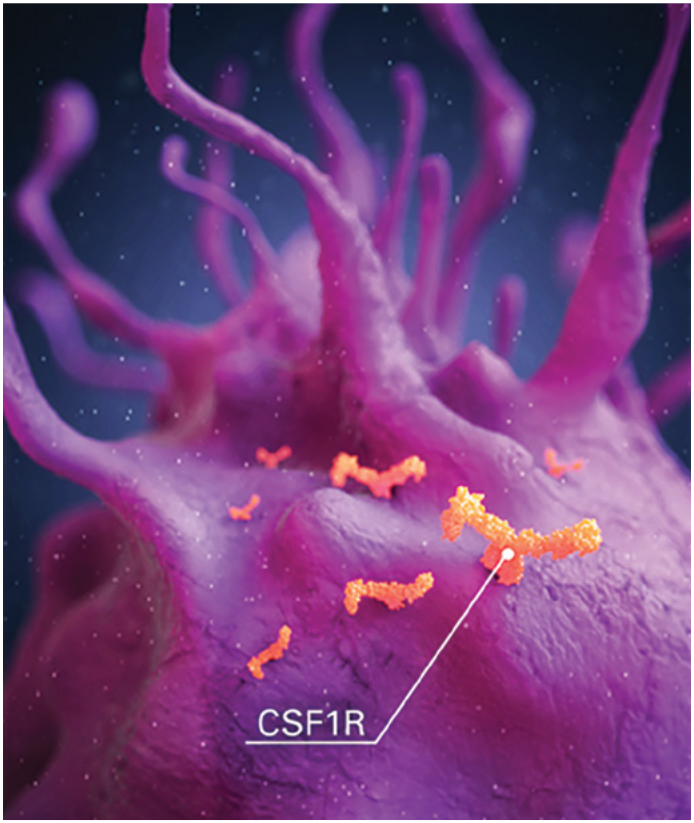
TUMOR IMMUNITY

Macrophage



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Tumor immunity

- CSF1R-mediated signaling is important for the differentiation and survival of macrophages[3]
- CSF1 signaling recruits anti-inflammatory tumor-associated macrophages (M2 macrophages) to the tumor microenvironment[3,4]
  - These tumor-associated macrophages may promote tumor immunity by suppressing the ability of T cells to recognize and kill the tumor cells

How STIVARGA works

- STIVARGA disrupts tumor immunity by inhibiting CSF1R, a receptor important for macrophage proliferation[1,5]

CSF1R=colony-stimulating factor 1 receptor; macrophage=a type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells; T cell=a type of white blood cell. T cells are part of the immune system and develop from stem cells in the bone marrow. They help protect the body from infection and might help fight cancer.

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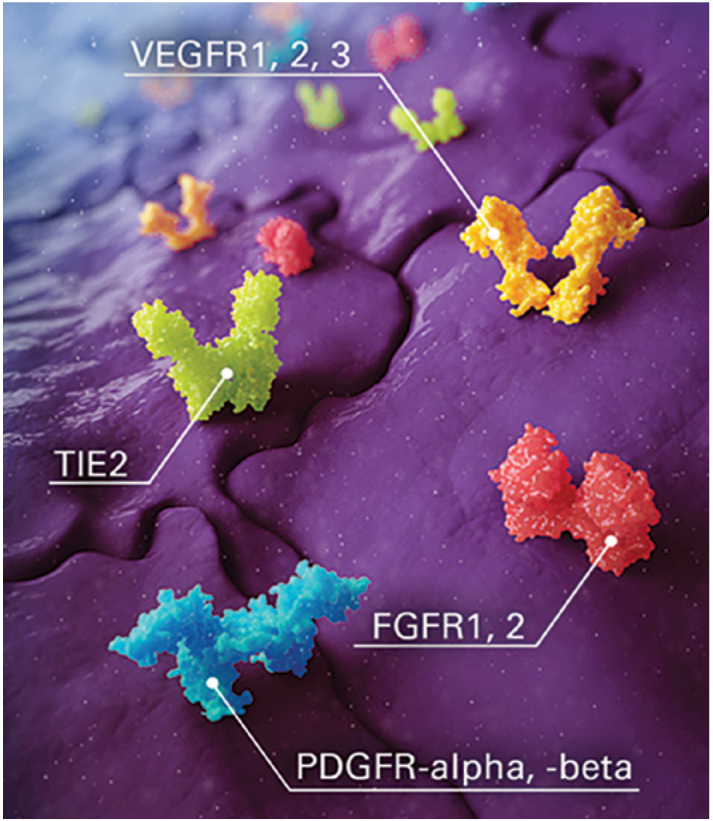
TUMOR ANGIOGENESIS

Endothelial Cell



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Tumor angiogenesis

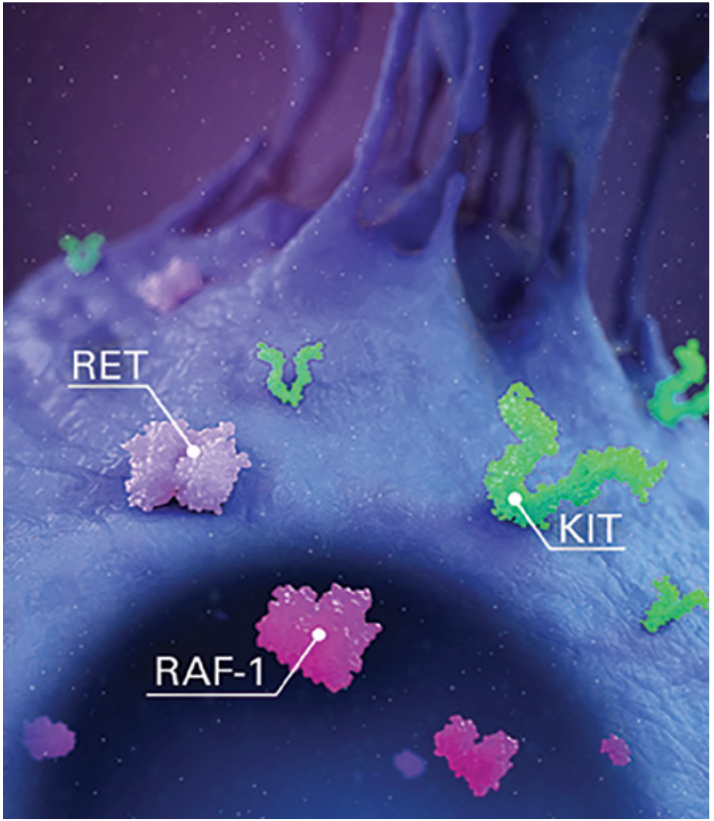
- Development of new blood vessels from pre-existing vessels allows for tumor progression[6]
- The tumor angiogenesis process includes endothelial cell migration and proliferation, vascular tube formation and conjunction of new blood vessels, and incorporation of the pericyte cells around the new vessels[6,7]
- Tyrosine kinases such as VEGFR1, 2, and 3; TIE2; PDGFR-alpha and -beta; and FGFR1 and 2 are involved in processes that promote angiogenesis[8-10]

