

**A SPECIAL MEETING REVIEW EDITION**

## Highlights in Metastatic Colorectal Cancer From the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium

A Review of Selected Presentations From the 2018 American Society of  
Clinical Oncology Gastrointestinal Cancers Symposium • January 18-20, 2018  
• San Francisco, California

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**Special Reporting on:**

- Regorafenib Dose Optimization Study (ReDOS): Randomized Phase II Trial to Evaluate Dosing Strategies for Regorafenib in Refractory Metastatic Colorectal Cancer—An ACCRU Network Study
- Nivolumab + Ipilimumab Combination in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report of the Full Cohort From CheckMate-142
- REVERCE: Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus the Reverse Sequence for Metastatic Colorectal Cancer Patients Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan
- A Phase Ib Study of Safety and Clinical Activity of Atezolizumab and Cobimetinib in Patients With Metastatic Colorectal Cancer
- Regorafenib in Antiangiogenic-Naive, Chemotherapy-Refractory Advanced Colorectal Cancer: A Phase IIb Trial
- SCOT: Tumor Sidedness and the Influence of Chemotherapy Duration on Disease-Free Survival
- Phase II Dose Titration Study of Regorafenib for Patients With Unresectable Metastatic Colorectal Cancer That Progressed After Standard Chemotherapy
- SAPPHERE: A Randomized Phase II Study of mFOLFOX6 + Panitumumab Versus 5-FU/LV + Panitumumab After 6 Cycles of Frontline mFOLFOX6 + Panitumumab in Patients With Colorectal Cancer

**PLUS Meeting Abstract Summaries**

**With Expert Commentary by:**

**Axel Grothey, MD**

Professor of Oncology, Mayo Clinic  
Rochester, Minnesota

**ON THE WEB:**  
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# ACT IN TIME



Prescribe STIVARGA® (regorafenib) in previously treated patients with metastatic colorectal cancer (mCRC) to help the survival potential of their treatment journey<sup>1</sup>

## 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.

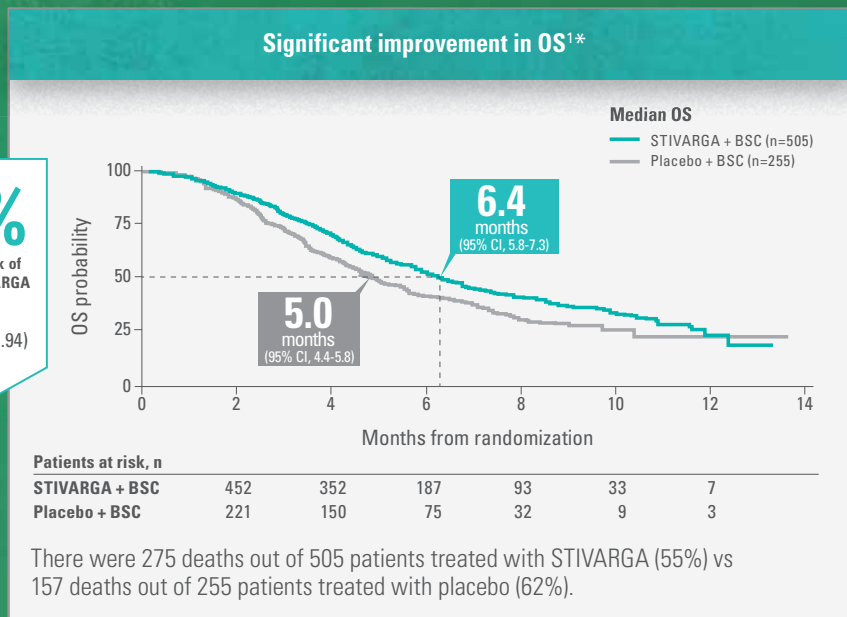
**Hepatotoxicity:** Severe drug-induced liver injury with fatal outcome occurred in STIVARGA-treated patients across all clinical trials. In most cases, liver dysfunction occurred within the first 2 months of therapy and was characterized by a hepatocellular pattern of injury. In metastatic colorectal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

# STIVARGA® (regorafenib) DEMONSTRATED A SIGNIFICANT IMPROVEMENT IN SURVIVAL<sup>1</sup>



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



\*OS was the primary endpoint of CORRECT.  
BSC, best supportive care; ORR, overall response rate; OS, overall survival; PFS, progression-free survival. 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).<sup>1</sup>

## SECONDARY ENDPOINTS

- 2.0 months (95% CI, 1.9-2.3) median PFS with STIVARGA vs 1.7 months (95% CI, 1.7-1.8) with placebo<sup>1</sup>
  - 51% reduction in the risk of disease progression or death in CORRECT (HR: 0.49; 95% CI, 0.42-0.58; *P*<0.0001)
  - 417 of 505 STIVARGA patients (83%) vs 231 of 255 placebo patients (91%) progressed or died
- 1% ORR (95% CI, 0.3%-2.3%) with STIVARGA vs 0.4% (95% CI, 0%-2.2%) with placebo<sup>1</sup>

**STIVARGA is an oral inhibitor of multiple kinases that targets normal cellular functions and pathological processes such as oncogenesis, tumor angiogenesis, metastasis, and tumor immunity<sup>1,2</sup>**

### 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.

**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.

**Please see additional Important Safety Information and brief summary of full Prescribing Information, including the Boxed Warning, on the following pages.**

  
**Stivarga**<sup>®</sup>  
(regorafenib) tablets

## COMPREHENSIVE PATIENT COVERAGE AND SUPPORT

**\$0 CO-PAY\***  
NO monthly cap and up to \$25,000 per year for privately insured patients. Annual enrollment is required.

### 3 WAYS TO ENROLL

1. Directly via [www.zerocopaysupport.com](http://www.zerocopaysupport.com) or call 1.866.581.4992
2. Via REACH® by phone 1.866.639.2827
3. SPP Network

For more information, REACH us by phone: 1.866.639.2827

\*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 REACH program at any time, including but not limited to this commercial co-pay assistance program.

### 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. 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.

**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:** 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.

**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%).

**Please see additional Important Safety Information on the previous page and brief summary of full Prescribing Information, including the Boxed Warning, on the following pages.**

**References:** 1. STIVARGA Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; April 2017. 2. Bruix J, Qin S, Merle P, et al; on behalf of the RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10064):56-66.



**STIVARGA® (regorafenib) tablets, for oral use**  
Initial U.S. Approval: 2012

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**  
**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

**WARNING: HEPATOTOXICITY**

- **Severe and sometimes fatal hepatotoxicity has occurred in clinical trials [see Warnings and Precautions (5.1)].**
- **Monitor hepatic function prior to and during treatment [see Warnings and Precautions (5.1)].**
- **Interrupt and then reduce or discontinue STIVARGA for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence [see Dosage and Administration (2.2)].**

**1 INDICATIONS AND USAGE**

**1.1 Colorectal Cancer**

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.

**1.2 Gastrointestinal Stromal Tumors**

STIVARGA is indicated 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.

**1.3 Hepatocellular Carcinoma**

STIVARGA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Hepatotoxicity**

Severe drug-induced liver injury with fatal outcome occurred in STIVARGA-treated patients in 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 the CORRECT study, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In the GRID study, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm. In the RESORCE study, there was no increase in the incidence of fatal hepatic failure as compared to placebo [see Adverse Reactions (6.1)].

Obtain liver function tests (ALT, AST, and bilirubin) before initiation of STIVARGA and monitor at least every two 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 ULN or baseline.

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 [see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].

**5.2 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% in STIVARGA-treated patients vs 0.2% in patients receiving placebo).

Withhold STIVARGA for Grade 3 or 4 infections, or worsening infection of any grade. Resume STIVARGA at the same dose following resolution of infection [see Dosage and Administration (2.2)].

**5.3 Hemorrhage**

STIVARGA caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 18.2% in 1142 patients treated with STIVARGA and 9.5% in patients receiving 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. Monitor INR levels more frequently in patients receiving warfarin [see Clinical Pharmacology (12.3)].

**5.4 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 0.2% of patients in placebo arm across randomized, placebo-controlled trials. Permanently discontinue STIVARGA in patients who develop gastrointestinal perforation or fistula.

**5.5 Dermatologic Toxicity**

In randomized, placebo-controlled trials, adverse skin reactions occurred in 71.9% of patients in the regorafenib arm and in 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%) than in the placebo-treated patients (8%). Most cases of HFSR in STIVARGA-treated patients appeared during the first cycle of treatment. The incidences of Grade 3 HFSR (16% versus <1%), Grade 3 rash (3% versus <1%), serious adverse reactions of erythema multiforme (<0.1% vs. 0%) and Stevens-Johnson Syndrome (<0.1% vs. 0%) were also higher in STIVARGA-treated patients [see Adverse Reactions (6.1)]. Across all trials, a higher incidence of HFSR was observed in Asian patients treated with STIVARGA (all grades: 72%; Grade 3: 18%) [see Use in Specific Populations (8.8)].

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 STIVARGA depending on the severity and persistence of dermatologic toxicity [see Dosage and Administration (2.2)]. Institute supportive measures for symptomatic relief.

**5.6 Hypertension**

In randomized, placebo-controlled trials, hypertensive crisis occurred in 0.2% of patients in the regorafenib arms and in none of the patients in the placebo arms. STIVARGA caused an increased incidence of hypertension (30% versus 8% in CORRECT, 59% versus 27% in GRID, and 31% versus 6% in RESORCE) [see Adverse Reactions (6.1)]. 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 unless 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 [see Dosage and Administration (2.2)].

**5.7 Cardiac Ischemia and Infarction**

STIVARGA increased the incidence of myocardial ischemia and infarction (0.9% vs 0.2%) in randomized placebo-controlled trials [see Adverse Reactions (6.1)]. Withhold STIVARGA in patients who develop new or acute onset cardiac ischemia or infarction. Resume STIVARGA only after resolution of acute cardiac ischemic events, if the potential benefits outweigh the risks of further cardiac ischemia.

**5.8 Reversible Posterior Leukoencephalopathy Syndrome**

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic 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.

**5.9 Wound Healing Complications**

No formal studies of the effect of regorafenib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as STIVARGA can impair wound healing, discontinue treatment with STIVARGA at least 2 weeks prior to scheduled surgery. The decision to resume STIVARGA after surgery should be based on clinical judgment of adequate wound healing. Discontinue STIVARGA in patients with wound dehiscence.

**5.10 Embryo-Fetal Toxicity**

Based on animal studies and its mechanism of action, STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose [see Use in Specific Populations (8.1), (8.3)].