How STIVARGA works

- STIVARGA inhibits key angiogenic receptors: VEGFR1, 2, and 3; TIE2; PDGFR-alpha and -beta; and FGFR1 and 2 via kinase inhibition[10-12]

ONCOGENESIS

Tumor Cell



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Oncogenesis

- A series of genetic changes can cause uncontrolled activation of signaling pathways in cell proliferation, survival, and invasion[13]
- c-KIT, RAF-1, and RET are protein kinases with important roles in processes implicated in oncogenesis[14-16]

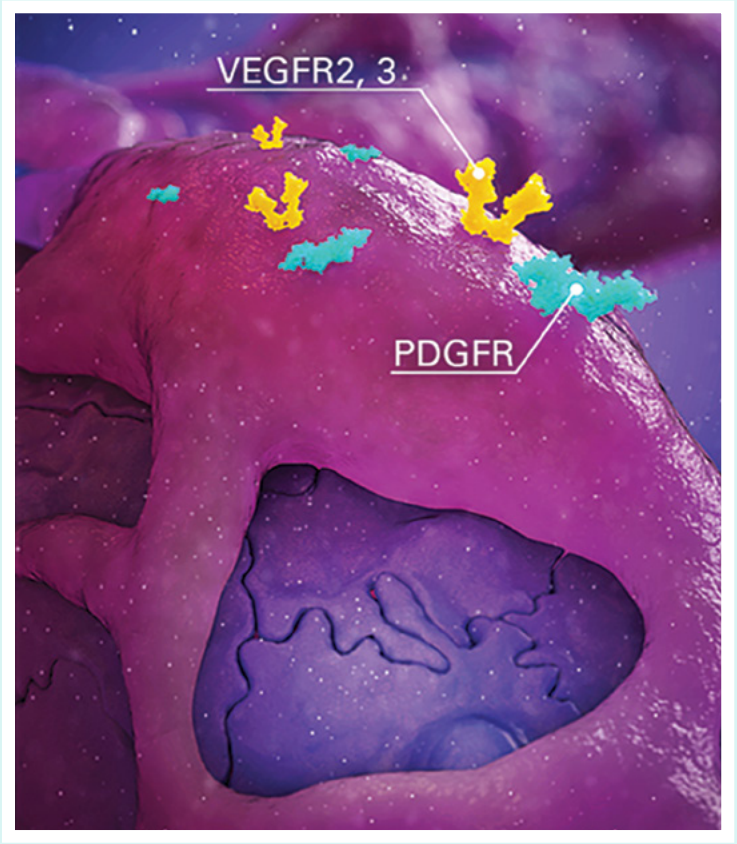
How STIVARGA works

- STIVARGA potently blocks multiple protein kinases, including KIT, RAF-1, and RET, which are important in oncogenesis[1,11,12]

BACK NEXT

METASTASIS

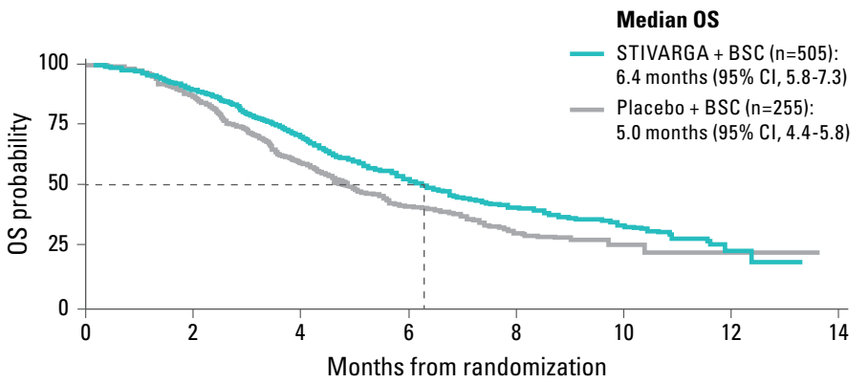
Pericyte



BACK NEXT

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

Significant improvement in OS in CORRECT[1,2]*



Patients at risk, n						
STIVARGA + BSC	452	352	187	93	33	7
Placebo + BSC	221	150	75	32	9	3

6.4 MONTHS vs 5.0 months
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 3 trial that evaluated the efficacy and safety of STIVARGA in patients with mCRC who had progressed after all approved standard therapies (N=760).[1,2]

- 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)

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. 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.

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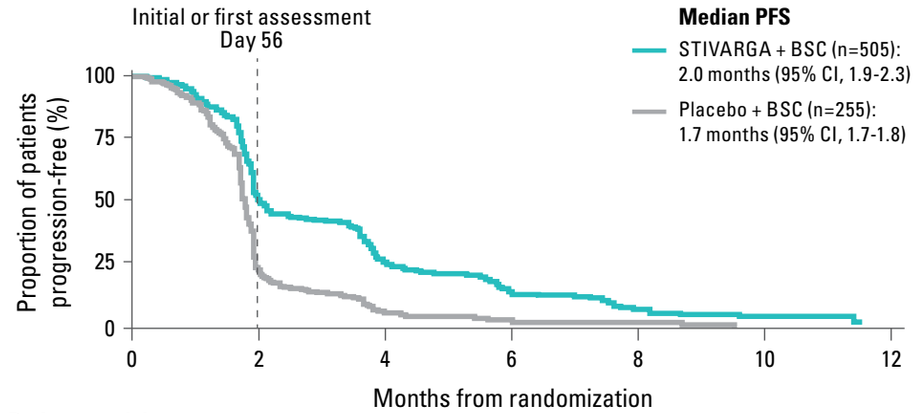
STIVARGA® (regorafenib) significantly improved PFS[1,2]

Significant improvement in PFS in CORRECT[1,2]*



Patients at risk, n					
STIVARGA + BSC	238	98	42	12	3
Placebo + BSC	51	9	2	2	0

2.0 MONTHS vs 1.7 months
HR: 0.49 (95% CI, 0.42-0.58)
P<0.0001

*Progression-free survival (PFS), time from randomization to progression or death.[2]

Important Safety Information (continued)

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.

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.

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.

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.