**6 ADVERSE REACTIONS**

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hepatotoxicity [see Warnings and Precautions (5.1)]
- Infections [see Warnings and Precautions (5.2)]
- Hemorrhage [see Warnings and Precautions (5.3)]
- Gastrointestinal Perforation or Fistula [see Warnings and Precautions (5.4)]
- Dermatological Toxicity [see Warnings and Precautions (5.5)]
- Hypertension [see Warnings and Precautions (5.6)]
- Cardiac Ischemia and Infarction [see Warnings and Precautions (5.7)]
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [see Warnings and Precautions (5.8)]

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to STIVARGA in more than 4800 patients who were enrolled in four randomized, placebo-controlled trials (n=1142), an expanded access program (CONSIGN, n=2864), or single arm clinical trials (single agent or in combination with other agents). There were 4518 patients who received STIVARGA as a single agent; the distribution of underlying malignancies was 80% CRC, 4% GIST, 10% HCC, 6% other solid tumors; and 74% were White, 11% Asian, and 15% race not known. Among these 4518 patients, 83% received STIVARGA for at least 21 days and 20% received STIVARGA for 6 months or longer.

In randomized placebo-controlled trials (CORRECT, GRID, RESORCE and CONCUR), the most frequently observed adverse drug reactions (≥20%) in patients receiving STIVARGA are pain (including gastrointestinal and abdominal pain), HFSR, asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea.

#### Colorectal Cancer

The safety data described below, except where noted, are derived from a randomized (2:1), double-blind, placebo-controlled trial (CORRECT) in which 500 patients (median age 61 years; 60% men) with previously-treated metastatic colorectal cancer (CRC) received STIVARGA as a single agent at the dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 253 patients (median age 61 years; 60% men) received placebo. The median duration of therapy was 1.7 months (range 2 days, 10.8 months) for patients receiving STIVARGA. Due to adverse reactions, 61% of the patients receiving STIVARGA required a dose interruption and 38% of the patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation occurred in 8.2% of STIVARGA-treated patients compared to 1.2% of patients who received placebo. Hand-foot skin reaction (HFSR) and rash were the most common reasons for permanent discontinuation of STIVARGA.

Table 1 provides the incidence of adverse reactions (≥10%) in patients in CORRECT.

**Table 1: Adverse drug reactions reported in ≥10% of patients treated with STIVARGA in CORRECT and reported more commonly than in patients receiving placebo<sup>a</sup>**

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

<sup>a</sup> Adverse reactions graded according to National Cancer Institute Common Toxicity for Adverse Events version 3.0 (NCI CTCAE v3.0).

<sup>b</sup> The term rash represents reports of events of drug eruption, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and pruritic rash.

<sup>c</sup> Fatal outcomes observed.

Table 2 provides laboratory abnormalities observed in CORRECT.

**Table 2: Laboratory test abnormalities reported in CORRECT**

Laboratory Parameter	STIVARGA (N=500 <sup>a</sup> )			Placebo (N=253 <sup>a</sup> )		
	Grade <sup>b</sup>			Grade <sup>b</sup>		
	All %	3 %	4 %	All %	3 %	4 %
<b>Blood and lymphatic system disorders</b>						
Anemia	79	5	1	66	3	0
Thrombocytopenia	41	2	<1	17	<1	0
Neutropenia	3	1	0	0	0	0
Lymphopenia	54	9	0	35	4	<1
<b>Metabolism and nutrition disorders</b>						
Hypocalcemia	59	1	<1	18	1	0
Hypokalemia	26	4	0	8	<1	0
Hyponatremia	30	7	1	22	4	0
Hypophosphatemia	57	31	1	11	4	0
<b>Hepatobiliary disorders</b>						
Hyperbilirubinemia	45	10	3	17	5	3
Increased AST	65	5	1	46	4	1
Increased ALT	45	5	1	30	3	<1
<b>Renal and urinary disorders</b>						
Proteinuria <sup>c</sup>	84	2	0	61	1	0

Table 2 continued at top of next column

Laboratory Parameter	STIVARGA (N=500 <sup>a</sup> )			Placebo (N=253 <sup>a</sup> )		
	Grade <sup>b</sup>			Grade <sup>b</sup>		
	All %	3 %	4 %	All %	3 %	4 %
<b>Investigations</b>						
Increased INR <sup>d</sup>	24	4	N/A	17	2	N/A
Increased Lipase	46	9	2	19	3	2
Increased Amylase	26	2	<1	17	2	<1

<sup>a</sup> % based on number of patients with post-baseline samples which may be less than 500 (regorafenib) or 253 (placebo).

<sup>b</sup> NCI CTCAE v3.0.

<sup>c</sup> Based on urine protein-creatinine ratio data.

<sup>d</sup> International normalized ratio: No Grade 4 denoted in NCI CTCAE, v3.0.

#### Gastrointestinal Stromal Tumors

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (GRID) in which 132 patients (median age 60 years; 64% men) with previously-treated GIST received STIVARGA as a single agent at a dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 66 patients (median age 61 years; 64% men) received placebo. The median duration of therapy was 5.7 months (range 1 day, 11.7 months) for patients receiving STIVARGA. Dose interruptions for adverse events were required in 58% of patients receiving STIVARGA and 50% of patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation were reported in 2.3% of STIVARGA-treated patients compared to 1.5% of patients who received placebo.

Table 3 provides the incidence of adverse reactions (≥10%) in patients in GRID.

**Table 3: Adverse reactions reported in ≥10% patients treated with STIVARGA in GRID and reported more commonly than in patients receiving placebo<sup>a</sup>**

Adverse Reactions	STIVARGA (N=132)		Placebo (N=66)	
	Grade		Grade	
	All %	≥ 3 %	All %	≥ 3 %
<b>Skin and subcutaneous tissue disorders</b>				
HFSR/PPE	67	22	12	2
Rash <sup>b</sup>	30	7	3	0
Alopecia	24	2	2	0
<b>General disorders and administration site conditions</b>				
Asthenia/Fatigue	52	4	39	2
Fever	21	0	11	2
<b>Vascular disorders</b>				
Hypertension	59	28	27	5
Hemorrhage	11	4	3	0
<b>Gastrointestinal disorders</b>				
Pain	60	8	55	14
Diarrhea	47	8	9	0
Mucositis	40	2	8	2
Nausea	20	2	12	2
Vomiting	17	<1	8	0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Dysphonia	39	0	9	0
<b>Infections and infestations</b>				
Infection <sup>c</sup>	32	5	5	0
<b>Metabolism and nutrition disorders</b>				
Decreased appetite and food intake	31	<1	21	3
Hypothyroidism <sup>d</sup>	18	0	6	0
<b>Nervous system disorders</b>				
Headache	16	0	9	0
<b>Investigations</b>				
Weight loss	14	0	8	0
<b>Musculoskeletal and connective tissue disorders</b>				
Muscle spasms	14	0	3	0

<sup>a</sup> Adverse reactions graded according to NCI CTCAE v4.0.

<sup>b</sup> The term rash represents reports of events of rash, erythematous rash, macular rash, maculo-papular rash, papular rash and pruritic rash.

<sup>c</sup> Fatal outcomes observed.

<sup>d</sup> Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

Table 4 provides laboratory abnormalities observed in GRID.

**Table 4: Laboratory test abnormalities reported in GRID**

Laboratory Parameter	STIVARGA (N=132 <sup>a</sup> )			Placebo (N=66 <sup>a</sup> )		
	Grade <sup>b</sup>			Grade <sup>b</sup>		
	All %	3 %	4 %	All %	3 %	4 %
<b>Blood and lymphatic system disorders</b>						
Thrombocytopenia	13	1	0	2	0	2
Neutropenia	16	2	1	12	3	0
Lymphopenia	30	8	0	24	3	0

Table 4 continued at top of next column

Laboratory Parameter	STIVARGA (N=132 <sup>a</sup> )			Placebo (N=66 <sup>a</sup> )		
	Grade <sup>b</sup>			Grade <sup>b</sup>		
	All %	3 %	4 %	All %	3 %	4 %
<b>Metabolism and nutrition disorders</b>						
Hypocalcemia	17	2	0	5	0	0
Hypokalemia	21	3	0	3	0	0
Hypophosphatemia	55	20	2	3	2	0
<b>Hepatobiliary disorders</b>						
Hyperbilirubinemia	33	3	1	12	2	0
Increased AST	58	3	1	47	3	0
Increased ALT	39	4	1	39	2	0
<b>Renal and urinary disorders</b>						
Proteinuria <sup>c</sup>	59	3	- <sup>d</sup>	53	3	- <sup>d</sup>
<b>Investigations</b>						
Increased Lipase	14	0	1	5	0	0

<sup>a</sup> Percent based on number of patients with post-baseline samples which may be less than 132 (regorafenib) or 66 (placebo).

<sup>b</sup> NCI CTCAE v4.0.

<sup>c</sup> Based on urine protein-creatinine ratio data.

<sup>d</sup> No Grade 4 denoted in NCI CTCAE v4.0.

#### Hepatocellular Carcinoma

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in which patients with previously-treated HCC received either STIVARGA (n=374) 160 mg orally on days 1-21 of each 4 week treatment cycle or placebo (n=193). The median age was 63 years, 88% were men, 98% had Child-Pugh A cirrhosis, 66% had an ECOG performance status (PS) of 0 and 34% had PS of 1. The median duration of therapy was 3.5 months (range 1 day to 29.4 months) for patients receiving STIVARGA. Of the patients receiving STIVARGA, 33% were exposed to STIVARGA for greater than or equal to 6 months and 14% were exposed to STIVARGA for greater than or equal to 12 months. Dose interruptions for adverse events were required in 58.3% of patients receiving STIVARGA and 48% of patients had their dose reduced. The most common adverse reactions requiring dose modification (interruption or dose reduction) were HFSR/PPES (20.6%), blood bilirubin increase (5.9%), fatigue (5.1%) and diarrhea (5.3%). Adverse reactions that resulted in treatment discontinuation were reported in 10.4% of STIVARGA-treated patients compared to 3.6% of patients who received placebo; the most common adverse reactions requiring discontinuation of STIVARGA were HFSR/PPES (1.9%) and AST increased (1.6%).

Table 5 provides the incidence of adverse reactions (≥10%) in patients in RESORCE.

**Table 5: Adverse reactions reported in ≥10% of patients treated with STIVARGA in RESORCE and reported more commonly than in patients receiving placebo<sup>a</sup>**

Adverse Reactions	STIVARGA (N=374)		Placebo (N=193)	
	Grade		Grade	
	All %	≥ 3 %	All %	≥ 3 %
<b>Skin and subcutaneous tissue disorders</b>				
HFSR/PPES	51	12	7	<1
<b>General disorders and administration site conditions</b>				
Pain	55	9	44	8
Asthenia/Fatigue	42	10	33	5
Fever	20	0	7	0
<b>Vascular disorders</b>				
Hypertension	31	15	6	5
Hemorrhage <sup>b</sup>	18	5	16	8
<b>Gastrointestinal disorders</b>				
Diarrhea	41	3	15	0
Nausea	17	<1	13	0
Vomiting	13	<1	7	<1
Mucositis	13	1	2	≤1
<b>Respiratory, thoracic and mediastinal disorders</b>				
Dysphonia	18	0	2	0
<b>Infections and infestations</b>				
Infection <sup>b</sup>	31	8	18	6
<b>Metabolism and nutrition disorders</b>				
Decreased appetite and food intake	31	3	15	2
<b>Investigations</b>				
Weight loss	13	2	4	0
<b>Musculoskeletal and connective tissue disorders</b>				
Muscle spasms	10	0	2	0

<sup>a</sup> Adverse reactions graded according to NCI CTCAE v4.0.

<sup>b</sup> Fatal outcomes observed.

Other clinically significant adverse reactions observed in less than 10% of STIVARGA-treated patients were: alopecia (7%), hypothyroidism (6.4%), pancreatitis (1.6%), exfoliative rash (1.3%), tremor (1.3%), erythema multiforme (0.8%), myocardial ischemia (0.8%), gastrointestinal fistula (0.3%), and myocardial infarction (0.3%).

Table 6 provides laboratory abnormalities observed in RESORCE.

**Table 6: Laboratory test abnormalities reported in RESORCE**

Laboratory Parameter	STIVARGA (N=374 <sup>a</sup> )			Placebo (N=193 <sup>a</sup> )		
	Grade <sup>b</sup>			Grade <sup>b</sup>		
	All %	3 %	4 %	All %	3 %	4 %
<b>Blood and lymphatic system disorders</b>						
Thrombocytopenia	63	5	<1	50	0	0
Neutropenia	14	3	0	15	<1	<1
Lymphopenia	68	16	2	59	11	<1
<b>Metabolism and nutrition disorders</b>						
Hypocalcemia	23	<1	0	10	0	0
Hypokalemia	31	4	<1	9	2	0
Hypophosphatemia	70	32	2	31	7	0
<b>Hepatobiliary disorders</b>						
Hyperbilirubinemia	78	13	3	55	11	5
Increased AST	93	16	2	84	17	3
Increased ALT	70	6	<1	59	5	0
<b>Renal and urinary disorders</b>						
Proteinuria <sup>c</sup>	51	17	- <sup>d</sup>	37	3	- <sup>d</sup>
<b>Investigations</b>						
Increased INR	44	<1	- <sup>d</sup>	35	2	- <sup>d</sup>
Increased Lipase	41	11	3	27	8	1
Increased Amylase	23	3	<1	19	2	<1

<sup>a</sup> Percent based on number of patients with post-baseline samples which may be less than 374 (regorafenib) or 193 (placebo).

<sup>b</sup> NCI CTCAE v4.0.

<sup>c</sup> Based on dipstick data.

<sup>d</sup> No Grade 4 denoted in NCI CTCAE v4.0.

## 6.2 Postmarketing Experience

The following adverse reaction has been identified during postapproval use of STIVARGA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- hypersensitivity reaction

## 7 DRUG INTERACTIONS

### 7.1 Effect of Strong CYP3A4 Inducers on Regorafenib

Co-administration of a strong CYP3A4 inducer with STIVARGA decreased the plasma concentrations of regorafenib, increased the plasma concentrations of the active metabolite M-5, and resulted in no change in the plasma concentrations of the active metabolite M-2 [see *Clinical Pharmacology* (12.3)], and may lead to decreased efficacy. Avoid concomitant use of STIVARGA with strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort).

### 7.2 Effect of Strong CYP3A4 Inhibitors on Regorafenib

Co-administration of a strong CYP3A4 inhibitor with STIVARGA increased the plasma concentrations of regorafenib and decreased the plasma concentrations of the active metabolites M-2 and M-5 [see *Clinical Pharmacology* (12.3)], and may lead to increased toxicity. Avoid concomitant use of STIVARGA with strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and voriconazole).

### 7.3 Effect of Regorafenib on Breast Cancer Resistance Protein (BCRP) Substrates

Co-administration of STIVARGA with a BCRP substrate increased the plasma concentrations of the BCRP substrate [see *Clinical Pharmacology* (12.3)]. Monitor patients closely for signs and symptoms of exposure related toxicity to the BCRP substrate (e.g. methotrexate, fluvastatin, atorvastatin). Consult the concomitant BCRP substrate product information when considering administration of such products together with STIVARGA.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on animal studies and its mechanism of action, STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Administration of regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations [see *Data*]. Advise pregnant women of the potential hazard to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 % and 15 to 20%, respectively.

#### Data

##### Animal Data

In embryo-fetal development studies, a total loss of pregnancy (100% resorption of litter) was observed in rats at doses as low as 1 mg/kg (approximately 6% of the recommended human dose, based on body surface area) and in rabbits at doses as low as 1.6 mg/kg (approximately 25% of the human exposure at the clinically recommended dose measured by AUC).

In a single dose distribution study in pregnant rats, there was increased penetration of regorafenib across the blood-brain barrier in fetuses compared to dams. Daily administration of regorafenib to pregnant rats during organogenesis resulted in fetal findings of delayed ossification at doses ≥ 0.8 mg/kg (approximately 5% of the recommended human dose based on body surface area) and dose-dependent increases in skeletal malformations including cleft palate and enlarged fontanelle at doses ≥ 1 mg/kg (approximately 10% of the

clinical exposure based on AUC). At doses  $\geq 1.6$  mg/kg (approximately 11% of the recommended human dose based on body surface area), there were dose-dependent increases in the incidence of cardiovascular malformations, external abnormalities, diaphragmatic hernia, and dilation of the renal pelvis.

In pregnant rabbits administered regorafenib daily during organogenesis, there were findings of ventricular septal defects evident at the lowest tested dose of 0.4 mg/kg (approximately 7% of the AUC in patients at the recommended dose). At doses of  $\geq 0.8$  mg/kg (approximately 15% of the human exposure at the recommended human dose based on AUC), administration of regorafenib resulted in dose-dependent increases in the incidence of additional cardiovascular malformations and skeletal anomalies, as well as significant adverse effects on the urinary system including missing kidney/ureter; small, deformed and malpositioned kidney; and hydronephrosis. The proportion of viable fetuses that were male decreased with increasing dose in two rabbit embryo-fetal toxicity studies.

## 8.2 Lactation

### Risk Summary

There are no data on the presence of regorafenib or its metabolites in human milk, the effects of regorafenib on the breastfed infant, or on milk production. In rats, regorafenib and its metabolites are excreted in milk. 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.

## 8.3 Females and Males of Reproductive Potential

### Contraception

#### Females

Use effective contraception during treatment and for 2 months after completion of therapy.

#### Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 months following the final dose of STIVARGA [see *Nonclinical Toxicology* (13.1)].

### Infertility

There are no data on the effect of STIVARGA on human fertility. Results from animal studies indicate that regorafenib can impair male and female fertility [see *Nonclinical Toxicology* (13.1)].

## 8.4 Pediatric Use

The safety and efficacy of STIVARGA in pediatric patients less than 18 years of age have not been established.

### Animal Data

In 28-day repeat-dose studies in rats there were dose-dependent findings of dentin alteration and angiectasis. These findings occurred at regorafenib doses as low as 4 mg/kg (approximately 25% of the AUC in humans at the recommended dose). In 13-week repeat-dose studies in dogs there were similar findings of dentin alteration at doses as low as 20 mg/kg (approximately 43% of the AUC in humans at the recommended dose). Administration of regorafenib in these animals also led to persistent growth and thickening of the femoral epiphyseal growth plate.

## 8.5 Geriatric Use

Of the 1142 STIVARGA-treated patients enrolled in randomized, placebo-controlled trials, 40% were 65 years of age and over, while 10% were 75 and over. No overall differences in efficacy were observed between these patients and younger patients. There was an increased incidence of Grade 3 hypertension (18% versus 9%) in the placebo-controlled trials among STIVARGA-treated patients 65 years of age and older as compared to younger patients. In addition, one Grade 4 hypertension event has been reported in the 65 years and older age group and none in the younger age group.

## 8.6 Hepatic Impairment

No dose adjustment is recommended in patients with mild (total bilirubin  $\leq$ ULN and AST  $>$ ULN, or total bilirubin  $>$ ULN to  $\leq 1.5$  times ULN) or moderate (total bilirubin  $> 1.5$  to  $\leq 3$  times ULN and any AST) hepatic impairment. [see *Clinical Pharmacology* (12.3)]. Closely monitor patients with hepatic impairment for adverse reactions [see *Warnings and Precautions* (5.1)].

STIVARGA is not recommended for use in patients with severe hepatic impairment (total bilirubin  $> 3 \times$  ULN) as STIVARGA has not been studied in this population.

## 8.7 Renal Impairment

No dose adjustment is recommended for patients with renal impairment. The pharmacokinetics of regorafenib have not been studied in patients who are on dialysis and there is no recommended dose for this patient population [see *Clinical Pharmacology* (12.3)].

## 8.8 Race

Based on pooled data from three placebo-controlled trials (CORRECT, GRID and CONCUR), a higher incidence of HFSR and liver function test abnormalities occurred in Asian patients treated with STIVARGA as compared with Whites [see *Warnings and Precautions* (5.1, 5.5)]. No starting dose adjustment is necessary based on race.

## 10 OVERDOSAGE

The highest dose of STIVARGA studied clinically is 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue. There is no known antidote for STIVARGA overdose. In the event of suspected overdose, interrupt STIVARGA, institute supportive care, and observe until clinical stabilization.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of regorafenib have not been conducted. Regorafenib itself did not demonstrate genotoxicity in *in vitro* or *in vivo* assays; however, a major human active metabolite of regorafenib, (M-2), was positive for clastogenicity, causing chromosome aberration in Chinese hamster V79 cells.

Dedicated studies to examine the effects of regorafenib on fertility have not been conducted; however, there were histological findings of tubular atrophy and degeneration in the testes, atrophy in the seminal vesicle, and cellular debris and oligospermia in the epididymides in male rats at doses similar to those in human at the clinical recommended dose based on AUC. In female rats, there were increased findings of necrotic corpora lutea in the ovaries at the same exposures. There were similar findings in dogs of both sexes in repeat dose studies at exposures approximately 83% of the human exposure at the recommended human dose based on AUC. These findings suggest that regorafenib may adversely affect fertility in humans.