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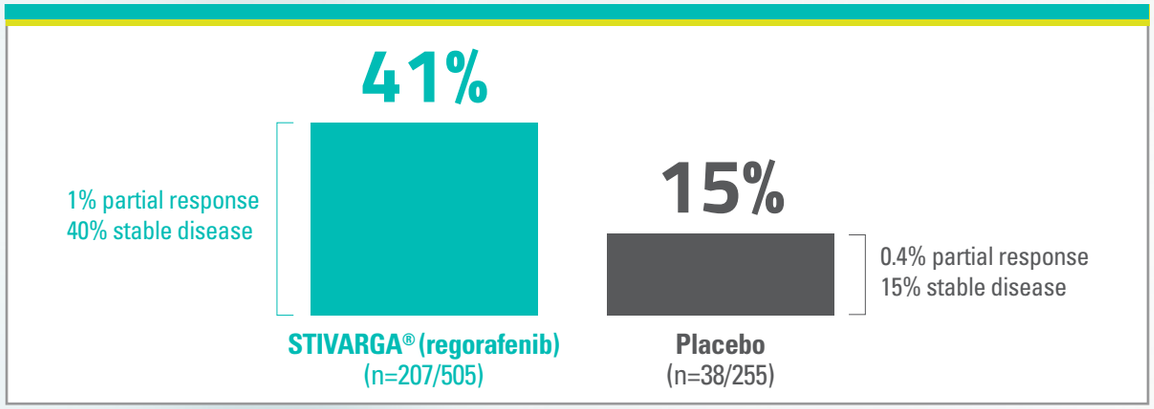
Disease control rates (DCR) in CORRECT[2]



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.

In CORRECT, patients were able to receive cytotoxic therapy following treatment with STIVARGA[2,21]

26% of patients in the CORRECT trial went on to receive subsequent cytotoxic therapy after STIVARGA[2,21]

Important Safety Information (continued)

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%).

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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STIVARGA® (regorafenib) safety profile

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

	STIVARGA (n=500)		Placebo (n=253)	
AEs	**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 Terminology 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.

STIVARGA works differently—it offers patients an alternative to chemotherapy and has a different safety profile[2,21-24]

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.

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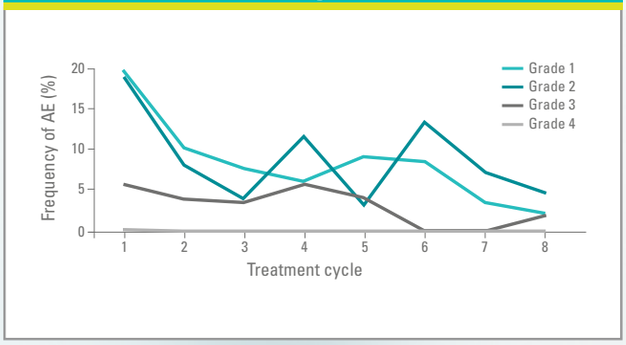
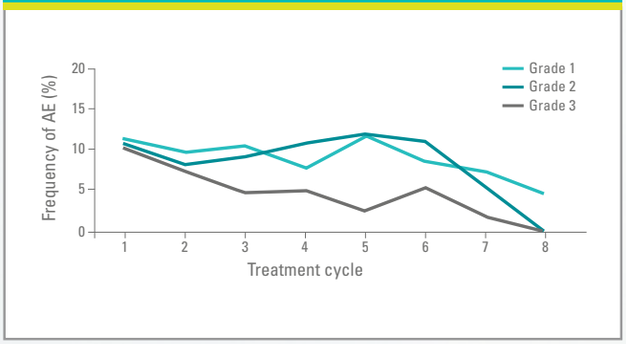
Frequency of specific AEs over time, according to grade of event, in regorafenib-treated patients in CORRECT[2,25]

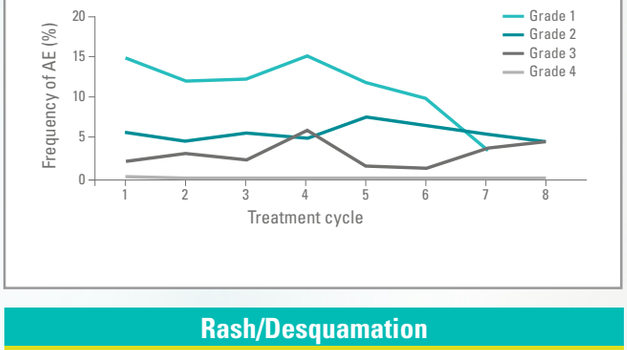
Fatigue



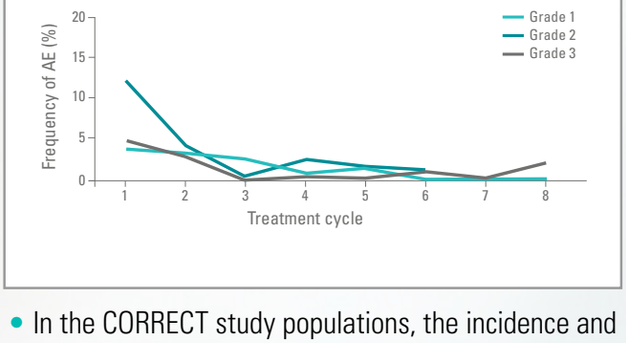
HFSR



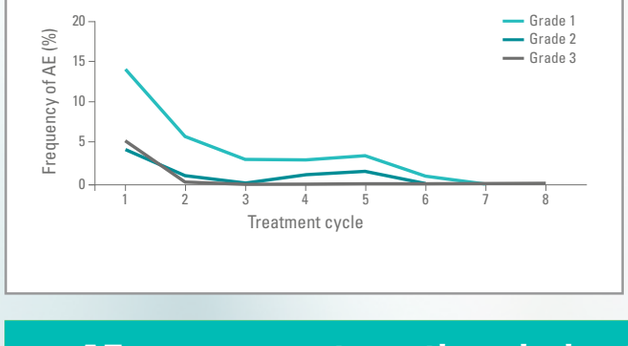
Diarrhea



Hypertension



Rash/Desquamation



- In the CORRECT study populations, the incidence and severity of fatigue, HFSR, diarrhea, hypertension, and rash/desquamation typically occurred early during treatment, and often reached their peak frequency and severity during the first cycle[25]
- Skin toxicity (HFSR/PPES or rash) was the most common cause of permanent drug discontinuation[1]
- 8.2% of STIVARGA® (regorafenib) patients discontinued treatment because of drug-related AEs vs 1.2% of placebo patients[1]

AEs can occur at any time during the course of treatment. Monitoring is critical during the first cycle and throughout therapy[26]

- Patients taking STIVARGA should be managed with monitoring at least every 2 weeks and proactive intervention during the first 2 cycles

Important Safety Information (continued)

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.