### 13.2 Animal Toxicology and/or Pharmacology

In a chronic 26-week repeat dose study in rats there was a dose-dependent increase in the finding of thickening of the atrioventricular valve. At a dose that resulted in an exposure of approximately 12% of the human exposure at the recommended dose, this finding was present in half of the examined animals.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Hepatotoxicity

Advise patients that they will need to undergo monitoring for liver damage and to report immediately any signs or symptoms of severe liver damage to their healthcare provider [see *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.6)].

### Infections

Advise patients to contact their healthcare provider if they experience signs and symptoms of infection [see *Warnings and Precautions* (5.2)].

### Hemorrhage

Advise patients to contact their healthcare provider for unusual bleeding, bruising, or symptoms of bleeding, such as lightheadedness [see *Warnings and Precautions* (5.3)].

### Gastrointestinal Perforation or Fistula

Advise patients to contact a healthcare provider immediately if they experience severe pains in their abdomen, persistent swelling of the abdomen, high fever, chills, nausea, vomiting, or dehydration [see *Warnings and Precautions* (5.4)].

### Dermatologic Toxicity

Advise patients to contact their healthcare provider if they experience skin changes including HFSR, rash, pain, blisters, bleeding, or swelling [see *Warnings and Precautions* (5.5)].

### Hypertension

Advise patients they will need to undergo blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms [see *Warnings and Precautions* (5.6)].

### Cardiac Ischemia and Infarction

Advise patients to seek immediate emergency help if they experience chest pain, shortness of breath, feel dizzy, or feel like passing out [see *Warnings and Precautions* (5.7)].

### Reversible Posterior Leukoencephalopathy Syndrome

Advise patients to contact their healthcare provider if they experience signs and symptoms of RPLS [see *Warnings and Precautions* (5.8)].

### Wound Healing Complications

Advise patients to contact their healthcare provider if they plan to undergo a surgical procedure or had recent surgery [see *Warnings and Precautions* (5.9)].

### Embryo-Fetal Toxicity

Advise patients that regorafenib can cause fetal harm. Advise a pregnant woman of the potential risk to a fetus [see *Warnings and Precautions* (5.10), *Use in Specific Populations* (8.1, 8.3)].

### Females and Males of Reproductive Potential

- Advise women of reproductive potential of the need for effective contraception during STIVARGA treatment and for 2 months after completion of treatment. Instruct women of reproductive potential to immediately contact her healthcare provider if pregnancy is suspected or confirmed during or within 2 months of completing treatment with STIVARGA [see *Warnings and Precautions* (5.10) and *Use in Specific Populations* (8.1, 8.3)].
- Advise men of reproductive potential of the need for effective contraception during STIVARGA treatment and for 2 months after completion of treatment [see *Use in Specific Populations* (8.3)].

### Lactation

Advise nursing mothers that it is not known whether regorafenib is present in breast milk and discuss whether to discontinue nursing or to discontinue regorafenib [see *Use in Specific Populations* (8.2)].

### Administration

- Advise patients to swallow the STIVARGA tablet whole with water at the same time each day following a low-fat meal. Inform patients that the low-fat meal should contain less than 600 calories and less than 30% fat [see *Dosage and Administration* (2.1)].
- Advise patients to store medicine in the original container. Do not place medication in daily or weekly pill boxes. Discard any remaining tablets 7 weeks after opening the bottle. Tightly close bottle after each opening and keep the desiccant in the bottle [see *How Supplied* (16)].

### Dosing Instructions

Advise patients to take STIVARGA after a low fat meal. Advise patients to take any missed dose on the same day, as soon as they remember, and that they must not take two doses on the same day to make up for a dose missed on the previous day [see *Dose and Administration* (2.1)].

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## Regorafenib Dose Optimization Study (ReDOS): Randomized Phase II Trial to Evaluate Dosing Strategies for Regorafenib in Refractory Metastatic Colorectal Cancer—An ACCRU Network Study

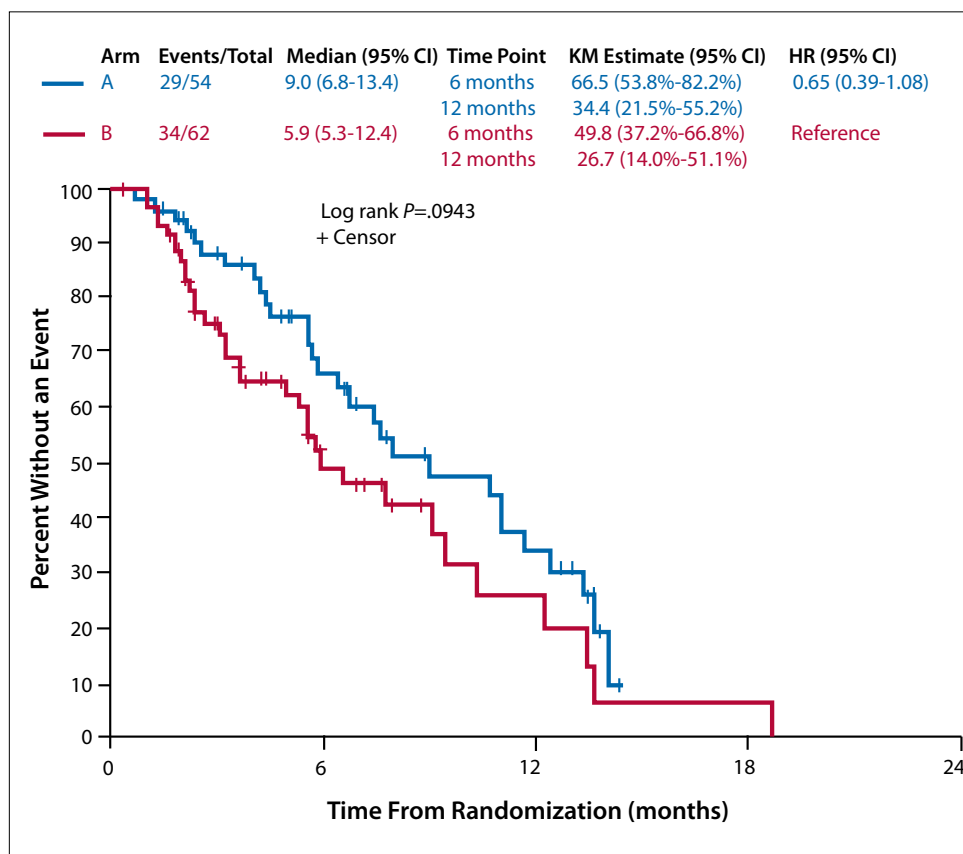
**R**egorafenib is an oral multi-kinase inhibitor that targets the receptor tyrosine kinases involved in angiogenesis and oncogenesis. In phase 3 trials of patients with previously treated metastatic colorectal cancer, regorafenib improved overall survival (OS).<sup>1,2</sup> However, the use of regorafenib has been associated with toxicities, such as hand-foot skin reaction and fatigue. In an effort to reduce toxicities while maintaining efficacy, the randomized phase 2 ReDOS trial (Regorafenib Dose Optimization Study) compared a fixed dose of regorafenib vs a dose-escalated regimen in patients with metastatic colorectal cancer.<sup>3</sup> Patients in arm A received regorafenib at 80 mg/day, with weekly dose escalation up to 160 mg/day in

the absence of significant drug-related toxicities. Patients in arm B received the standard dose of regorafenib at 160 mg/day. Both arms received regorafenib for 21 days during each 28-day cycle. In addition to the regorafenib dose randomization, patients within each regorafenib arm were randomly assigned to receive clobetasol either preemptively or to treat hand-foot skin reaction. The primary endpoint was the proportion of patients who completed 2 treatment cycles and initiated treatment cycle 3.

Among 123 patients, evaluable data were available for 54 patients in the escalated-dose arm and 62 patients in the standard-dose arm. Patient demographics were evenly balanced between the 2 arms. The 116 patients

had a median age of 61 years (range, 53-68 years), and 61.2% were male. All patients had a performance score of 0 or 1. The primary tumor had been resected in 69.8% of patients, and two-thirds of patients had 3 or more metastatic sites. *KRAS* was mutated in 47% of patients, wild type in 44%, and of unknown status in 9%.

The trial met its primary endpoint, with 43% of patients in the escalated-dose arm entering the third treatment cycle vs 24% in the standard-dose arm ( $P=.028$ ). Escalation of regorafenib was also associated with an improved OS (9.0 months vs 5.9 months;  $P=.094$ ; Figure 1). Median progression-free survival (PFS) was 2.5 months for the escalated-dose arm vs 2.0 months for the standard-



**Figure 1.** Overall survival in the randomized phase 2 ReDOS trial, which compared a fixed dose of regorafenib vs a dose-escalated regimen in patients with metastatic colorectal cancer. Patients in arm A received regorafenib at 80 mg/day, with weekly dose escalation up to 160 mg/day in the absence of significant drug-related toxicities. Patients in arm B received the standard dose of regorafenib at 160 mg/day. HR, hazard ratio; KM, Kaplan-Meier; ReDOS, Regorafenib Dose Optimization Study. Adapted from Bekaii-Saab T et al. ASCO GI abstract 611. *J Clin Oncol.* 2018;36(suppl 4S).<sup>3</sup>

**ABSTRACT SUMMARY A Phase II Trial of the Effect of Perindopril on Hand-Foot Syndrome Incidence and Severity in Patients Receiving Regorafenib With Refractory Metastatic Colorectal Carcinoma**

In the CORRECT trial, any-grade hand-foot skin reaction was observed in 47% of patients, and 17% experienced grade 3 hand-foot skin reaction (Grothey A et al. *Lancet*. 2013;381[9863]:303-3012). The pathogenesis of hand-foot skin reaction is not well-understood, but it may involve alterations to the capillary endothelium. Perindopril is an angiotensin-converting enzyme. A single-center, phase 2 study investigated whether the use of perindopril with regorafenib would reduce hand-foot skin reaction in patients with refractory metastatic colorectal cancer (Abstract 824). The study had a planned interim analysis of 10 evaluable patients who had completed 1 treatment cycle. Among the 10 patients in the interim analysis, 5 (50%) experienced a grade 3 hand-foot skin reaction. Based on the statistical plan, perindopril was considered unlikely to be effective in reducing hand-foot skin reaction, and enrollment in the trial was stopped.