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Stivarga® (regorafenib) tablets

CONCUR: a randomized, double-blind, placebo-controlled, phase 3 trial[27]

- CONCUR was a multicenter, double-blind, placebo-controlled, randomized, phase 3 trial that evaluated the efficacy and safety of STIVARGA® (regorafenib) in Asian patients with mCRC progressing after standard therapies (N=204). Prior anti-VEGF or anti-EGFR targeted therapy was allowed, but not mandatory[27]

CONCUR study objectives[27]

- Primary endpoint: OS
- Secondary endpoints: PFS, objective response rate (ORR), and DCR

CONCUR study procedures[27]

- Patients received STIVARGA 160 mg or matching placebo orally once a day for the first 21 days of each 28-day treatment cycle until disease progression, death, unacceptable toxicity, or patient withdrawal or discontinuation
- 204 total patients were evaluated; 136 were enrolled in the STIVARGA arm and 68 were in the placebo arm

CONCUR study: baseline characteristics[27]

		STIVARGA (n=136)	Placebo (n=68)
Age, years (range)	Median	57.5 (50.0-66.0)	55.5 (48.5-62.0)
Sex (male)		85 (63%)	33 (49%)
Region	China (mainland China; Taiwan; Hong Kong)	112 (82%)	60 (88%)
	Asia (other than China)	24 (18%)	8 (12%)
ECOG PS	0	35 (26%)	15 (22%)
	1	101 (74%)	53 (78%)
***KRAS* mutation**	Yes	46 (34%)	18 (26%)
	No	50 (37%)	29 (43%)
	Unknown	40 (29%)	21 (31%)
Previous systemic anticancer treatment lines (On or after diagnosis of metastatic disease*)	1-2	48 (35%)	24 (35%)
	3	32 (24%)	17 (25%)
	≥4	52 (38%)	27 (40%)
Primary tumor site	Colon	79 (58%)	48 (71%)
	Rectum	53 (39%)	19 (28%)
	Colon and rectum	4 (3%)	1 (1%)

*4 patients (3%) in the STIVARGA arm received no prior treatment for metastatic disease.

Important Safety Information (continued)

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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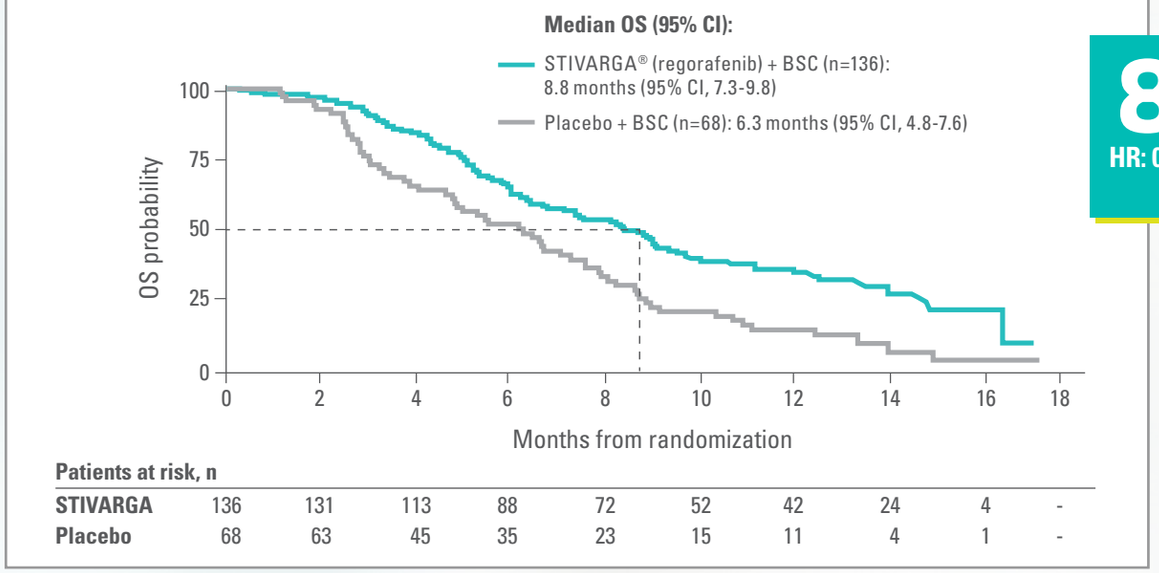
Stivarga® (regorafenib) tablets

OS results from CONCUR

Median OS (primary endpoint) in CONCUR[27]



8.8 MONTHS vs 6.3 months
HR: 0.55 (95% CI, 0.40-0.77)
P=0.00016

- AEs leading to death occurred in 12 (9%) patients receiving STIVARGA and 7 (10%) patients receiving placebo[27]

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.

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. 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.

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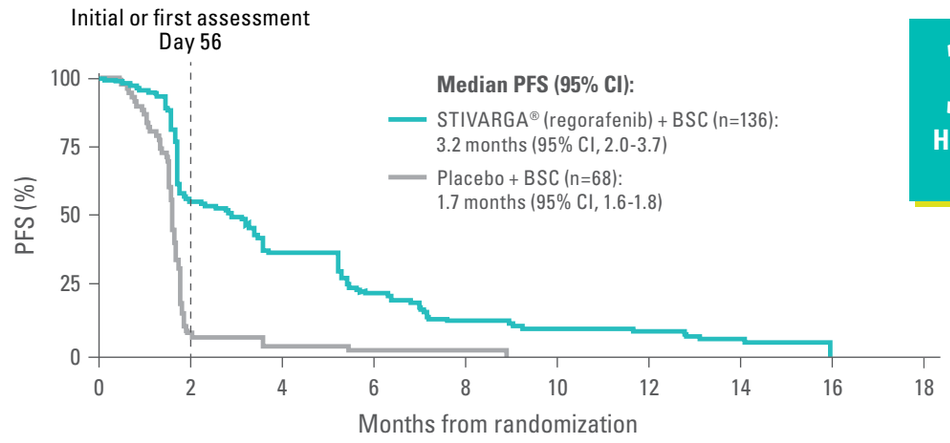
Stivarga® (regorafenib) tablets

PFS results from CONCUR

PFS in CONCUR[27]



Patients at risk, n

STIVARGA	136	74	46	27	14	10	9	5	1
Placebo	68	6	2	1	1	0	0	0	0

3.2 MONTHS vs 1.7 months
HR: 0.31 (95% CI, 0.22-0.44)
P < 0.0001

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.

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.

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%).

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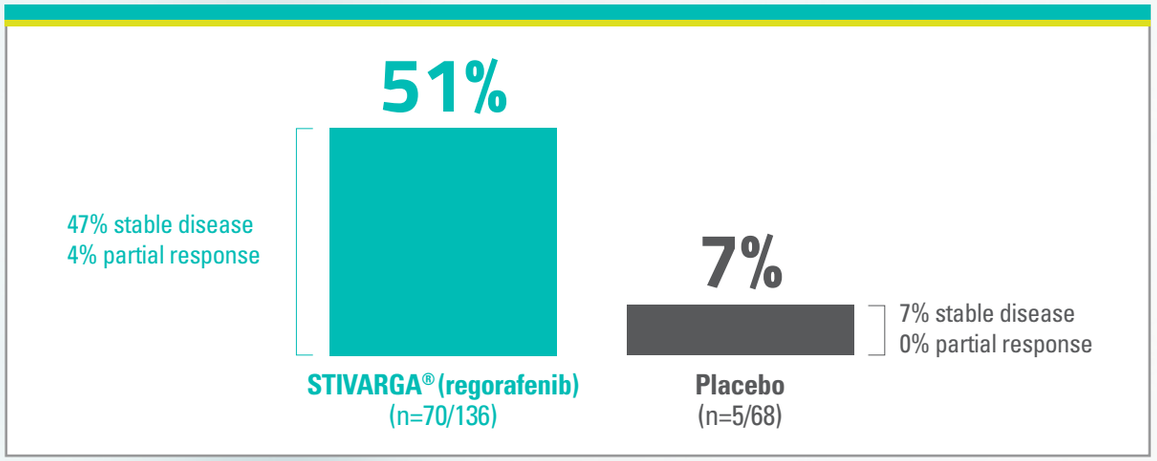
Stivarga® (regorafenib) tablets

DCR in CONCUR[27]



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.

In CONCUR, patients were able to receive cytotoxic therapy following treatment with STIVARGA[28]

29% of patients in the CONCUR trial went on to receive subsequent cytotoxic therapy after STIVARGA[28]

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.**

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.

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Stivarga® (regorafenib) tablets

STIVARGA® (regorafenib) safety profile in CONCUR

Drug-related AEs occurring at any grade in ≥10% of patients or at Grade 3 or higher[27]

	STIVARGA (160 mg) + BSC (n=136), n (%)				Placebo + BSC (n=68), n (%)			
AEs	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Any event	58 (43)	67 (49)	5 (4)	2 (1)	21 (31)	9 (13)	1 (1)	0
HFSR	78 (57)	22 (16)	NA	NA	3 (4)	0	NA	NA
Hyperbilirubinemia	41 (30)	6 (4)	3 (2)	NA	4 (6)	1 (1)	0	NA
ALT concentration increased	23 (17)	9 (7)	0	NA	5 (7)	0	0	NA
AST concentration increased	24 (18)	7 (5)	1 (1)	NA	6 (9)	0	0	NA
Hypertension	16 (12)	15 (11)	0	0	1 (1)	2 (3)	0	0
Hoarseness	27 (20)	1 (1)	NA	NA	0	0	NA	NA
Diarrhea	23 (17)	1 (1)	0	0	1 (1)	1 (1)	0	0
Fatigue	19 (14)	4 (3)	NA	NA	4 (6)	1 (1)	NA	NA
Proteinuria	11 (8)	2 (1)	NA	NA	0	1 (1)	NA	NA

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

- AEs occurred in 100% of patients receiving STIVARGA (n=136) and 88% of patients receiving placebo (n=60) during treatment (or up to 30 days after end of treatment)[27]
- Treatment-related AEs occurred in 97% of STIVARGA patients (n=132) and 46% of placebo patients (n=31)[27]
- Grade 3 or higher treatment-related AEs were reported in 54% of patients receiving STIVARGA (n=74) and 15% of those receiving placebo (n=10)[27]
- 32% of STIVARGA patients (n=43) experienced a serious AE vs 26% of placebo patients (n=18)[27]
- 14% of patients (n=19) discontinued STIVARGA due to an AE vs 6% of placebo patients (n=4)[27]

NEXT PAGE FOR NCCN GUIDELINES®

Important Safety Information (continued)

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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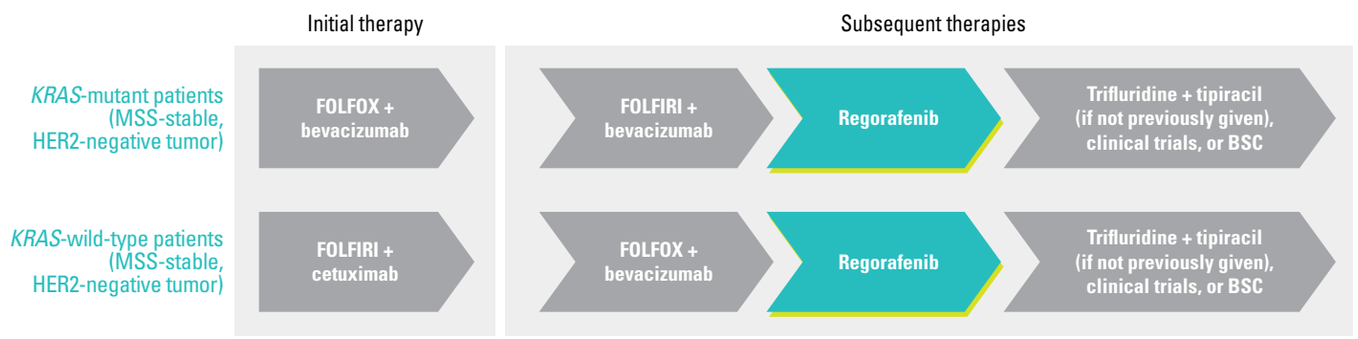
Stivarga® (regorafenib) tablets

NCCN Guidelines® list regorafenib (STIVARGA®) as a potential option for patients who have been previously treated with at least 2 lines of systemic therapy (Category 2A)[29,30*†]

Potential treatment algorithms[29,30‡]



Designated Category 2A by the NCCN.[29,30†]

*Regorafenib and trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.

NCCN=National Comprehensive Cancer Network® (NCCN®).

†Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[29,30]

‡For a complete listing of treatment options, see NCCN.org.

STIVARGA is indicated for the treatment of patients with mCRC 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[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.

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Stivarga® (regorafenib) tablets

Standard starting dose with options for dose management

STIVARGA® (regorafenib) dosing in the CORRECT, phase 3 trial[1]

The recommended starting dose is 160 mg STIVARGA (4 40-mg tablets) taken orally once daily for the first 3 weeks, followed by a 1-week treatment break.

One cycle of STIVARGA treatment[1]

Week	1	2	3	4
Once-daily dose	4 × 40 mg tablets 160 mg	4 × 40 mg tablets 160 mg	4 × 40 mg tablets 160 mg	Dosing-free interval

REPEAT EVERY MONTH

Dosage and administration for STIVARGA[1]

- Treatment should continue until disease progression or until unacceptable toxicity occurs
- STIVARGA should be taken whole with water after a low-fat meal that contains <600 calories and <30% fat at the same time each day
- Advise patients to take any missed dose on the same day, as soon as they remember, and that they must not take 2 doses on the same day to make up for a dose missed on the previous day
- No dose adjustment is recommended for patients with renal impairment
- The pharmacokinetics of STIVARGA have not been studied in patients who are on dialysis and there is no recommended dose for this patient population
- No dose adjustments are required based on mild (total bilirubin ≤upper limit of normal [ULN] and AST >ULN, or total bilirubin >ULN to ≤1.5x ULN) or moderate (total bilirubin >1.5 to ≤3x ULN and any AST) hepatic impairment. Closely monitor patients with hepatic impairment for adverse reactions. STIVARGA is not recommended for use in patients with severe hepatic impairment (total bilirubin >3x ULN), as STIVARGA has not been studied in this population

Follow up with your patients within the first 2 weeks of treatment

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.