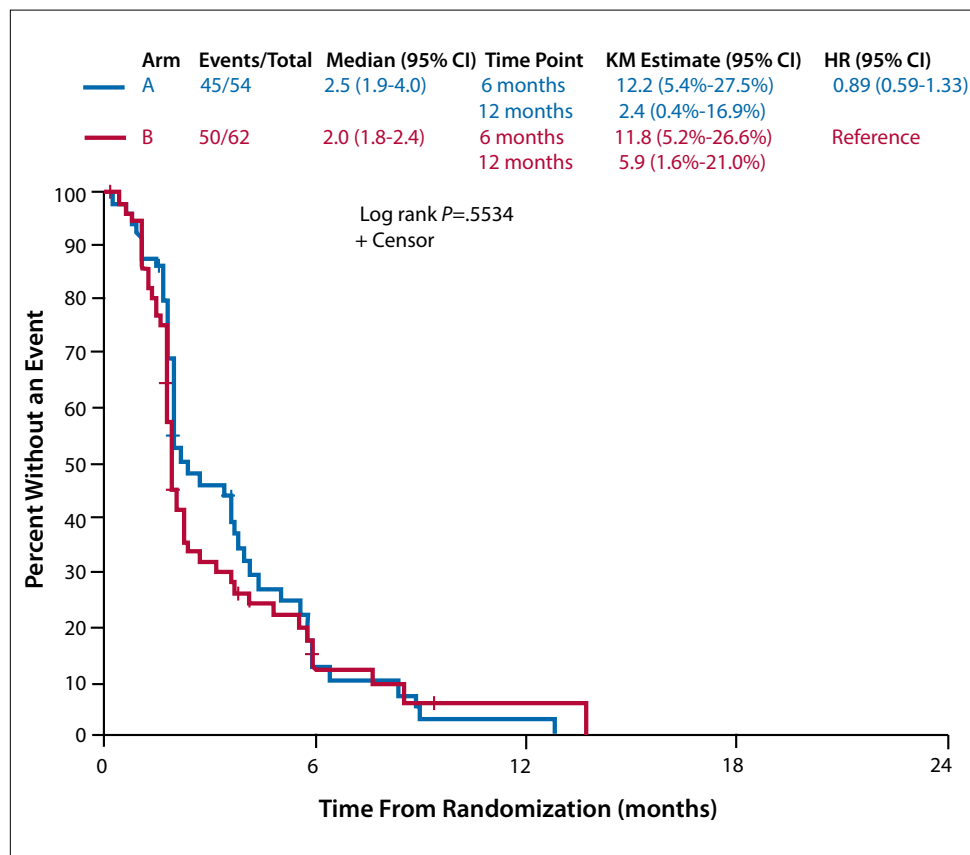
dose arm ( $P=.553$ ; Figure 2). Overall quality of life decreased more in the standard-dose arm compared with the escalated-dose arm, particularly at week 2 of treatment cycle 1. In the escalated-dose arm, 18.5% of patients

discontinued treatment owing to adverse events (AEs), side effects, or other complications, compared with 9.7% of patients in the standard-dose arm. However, patients in the escalated-dose arm had lower rates of

grade 3/4 toxicity, including fatigue (13.0% vs 17.7%), hand-foot skin reaction (14.8% vs 16.1%), and hypertension (7.4% vs 14.5%). The results support the use of regorafenib dose escalation in patients with previously treated metastatic colorectal cancer. Outcomes with preemptive vs reactive clobetasol will be presented at a later date.

**References**

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2. Li J, Qin S, Xu R, et al; CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16(6):619-629.
3. Bekaii-Saab T, Ou FS, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC)—an ACCRU Network study [ASCO GI abstract 611]. *J Clin Oncol*. 2018;36(suppl 4S).



**Figure 2.** Progression-free survival in the randomized phase 2 ReDOS trial, which compared a fixed dose of regorafenib vs a dose-escalated regimen in patients with metastatic colorectal cancer. Patients in arm A received regorafenib at 80 mg/day, with weekly dose escalation up to 160 mg/day in the absence of significant drug-related toxicities. Patients in arm B received the standard dose of regorafenib at 160 mg/day. HR, hazard ratio; KM, Kaplan-Meier; ReDOS, Regorafenib Dose Optimization Study. Adapted from Bekaii-Saab T et al. ASCO GI abstract 611. *J Clin Oncol*. 2018;36(suppl 4S).<sup>3</sup>

## Nivolumab + Ipilimumab Combination in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report of the Full Cohort From CheckMate-142

The DNA mismatch repair (dMMR) system is defective in approximately 4% of patients with metastatic colorectal cancer. The defect confers high microsatellite instability (MSI-H) and decreases benefit from conventional chemotherapy.<sup>1,2</sup> The multicenter, open-label, nonrandomized, phase 2 CheckMate 142 trial (An Investigational Immuno-Therapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-Cancer Drugs, in Colon Cancer That Has Come Back or Has Spread) was designed to evaluate nivolumab, alone or in combination with other therapies, in patients with dMMR/MSI-H metastatic or recurrent colorectal cancer. Eligible patients had progressed on, or were intolerant of, at least 1 prior line of therapy, including a fluoropyrimidine and oxaliplatin or irinotecan. After a median follow-up of 12.0 months, 74 patients treated with nivolumab monotherapy in the CheckMate 142 trial demonstrated an objective response rate (ORR) of 31.1%, as assessed by the investigators.<sup>3</sup>

One cohort of the CheckMate 142 trial investigated the combination of nivolumab plus ipilimumab. These 2 checkpoint inhibitors synergistically promote T-cell antitumor activity.<sup>4,6</sup> Patients in the monotherapy cohort received nivolumab at 3 mg/kg every 2 weeks. Those in the combination cohort received 4 doses of nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks, followed by nivolumab at 3 mg/kg every 2 weeks. Among the 119 patients in the nivolumab-plus-ipilimumab cohort, the median age was 58 years (range, 21-88 years), and 59% were male. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Forty-five percent of patients had stage IV disease, and 40% had received 3 or more prior lines of therapy.

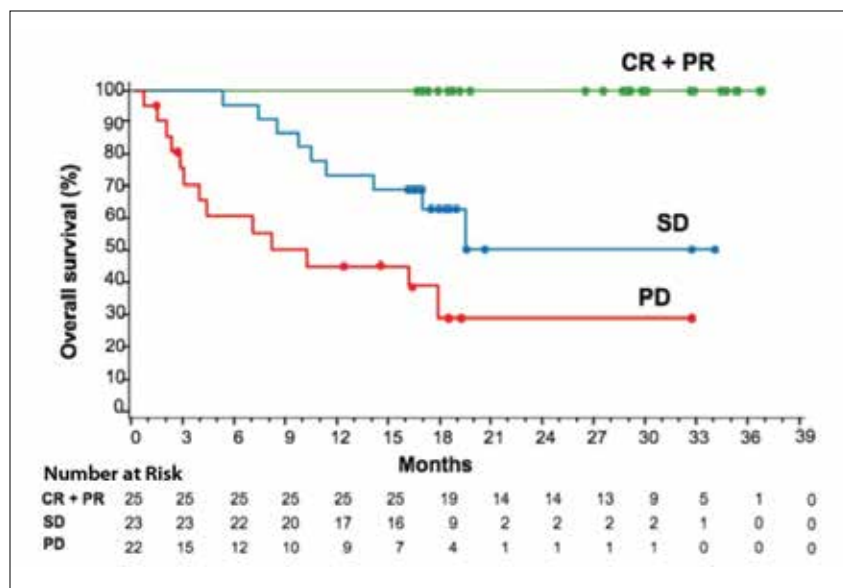
In the combination analysis, the median follow-up was 13.4 months among patients treated with nivolumab plus ipilimumab followed by nivolumab.<sup>3</sup> The investigator-assessed ORR was 55%, and an additional 31% of patients had stable disease. The median follow-up was also 13.4 months in the cohort of patients treated with nivolumab monotherapy. These patients exhibited an ORR of 31%, and 38% of patients had stable disease.<sup>3</sup> In the combination cohort, the median time to response was 2.8 months (range, 1-14 months), and responses were durable. Responses occurred irrespective of expression of programmed death ligand 1 (PD-L1), mutation status of *BRAF* or *KRAS*, and

clinical history of Lynch syndrome. Twelve-month PFS was 71% (95% CI, 61.4%-78.7%), and 12-month OS was 85% (95% CI, 77.0%-90.2%). These outcomes were also superior to those observed in the nivolumab monotherapy cohort. Grade 3/4 AEs were more common in the combination therapy cohort (32% vs 20%), but no new safety signals were raised.

After a longer follow-up of 21 months in the monotherapy cohort, nivolumab continued to demonstrate a durable clinical benefit in patients with dMMR/MSI-H metastatic colorectal cancer, based on blinded independent central review.<sup>7</sup> The 74 patients in the monotherapy cohort had a median age of 52.5 years (range, 26-79 years), and 59% were male. All of the patients had an ECOG performance status of 0 or 1,

### ABSTRACT SUMMARY Clinical Efficacy and Safety of Regorafenib in the Treatment of Metastatic Colorectal Cancer in Daily Practice in Germany: Final Results of the Prospective Multicentre Non-Interventional RECORA Study

The noninterventional, open-label, multicenter RECORA study (Investigating the Use of Regorafenib [Stivarga] in Patients With Metastatic Colorectal Cancer [mCRC] After Failure of Standard Therapy) investigated OS in real-world practice conditions (Abstract 748). Patient data were collected during visits according to local practice. The 481 enrolled patients had a median age of 67 years (range, 30-89 years), and 63% had primary colon cancer. The median OS was 5.9 months (95% CI, 5.3-6.6 months), which is similar to the median OS of 6.4 months observed in the CORRECT study (Grothey A et al. *Lancet*. 2013;381[9863]:303-312). The median PFS was 3.1 months (95% CI, 2.8-3.3 months) vs 1.9 months (95% CI, 0.42-0.58) in the CORRECT study. The study authors suggested that this longer PFS was likely attributable to irregular tumor assessment intervals. The RECORA study had fewer treatment-related AEs than CORRECT, but this lower incidence may have resulted from the noninterventional nature of the study and differences in reporting criteria.



**Figure 3.** Overall survival according to best overall response with nivolumab plus ipilimumab among patients with DNA mismatch repair/high microsatellite instability metastatic colorectal cancer. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Overman MJ et al. ASCO GI abstract 554. *J Clin Oncol.* 2018;36(suppl 4S).<sup>7</sup>

45% had stage IV disease, and 54% had received 3 or more prior lines of therapy.

The ORR was 34%, and 31% of patients had stable disease. A reduction in tumor burden from baseline occurred in 60% of patients. The median duration of response was not reached (range, 1.4+ to 31.6+ months), and 64% of patients had responses that lasted 12 months or lon-

ger. The complete response (CR) rate increased from 32% after 13 months of follow-up to 34% after 21 months of follow-up. The median PFS was 6.6 months (95% CI, 3.0 months to not reached), and the median OS was not reached (95% CI, 19.6 months to not reached; Figure 3). Fifty-three patients had received 3 or more prior chemotherapies, most commonly a fluoropyrimidine, oxaliplatin, irinote-

can, and a vascular endothelial growth factor (VEGF) inhibitor. Among these patients, the median PFS was 4.2 months, and the median OS was not reached.

Treatment-related grade 3/4 AEs were reported in 20% of patients. No new safety signals were raised.

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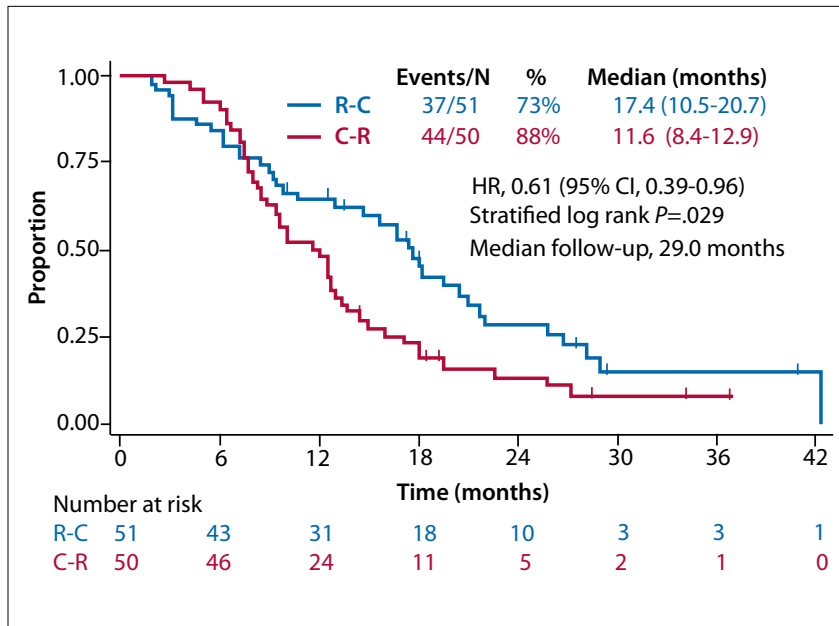
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## REVERCE: Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus the Reverse Sequence for Metastatic Colorectal Cancer Patients Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan

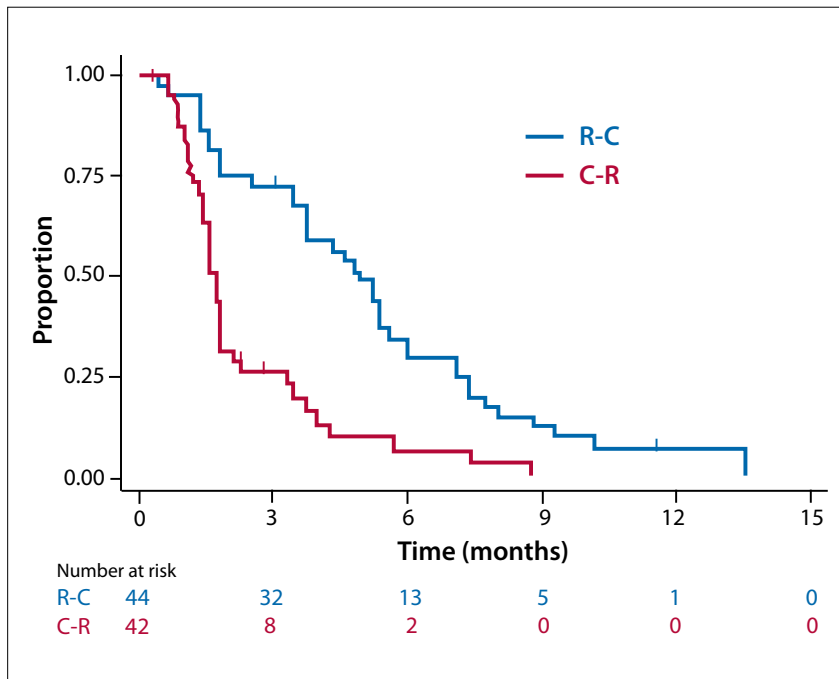
**R**egorafenib is approved by the US Food and Drug Administration for the treatment of patients with metastatic colorectal cancer who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy;

an anti-VEGF therapy; and, for patients with wild-type *KRAS*, a therapy that targets the epidermal growth factor receptor (EGFR).<sup>1</sup> Treatment with an anti-EGFR agent is therefore followed by regorafenib, but the optimal sequencing of agents is unknown.<sup>2</sup>

The phase 2 REVERCE trial evaluated the efficacy and safety of regorafenib followed by cetuximab vs cetuximab followed by regorafenib in patients with metastatic colorectal cancer.<sup>3</sup> Eligible patients had developed relapsed or refractory disease after treatment



**Figure 4.** Overall survival in the phase 2 REVERCE trial, which evaluated the efficacy and safety of regorafenib followed by cetuximab (R-C) vs cetuximab followed by regorafenib (C-R) in patients with metastatic colorectal cancer. The hazard ratio was adjusted by the intent to use irinotecan. Adapted from Shitara K et al. ASCO GI abstract 557. *J Clin Oncol.* 2018;36(suppl 4S).<sup>3</sup>



**Figure 5.** In the phase 2 REVERCE trial, the median progression-free survival was 5.2 months for regorafenib followed by cetuximab (R-C) vs 1.8 months for cetuximab followed by regorafenib (C-R) after treatment was completed. Adapted from Shitara K et al. ASCO GI abstract 557. *J Clin Oncol.* 2018;36(suppl 4S).<sup>3</sup>

with fluoropyrimidines, oxaliplatin, and irinotecan, and had not received anti-EGFR therapy. Eligible patients also had wild-type *KRAS* exon 2. Patients with minor *RAS* mutations were excluded during the latter part of the trial. Treatment consisted of regorafenib at 160 mg for 3 weeks on and 1 week off, followed by cetuximab (with irinotecan), or the reverse treatment. Patients received treatment until disease progression or unacceptable toxicity. The trial's primary endpoint was to demonstrate a similar OS in both arms (hazard ratio [HR], 0.8-1.25), with an expected median OS of 12 months.

The study randomly assigned 51 patients to treatment with regorafenib followed by cetuximab and 50 patients to cetuximab followed by regorafenib. The baseline characteristics were well-balanced between the 2 arms. Patients had a median age of approximately 67 years (range, 34-83 years), and 64% were male. The primary tumor was located on the left side in more than three-fourths of patients. Nearly all patients (97%) had received prior bevacizumab.

After a median follow-up of 29 months, the median OS was 17.4 months for the regorafenib-first arm vs 11.6 months for the cetuximab-first arm (HR, 0.61; 95% CI, 0.39-0.96;  $P=.029$ ; Figure 4). At the end of treatment with the first therapy, the median PFS was 2.4 months with regorafenib vs 4.2 months with cetuximab (HR, 0.97; 95% CI, 0.62-1.54;  $P=.91$ ). At the end of the complete regimens, the median PFS was 5.2 months for regorafenib followed by cetuximab vs 1.8 months for cetuximab followed by regorafenib (HR, 0.29; 95% CI, 0.17-0.50;  $P<.0001$ ; Figure 5).

In subgroup analysis, a primary tumor on the left side was associated with an HR of 0.51 (95% CI, 0.30-0.86), whereas a primary tumor on the right side was associated with an HR of 0.88 (95% CI, 0.32-2.40). Among the 81 patients with a left-sided primary tumor, the median OS

### ABSTRACT SUMMARY BEACON CRC Study Safety Lead-In in Patients With *BRAF*<sup>V600E</sup> Metastatic Colorectal Cancer: Efficacy and Tumor Markers

The phase 3 BEACON study is assessing the safety and efficacy of a combination regimen consisting of binimetinib, cetuximab, and the BRAF inhibitor encorafenib in patients with *BRAF*<sup>V600E</sup>-mutant CRC who developed relapsed/refractory disease after 1 or 2 prior regimens. Results for the safety lead-in study were presented (Abstract 627). These patients received the triplet of encorafenib at 300 mg once daily, binimetinib at 45 mg twice daily, and cetuximab at 400 mg/m<sup>2</sup> for the initial dose, followed by 250 mg/m<sup>2</sup> every week in 28-day cycles. Data were evaluable for 30 patients. Among the 29 patients with a *BRAF*<sup>V600E</sup> mutation, the median time on study treatment was 5.6 months, and 76% remained on study treatment at the time of data cut-off. The ORR was 41%, with 1 CR and 11 partial responses. Nine patients had prolonged stable disease, reaching 9.3 months. The triplet was generally well-tolerated. Adverse events were consistent with those seen with other BRAF, MEK, and EGFR inhibitors. The rate of grade 3/4 skin toxicities was lower than that generally observed with cetuximab in metastatic CRC.

was 20.5 months in the regorafenib-first arm vs 11.9 months in the cetuximab-first arm ( $P=.011$ ). Among the 86 patients with wild-type *RAS* and *RAF*, the median OS was 18.2 months with regorafenib first vs 12.7 months with cetuximab first (HR, 0.60; 95% CI, 0.37-0.98;  $P=.036$ ).

No new safety signals were observed in either arm. Quality of life was comparable between the arms, and decreased during treatment with regorafenib vs cetuximab.

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## A Phase Ib Study of Safety and Clinical Activity of Atezolizumab and Cobimetinib in Patients With Metastatic Colorectal Cancer

For patients with locally advanced, metastatic, or chemotherapy-refractory colorectal cancer, standard-of-care treatment is associated with a survival that is measured in months.<sup>1,2</sup> Although PD-1 pathway inhibitors have shown activity in many tumor types, approximately 95% of patients with metastatic colorectal cancer have microsatellite-stable disease, which correlates with a poor response to inhibition of PD-1 or PD-L1.<sup>3</sup> Combination therapy may be necessary to enable effective outcomes with immune checkpoint inhibitors in this setting. Atezolizumab binds to PD-L1, restoring tumor-specific immunity.<sup>4,5</sup> Cobimetinib is a potent inhibitor of MEK1 and MEK2, and it promotes T-cell accumulation in tumors while limiting T-cell exhaustion.<sup>6</sup> In a mouse tumor model, simultaneous inhibi-