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Stivarga® (regorafenib) tablets

Dose modifications with STIVARGA® (regorafenib) may help keep therapy manageable[1]

- If dose modifications are required, reduce the dose in 40-mg (1 tablet) increments[1]
- The lowest recommended daily dose is 80 mg[1]
- Resume STIVARGA at the same dose following resolution of infection[1]

	Interrupt STIVARGA for the following	Reduce STIVARGA dose to 120 mg	Reduce STIVARGA dose to 80 mg	Discontinue STIVARGA permanently for the following
Hand-foot skin reaction (HFSR)	• Grade 2 HFSR that is recurrent or does not improve within 7 days despite dose reduction • Grade 3 HFSR (interrupt for a minimum of 7 days)	• First occurrence of Grade 2 HFSR of any duration • After recovery of Grade 3 HFSR	• Re-occurrence of Grade 2 HFSR at the 120-mg dose • After recovery of Grade 3 HFSR at 120-mg dose	• Failure to tolerate the 80-mg dose
Liver function test abnormalities	• Grade 3 aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevation	• Grade 3 AST/ALT elevation – only resume if the potential benefit outweighs the risk of hepatotoxicity		• Any occurrence of AST/ ALT >20x upper limit of normal (ULN) • Any occurrence of AST/ALT >3x ULN with concurrent bilirubin >2x ULN • Re-occurrence of AST/ ALT >5x ULN despite dose reduction to 120 mg
All other adverse reactions	• Symptomatic Grade 2 hypertension • Any Grade 3 or 4 adverse event (AE) • Worsening infection of any grade	• After recovery from any Grade 3 or 4 adverse reaction except infection	• After recovery from any Grade 3 or 4 adverse reaction at the 120-mg dose (except hepatotoxicity or infection)	• Failure to tolerate the 80-mg dose • Any Grade 4 AE (only resume if the potential benefit outweighs the risks)

Important Safety Information (continued)

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. 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.

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Stivarga® (regorafenib) tablets

NCCN Guidelines include the option for the following dose-escalation schedule (Category 2A)[29,30]*

Dose escalation is supported by the ReDOS clinical study[31†]

Regorafenib (STIVARGA®) dose escalation schedule in mCRC[31]

	Cycle 1				Cycle 2
Week	**1**	**2**	**3**	**4**	**1**
Once-daily dose	40 mg 40 mg 80 mg	40 mg 40 mg 40 mg 120 mg	40 mg 40 mg 40 mg 40 mg 160 mg	Dosing-free interval	Last dose from Cycle 1

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[29,30]

†The study supporting the dose-escalation schedule has not been reviewed by the FDA. The study was a randomized, phase 2, US-based trial through the Academic and Community Cancer Research United (ACCRU) research network that looked at the proportion of patients who completed 2 cycles of STIVARGA and initiated a third cycle (N=116). The efficacy of the alternative dosing schedule cannot be compared to the efficacy of other trials.[31]

- Dosing escalation takes place during the first 4-week cycle[29,30]
- Week 1: 80 mg of STIVARGA (2 40-mg tablets) taken orally once daily, Week 2: 120 mg (3 40-mg tablets), Week 3 dose is 160 mg (4 40-mg tablets), followed by Week 4 dose-free interval[29,30]
- Subsequent cycles are dosed at the last dose from Cycle 1[29,30]
- See additional information about dosing modifications on page 26

Important Safety Information (continued)

Dermatological Toxicity (continued): 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.

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Stivarga® (regorafenib) tablets

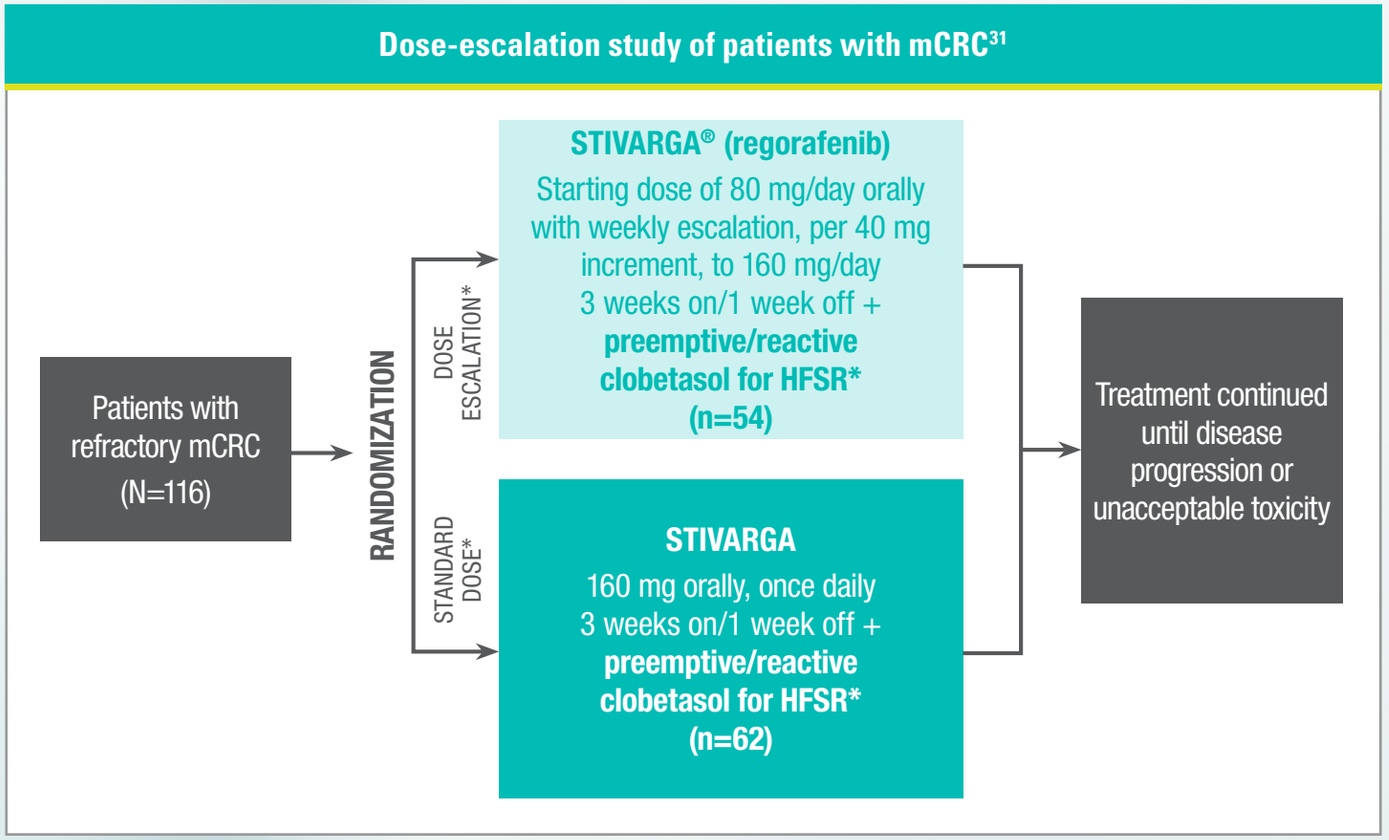
ReDOS: a randomized, multicenter, open-label, phase 2 trial[31]