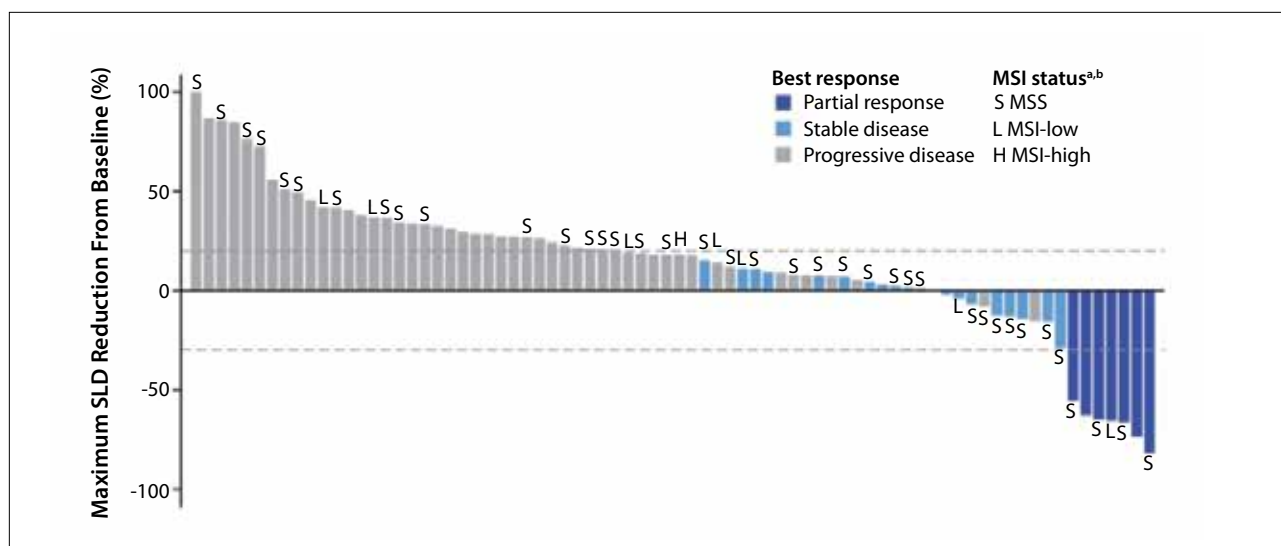
tion of the MEK pathway and PD-L1 resulted in synergistic and durable tumor inhibition.<sup>6</sup>

The combination of atezolizumab plus cobimetinib was investigated in a phase Ib dose escalation and cohort expansion study of patients with metastatic colorectal cancer.<sup>7</sup> Eligible patients were not screened for PD-L1 status. MSI status was locally reported and centrally confirmed. The atezolizumab dose was fixed at 800 mg every 2 weeks. In the dose-escalation stage, patients received cobimetinib at doses ranging from 20 mg/day to 60 mg/day, for 21 days of each 28-day cycle. The combination of atezolizumab administered at 800 mg every 2 weeks plus the highest dose of cobimetinib was chosen for dose expansion.

The 84 patients had a median age of 56.5 years (range, 23-81 years).

Seventy-nine percent of patients had received 5 or more prior therapies, and 68% of patients had mutant *KRAS*. PD-L1 expression was less than 5% in 57% of patients, 5% or higher in 8% of patients, and unknown in the remainder. Fifty percent of patients had microsatellite-stable disease.

The 2-drug combination yielded an ORR of 8%. All of the responses were partial, and 23% of patients had stable disease (Figure 6). Among the 7 patients who experienced a partial response, 4 had microsatellite-stable disease. Similar ORRs were observed in the *KRAS* wild-type and *KRAS* mutant subpopulations. The median duration of response was 14.3 months (95% CI, 6.0 months to not estimable). The median PFS was 1.9 months (95% CI, 1.9-2.3 months) in the 84 metastatic colorectal cancer patients



**Figure 6.** Best overall response in a phase Ib study of atezolizumab plus cobimetinib. <sup>a</sup>Based on combined local or centralized testing results.

<sup>b</sup>Unlabeled bars represent patients with an unknown MSI status. L, low; MSI, microsatellite instability; MSS, microsatellite stable; S, stable; SLD, sum of longest diameters. Adapted from Bendell JC et al. ASCO GI abstract 560. *J Clin Oncol.* 2018;36(suppl 4S).<sup>7</sup>

#### ABSTRACT SUMMARY Impact of Primary Tumor Side on Outcomes of Once-Every-2-Weeks Cetuximab + First-Line FOLFOX or FOLFIRI in Patients With RAS Wild-Type Metastatic Colorectal Cancer in the Phase 2 APEC Trial

A multicenter, nonrandomized, open-label study evaluated the impact of left-sided vs right-sided primary tumors in patients with metastatic colorectal cancer (Abstract 747). Eligible patients were treatment-naïve and had wild-type *KRAS*. Treatment was administered every 2 weeks and consisted of cetuximab plus FOLFOX or standard treatment with 5-FU, LV, and irinotecan (FOLFIRI). Among 159 evaluable patients, 130 (81.8%) had left-sided tumors and 29 (18.2%) had right-sided tumors. The ORR was 68.5% for patients with left-sided tumors vs 51.7% for patients with right-sided tumors. The median PFS was 14.0 months (95% CI, 11.4-14.9 months) for left-sided tumors vs 8.9 months (95% CI, 5.5-15.4 months) for right-sided tumors. The median OS was 30.6 months (95% CI, 25.7-34.3 months) vs 24.6 months (95% CI, 13.8-31.2 months), respectively.

and 2.5 months (95% CI, 1.9-3.7 months) in the microsatellite-stable subgroup of 42 patients. The median OS was 9.8 months (95% CI, 6.2-14.1 months) in the 84 patients with metastatic colorectal cancer, and 13.0 months (95% CI, 6.0-25.8 months) in patients with microsatellite-stable disease. Median PFS and median OS were similar in patients with wild-type or mutant *KRAS*. The combination of atezolizumab plus cobimetinib vs

regorafenib is being investigated in a phase 3 trial.<sup>8</sup>

Most AEs were manageable. Treatment-related AEs of any grade occurred in 96% of patients. The most common treatment-related grade 3/4 AEs were rash, diarrhea, fatigue, and increased blood creatine phosphokinase, each occurring in 5% of patients. AEs caused 13% of patients to discontinue atezolizumab and 24% to discontinue cobimetinib. Treatment-

related serious AEs were reported in 12% of patients. No treatment-related deaths occurred.

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## Regorafenib in Antiangiogenic-Naive, Chemotherapy-Refractory Advanced Colorectal Cancer: A Phase IIb Trial

Regorafenib was investigated in patients with chemotherapy-refractory, advanced colorectal cancer in an open-label, single-arm, phase 2b study performed at a single center.<sup>1</sup> Patients were excluded from enrollment if they had received prior antiangiogenic treatment, such as bevacizumab. Patients received daily regorafenib at 160 mg for 21 days of each 28-day cycle. Treatment was administered until disease progression, unacceptable toxicity, withdrawal of patient consent, or investigator decision. The primary endpoint was PFS at week 8, tested against the null hypothesis that the true PFS at 8 weeks would be less than or equal to 30%, based on the inclusion of patients with potentially more advanced disease than those in the CORRECT study (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo

After Failure of Standard Therapy).<sup>2</sup> Tumor response was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.<sup>3</sup> Tumor metabolic response was assessed by <sup>18</sup>F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), based on criteria from the European Organization for Research and Treatment of Cancer (EORTC).<sup>4</sup>

Fifty-nine patients received at least 1 dose of regorafenib. Patients had a median age of 58 years (range, 30-74 years), and 59% were male. The primary disease sites were the rectum (30.5%), proximal colon (27.1%), distal colon (23.7%), and colon and rectum (18.6%). A *KRAS* mutation was observed in 57.6% of patients. The time since first diagnosis until treatment assignment was 18 months or longer in three-fourths of patients.

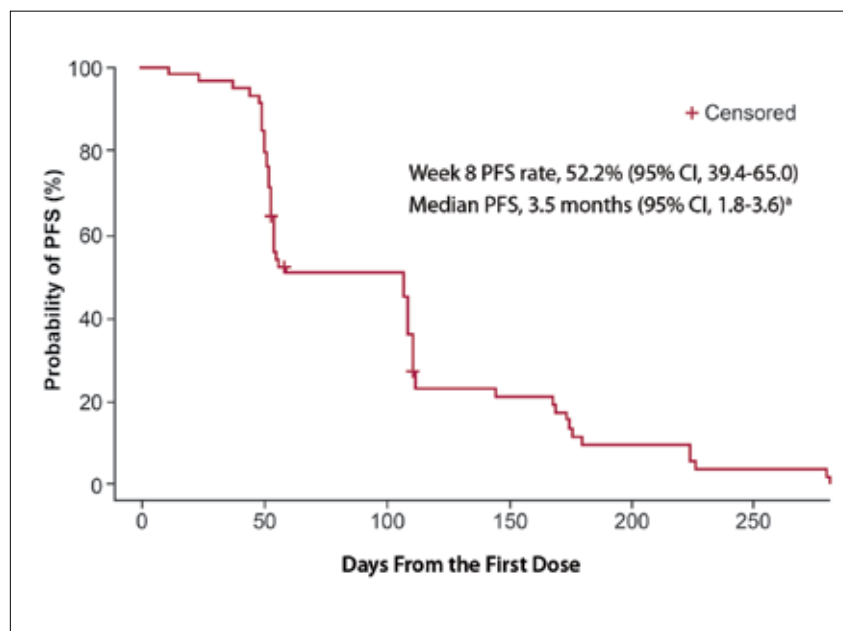
Prior to study enrollment, 28.8% of patients had undergone radiotherapy, and 47.5% of patients had received 4 or more prior lines of systemic therapy.

Among the 59 enrolled patients, the PFS rate at week 8 was 52.2% (Figure 7), and the OS rate at week 8 was 98.3%. The median PFS was 3.5 months (95% CI, 1.8-3.6 months), and the median OS was 7.4 months (95% CI, 5.3-8.9 months). Based on RECIST, the disease control rate was 50.8%. Tumor response according to FDG PET/CT assessment was greater using EORTC criteria compared with RECIST criteria (40.7% vs 1.7%). The median OS was 8.5 months in responders vs 6.0 months in nonresponders (based on EORTC criteria;  $P=.1079$ ).

No new safety signals emerged. The most common treatment-emergent grade 3/4 AEs included hypertension (36.6%), hand-foot skin reaction (25.4%), and hypophosphatemia (22.0%). Serious treatment-related AEs were reported in 8.5% of patients. No treatment-related deaths occurred. An AE, primarily hand-foot skin reaction, led to a dose reduction in 42.4% and a dose interruption in 64.4%.