Regorafenib dose-optimization study (ReDOS) compared patients in 2 distinct regorafenib dosing strategies (standard dose vs dose escalation)[31]

ReDOS study objectives

- Primary endpoint: Proportion of patients completing 2 cycles of treatment and initiating Cycle 3[31]
- Secondary endpoints: PFS, OS, time to progression in dose-escalation group vs standard dose group, cumulative dose and dose intensity within first 2 cycles in both groups, proportion of patients with Grade 3 HFSR or fatigue, and comparison of quality of life (QoL) between both groups[31]

ReDOS study design[31]



*Each arm was divided into preemptive and reactive strategy groups. Patients in the preemptive strategy groups had clobetasol 0.05% cream prophylactically applied to their hands and soles starting at Cycle 1 Day 1 of treatment. Patients in the reactive strategy groups were treated with clobetasol 0.05% cream when they developed HFSR, at the discretion of the investigator.[31]

Important Safety Information (continued)

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.

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ReDOS study limitations[31]

- As with all phase 2 studies, a small sample size represents a limitation for data interpretation
- Pooling of study data potentially increases overall outcome variability
- QoL was assessed with complete-case analysis, which may have introduced bias to the results

ReDOS study: baseline characteristics[31]

		Dose-escalation group (n=54)	Standard-dose group (n=62)
Age, years (range)	Median	62 (53-68)	61 (53-68)
Sex (male)		36 (67%)	35 (56%)
Race	White	44 (81%)	55 (89%)
	Black or African American	5 (9%)	4 (6%)
	Asian	3 (6%)	2 (3%)
	American Indian or Alaska native	1 (2%)	0
	Not reported or unknown	1 (2%)	1 (2%)
ECOG PS	0	20 (37%)	23 (37%)
	1	34 (63%)	39 (63%)
***KRAS* mutation**	Yes	21 (39%)	34 (55%)
	No	31 (57%)	27 (44%)
	Unknown	2 (4%)	1 (2%)
Primary tumor status	Local recurrence	4 (7%)	1 (2%)
	Resected	37 (69%)	44 (71%)
	Unresected	13 (24%)	17 (27%)

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.

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.

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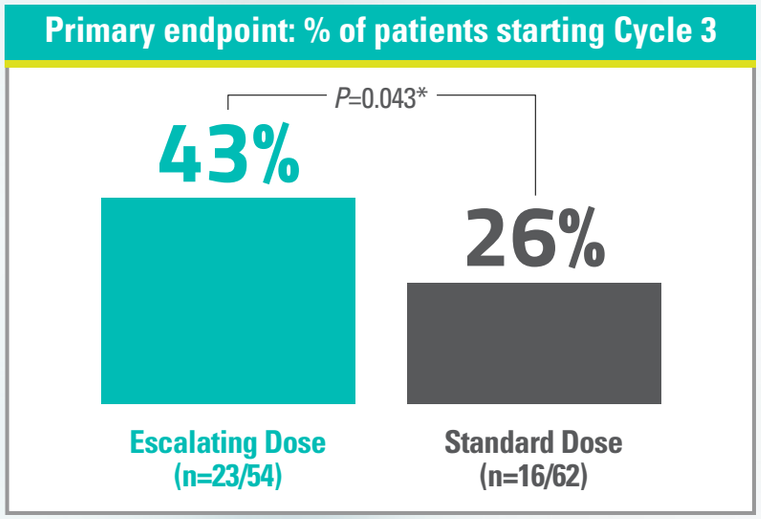
Stivarga® (regorafenib) tablets

ReDOS study results[31,32]



*Fisher's exact test (1 sided).

- **43% of patients in the dose-escalation group (95% CI, 29-56) vs 26% of patients in the standard-dose group (95% CI, 15-37) completed 2 cycles of therapy and initiated Cycle 3 (*P*=0.043)**
  - Disease progression was the primary reason patients did not initiate Cycle 3 and occurred in 37% of dose-escalation patients (n=20) and 47% of standard-dose patients (n=29)
- Median OS was 9.8 months (95% CI, 7.5-11.9) with the STIVARGA® (regorafenib) escalating dose vs 6.0 months (95% CI, 4.9-10.2) with the STIVARGA standard dose (HR: 0.72 [95% CI, 0.47-1.10]; *P*=0.12)
  - By the time of data cutoff, 74% of patients in the dose-escalation group (n=40) and 74% of those in the standard-dose group (n=46) had died
- Median PFS was 2.8 months (95% CI, 2.0-5.0) with the STIVARGA escalating dose vs 2.0 months (95% CI, 1.8-2.8) with the STIVARGA standard dose (HR: 0.84 [95% CI, 0.57-1.24]; *P*=0.38)
- In the dose-escalation group, patients took an average of 77% of the planned dose in Cycle 1 and 93% in Cycle 2. In the standard-dose group, patients took an average of 83% of the planned dose in Cycle 1 and 73% in Cycle 2
- In Cycle 1, 7.4% of patients in the dose-escalation group and 12.9% of those in the standard-dose group experienced Grade 3 HFSR. In Cycle 2, 4.9% of dose-escalation patients and 8.5% of standard-dose patients experienced Grade 3 HFSR
- In Cycle 1, 5.6% of patients in the dose-escalation group and 11.3% in the standard-dose group experienced Grade 3 fatigue. In Cycle 2, 4.9% of dose escalation patients and 8.5% of standard-dose patients experienced Grade 3 fatigue
- Overall, patients in the dose-escalation group reported a slightly higher QoL score per HFS-14 and LASA questionnaires than those in the standard-dose group, though this difference was not significant

HFS-14=Hand-Foot Syndrome 14; LASA=Linear Analogue Self-Assessment.

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.

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Stivarga® (regorafenib) tablets

STIVARGA® (regorafenib) safety profile in ReDOS

AEs occurring at any grade in ≥10% of patients or at Grade 3 or higher[31]

	Dose-escalation group (n=54), n (%)				Standard-dose group (n=62), n (%)			
AEs	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Fatigue	42 (78)	7 (13)	0	0	44 (71)	11 (18)	0	0
HFSR	27 (50)	8 (15)	0	0	33 (53)	10 (16)	0	0
Hypertension	34 (63)	4 (7)	0	0	29 (47)	9 (15)	0	0
Nausea	23 (43)	0	0	0	31 (50)	0	0	0
Diarrhea	23 (43)	1 (2)	0	0	25 (40)	2 (3)	0	0
Anorexia	14 (26)	1 (2)	0	0	16 (26)	2 (3)	0	0
Rash maculopapular	10 (19)	0	0	0	16 (26)	3 (5)	0	0
Vomiting	13 (24)	0	0	0	14 (23)	1 (2)	0	0
Blood bilirubin increased	7 (13)	2 (4)	0	0	13 (21)	5 (8)	0	0
Anemia	12 (22)	1 (2)	0	0	12 (19)	1 (2)	0	0
AST concentration increased	8 (15)	1 (2)	0	0	12 (19)	4 (6)	0	0
Alkaline phosphatase concentration increased	6 (11)	3 (6)	0	0	10 (16)	1 (2)	1 (2)	0
Abdominal pain	1 (2)	9 (17)	0	0	5 (8)	4 (6)	0	0
Dyspnea	5 (9)	1 (2)	1 (2)	0	8 (13)	4 (6)	0	0
ALT concentration increased	8 (15)	0	0	0	8 (13)	1 (2)	0	0
Hoarseness	8 (15)	0	0	0	8 (13)	0	0	0
Weight loss	4 (7)	1 (2)	0	0	10 (16)	1 (2)	0	0

Important Safety Information (continued)

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.

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Stivarga® (regorafenib) tablets

STIVARGA® (regorafenib) safety profile in ReDOS (continued)

AEs occurring at any grade in ≥10% of patients or at Grade 3 or higher[31]

	Dose-escalation group (n=54), n (%)				Standard-dose group (n=62), n (%)			
AEs	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Hyponatremia	0	2 (4)	1 (2)	0	7 (11)	4 (6)	1 (2)	0
Platelet count decreased	7 (13)	0	0	0	8 (13)	0	0	0
Mucositis oral	4 (7)	1 (2)	0	0	8 (13)	1 (2)	0	0
Hypoalbuminemia	5 (9)	1 (2)	0	0	7 (11)	0	0	0
Peripheral sensory neuropathy	6 (11)	0	0	0	6 (10)	0	0	0
Lymphocyte count decreased	1 (2)	4 (7)	0	0	6 (10)	0	0	0
Hypocalcemia	6 (11)	0	0	0	3 (5)	1 (2)	0	0
Hypokalemia	3 (6)	1 (2)	0	0	5 (8)	0	1 (2)	0
Generalized muscle weakness	5 (9)	1 (2)	0	0	2 (3)	1 (2)	0	0
Myalgia	0	1 (2)	0	0	6 (10)	2 (3)	0	0

- The most common Grade 3-4 AEs in the dose-escalation group were fatigue (13% [n=7]), HFSR (15% [n=8]), abdominal pain (17% [n=9]), and hypertension (7% [n=4])[31]
- The most common Grade 3-4 AEs in the standard-dose group were fatigue (18% [n=11]), HFSR (16% [n=10]), abdominal pain (6% [n=4]), and hypertension (15% [n=9])[31]
- 26% of patients in the dose-escalation group (n=14) experienced a serious AE vs 34% of those in the standard-dose group (n=21)[31]
- Serious treatment-related AEs occurred in 6 dose-escalation patients and 8 standard-dose patients[31]
- 6 patients in the STIVARGA dose-escalation group and 5 patients in the standard-dose group discontinued treatment due to an AE, and did not initiate the third cycle of therapy[31]

Important Safety Information (continued)

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%).

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Stivarga® (regorafenib) tablets

The power of patient support and expert assistance

Access Services by Bayer is a support program available to patients who have been prescribed STIVARGA® (regorafenib). It offers a range of services to help patients access STIVARGA.

Services available through Access Services by Bayer

Nurse Counselors:
10 AM-6:30 PM EST/EDT

Financial Access Counselors:
9 AM-8 PM EST/EDT

A resource for patient education and support	A resource for access and reimbursement support	A resource for financial support
• Provide information and answer questions for patients and caregivers • Educate on potential AEs • Supply patient educational materials – Starter kits – Refill reminders	• Perform benefits investigation • Assist with prior authorization denials and appeals process • Conduct alternative coverage research for uninsured or underinsured patients • Coordinate with specialty pharmacy providers (SPPs), self-dispensing practices, and outpatient pharmacies	• $0 Co-pay Program assistance for commercially insured patients* • Refer qualified patients to independent organizations that may assist with out-of-pocket expenses† • Refer eligible patients to the Bayer US Patient Assistance Foundation

For more information, call 1.800.288.8374

Qualifying patients may be eligible for $0 co-pay

$0 CO-PAY

NO monthly cap and up to $25,000 per year for privately insured patients. Annual enrollment is required.

- Once enrolled, eligible patients may pay as little as $0
  - Eligible patients will be automatically re-enrolled every January
- Maximum co-pay program benefit of $25,000 per calendar year
- No monthly cap

3 WAYS TO ENROLL IN $0 CO-PAY

1. Directly via www.zerocopaysupport.com or call 1.866.581.4992
2. Via phone 1.800.288.8374
3. Contact the SPP Network

*Patients who are enrolled in any type of government insurance or reimbursement programs are not eligible. As a condition precedent of the co-payment support provided under this program, e.g., co-pay refunds, participating patients and pharmacies are obligated to inform insurance companies and third-party payors of any benefits they receive and the value of this program, and may not participate if this program is prohibited by or conflicts with their private insurance policy, as required by contract or otherwise. Void where prohibited by law, taxed, or restricted. Patients enrolled in Bayer's Patient Assistance Program are not eligible. Bayer may determine eligibility, monitor participation, equitably distribute product and modify or discontinue any aspect of the Access Services by Bayer program at any time, including but not limited to this commercial co-pay assistance program.

†Access Services by Bayer provides referrals to third party organizations; eligibility criteria apply.

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For your previously treated patients with mCRC

HARNESS THE CLINICALLY PROVEN POWER OF STIVARGA® (regorafenib)

Demonstrated significant OS advantage and helped patients achieve stable disease in the CORRECT trial:

23% **REDUCTION IN RISK OF DEATH WITH STIVARGA**[1]
(HR: 0.77, 95% CI, 0.64-0.94; *P*=0.0102)[1]

- There were 275 deaths out of 505 patients treated with STIVARGA (55%) vs 157 deaths out of 255 patients treated with placebo (62%)[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*)

51% **REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH** vs placebo
(HR: 0.49, 95% CI, 0.42-0.58; *P*<0.0001)[1]

- 417 of 505 STIVARGA patients (83%) vs 231 of 255 placebo patients (91%) progressed or died[1]

26% **PATIENTS WERE ABLE TO RECEIVE CYTOTOXIC THERAPY** following treatment with STIVARGA in the CORRECT trial[2]

- During the CORRECT trial follow-up[21]:
  – 26% (131) and 30% (76) of patients received ≥1 systemic anticancer treatment in the STIVARGA and placebo groups, respectively
  – 26% (130) of patients and 29% (74) of patients received an antineoplastic or immunomodulation agent in the STIVARGA and placebo groups, respectively

- 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/PPES (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%)[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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