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**Figure 7.** Progression-free survival in a phase 2b study of regorafenib in patients with chemotherapy-refractory, advanced colorectal cancer. \*The median PFS of 107 days was converted to months (1 month = 30.44 days). PFS, progression-free survival. Adapted from Riechelmann R et al. ASCO GI abstract 782. *J Clin Oncol*. 2018;36(suppl 4S).<sup>1</sup>



## SCOT: Tumor Sidedness and the Influence of Chemotherapy Duration on Disease-Free Survival

For more than a decade, the standard adjuvant treatment for colorectal cancer has been 6 months of oxaliplatin-based therapy. However, oxaliplatin is associated with cumulative neurotoxicity that is dose-limiting and potentially irreversible. The international, noninferiority, phase 3 SCOT trial (Combination Chemotherapy After Surgery in Treating Patients With High-Risk Stage II or Stage III Colorectal Cancer) evaluated 3 months vs 6 months of oxaliplatin-based chemotherapy in patients with stage III or high-risk stage II colorectal cancer.<sup>1</sup> Patients were treated with capecitabine plus oxaliplatin or folinic acid, fluorouracil, and oxaliplatin (FOLFOX), based on patient and physician choice. Patients were randomly assigned to receive 3 or 6 months of treatment. Noninferiority was defined as a reduction of 2.5% or less in 3-year disease-free survival after 3 months of treatment compared with 6 months of treatment. The study was

designed to achieve 90% power at the 2.5% level of statistical significance based on recruitment of 9000 patients and 2750 disease-free survival events, including relapses, deaths, and the emergence of new colorectal cancer tumors. However, based on slow recruitment, the trial enrolled 6088 patients in 244 centers in 6 countries. FOLFOX was administered to 1981 patients, and capecitabine plus oxaliplatin to 4107 patients. The SCOT trial met its primary endpoint, demonstrating a reduction of 0.4% in 3-year disease-free survival for treatment of 3 months (76.7%) vs 6 months (77.1%; HR for noninferiority, 1.008;  $P=.014$ ).

A recent study of 1869 patients with stage III colon cancer suggested that the anatomic location of the primary tumor may influence outcomes, such that patients with right-sided tumors have a worse survival after relapse.<sup>2</sup> To further evaluate this possibility, data from the SCOT trial

were analyzed for the impact of tumor sidedness on disease-free survival.<sup>3</sup> Information on the primary tumor location was collated from pathologic reports and available for 3219 patients. Right-sided tumors included those in the cecum or ascending or transverse colon. Left-sided tumors included all those distal to and including the splenic flexure.

The 1207 patients with right-sided tumors had a median age of 66 years. Fifty-three percent were male, 41% had T4 tumors, and 17% had stage II disease. The 2012 patients with left-sided tumors had a median age of 64 years. Sixty-six percent were male, 24% had T4 tumors, and 21% had stage II disease. Patient characteristics were well-balanced between the 2 groups ( $P<.001$ ).

Three-year disease-free survival was significantly worse in patients with tumors on the right vs the left (73% vs 80%; HR, 1.401; 95% CI, 1.216-1.615;  $P<.0001$ ). Adjusting for tumor, node, and metastasis staging reduced the HR to 1.215 (95% CI, 1.051-1.404;  $P=.009$ ). The analysis did not suggest that sidedness affected the impact of chemotherapy duration on 3-year disease-free survival (right-sided HR, 1.049; 95% CI, 0.849-1.296; left-sided HR, 0.910; 95% CI, 0.753-1.099; test for heterogeneity,  $P=.327$ ).

### ABSTRACT SUMMARY Randomized Phase II Trial of CapOX Plus Bevacizumab Versus Cap(R) Plus Bevacizumab as First-Line Treatment in Japanese Patients With Metastatic Colorectal Cancer (CCOG-1201 Study)

A multicenter, randomized phase 2 trial evaluated bevacizumab in combination with capecitabine plus oxaliplatin or capecitabine plus irinotecan as first-line treatment in Japanese patients with metastatic colorectal cancer (Abstract 781). The 107 enrolled patients had a median age of 68 years (range, 40-82 years). The primary tumor was located in the left colon or rectum in 60% of patients. The median number of treatment cycles was 9 in both arms (range, 0-34). The ORR was 56% (95% CI, 41%-69%) in the bevacizumab, capecitabine, and oxaliplatin arm and 55% (95% CI, 40%-68%) in the bevacizumab, capecitabine, and irinotecan arm ( $P=.54$ ). The median tumor shrinkage rate at the nadir was 36% in both arms. The median PFS was 12.4 months (95% CI, 10.6-14.3 months) among patients treated with bevacizumab, capecitabine, and oxaliplatin vs 11.5 months (95% CI, 9.6-13.4 months) among those treated with bevacizumab, capecitabine, and irinotecan ( $P=.57$ ). The median OS was also similar in both arms ( $P=.49$ ). No new safety signals were raised.

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## Phase II Dose Titration Study of Regorafenib for Patients With Unresectable Metastatic Colorectal Cancer That Progressed After Standard Chemotherapy

The CORRECT study showed a significant improvement in OS with regorafenib compared with placebo in patients with metastatic colorectal cancer that had progressed after standard therapy.<sup>1</sup> The OS improvement was also observed in a subgroup of Japanese patients.<sup>2</sup> The standard starting dose of regorafenib is 160 mg/day, irrespective of the patient's body weight or other parameters. In the CORRECT study, dose reduction owing to an AE was common among both Japanese and non-Japanese patients (84.6% vs 51.3%, respectively). Rates of discontinuation owing to AEs were relatively low, but these rates were higher in Japanese patients than in non-Japanese patients (13.8% vs 7.4%).

A single-arm, multicenter, phase 2 dose-titration study investigated a

reduced starting dose of regorafenib in Japanese patients with unresectable, metastatic colorectal cancer.<sup>3</sup> The study design included an option of increasing to the standard dose. Eligible patients were at least 20 years old and had histopathologically diagnosed colorectal cancer that had progressed during standard chemotherapy or within 3 months of the last chemotherapy cycle. Prior treatment with trifluridine/tipiracil was not permitted. All patients had an ECOG performance status of 0 or 1.

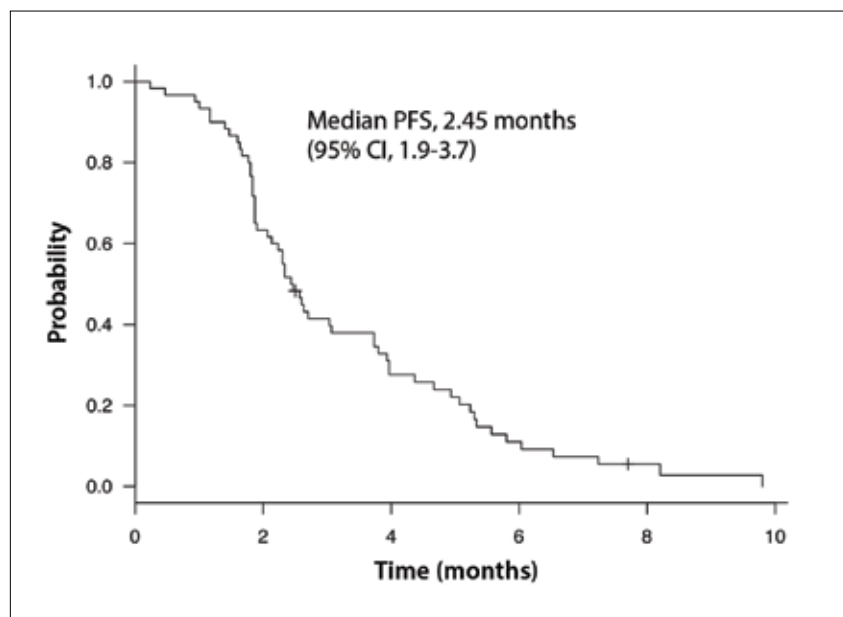
Patients initially received regorafenib at 120 mg every day for 3 weeks, followed by 1 week off. In subsequent cycles, dose escalation to 160 mg was permitted in patients who did not experience an AE of grade 2 or higher. An exception was made for patients with any grade of

liver toxicity, including transaminase elevation or increased bilirubin, in whom the dose was not increased. Radiographic evaluation was performed every 8 weeks. The primary endpoint was the disease control rate after 6 weeks. A disease control rate of 40% was defined as evidence of activity, and the confidence interval lower limit was set at 27%.

The 60 enrolled patients had a median age of 68.5 years (range, 47-80 years), and half were male. Most primary tumors were located in the sigmoid colon (45%), followed by the rectum (30%) and the ascending colon (15%). Sixty percent of patients had moderately differentiated adenocarcinoma, 36.7% had well-differentiated adenocarcinoma, and 3.3% had mucinous adenocarcinoma. Metastases were observed primarily in the liver (67.3%), the lung (53.8%), and the peritoneum (28.8%). Patients received up to 9 cycles of treatment.

The regorafenib dose was escalated from 120 mg to 160 mg in 2 patients (3.3%): 1 during cycle 2 and 1 during cycle 4. In 24 patients (40%), the regorafenib dose was decreased to 80 mg owing to an AE that occurred in at least 1 of the treatment cycles. The trial met its primary endpoint, with a disease control rate of 38.3%, exceeding the prespecified threshold of 27%. The disease control rate represented 23 patients (38.3%) with stable disease. There were no CRs or partial responses. The median PFS was 2.45 months (95% CI, 1.9-3.7 months; Figure 8), and the median OS was 6.93 months (95% CI, 5.7-9.1 months).

AEs were consistent with the known safety profile of regorafenib. Fifty-two percent of patients experienced a grade 3/4 AE. The most common grade 3/4 AEs were grade



**Figure 8.** Median progression-free survival in a phase 2 dose titration study of regorafenib for Japanese patients with unresectable metastatic colorectal cancer that progressed after standard chemotherapy. Adapted from Kudo T et al. ASCO GI abstract 821. *J Clin Oncol.* 2018;36(suppl 4S).<sup>3</sup>

3 hand-foot skin reaction and hypertension, each occurring in 20% of patients. Grade 4 AEs included increased aspartate transaminase (3%), increased alanine transaminase (2%), and hyperglycemia (2%).

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## SAPPHIRE: A Randomized Phase II Study of mFOLFOX6 + Panitumumab Versus 5-FU/LV + Panitumumab After 6 Cycles of Frontline mFOLFOX6 + Panitumumab in Patients With Colorectal Cancer

FOLFOX therapy is a common first-line option for patients with unresectable, advanced, or recurrent colorectal cancer. However, long-term exposure to oxaliplatin is associated with dose-limiting peripheral neuropathy.<sup>1</sup> Oxaliplatin can be discontinued after 6 cycles of first-line therapy. In patients who do not develop peripheral neuropathy, inclusion of oxaliplatin in later treatment cycles could be beneficial. Panitumumab is a fully human monoclonal antibody that binds to EGFR. In 2010, panitumumab was approved in Japan as monotherapy and in combination with chemotherapy for the treatment of *KRAS* wild-type metastatic colorectal cancer.

SAPPHIRE (Safety and Efficacy Study of mFOLFOX6 + Panitumumab Combination Therapy and 5-FU/LV + Panitumumab Combination Therapy in Patients With Chemotherapy-Naïve Unresectable Advanced Recurrent Colorectal Carcinoma) was an open-label, randomized phase 2 study that investigated panitumumab plus either modified FOLFOX6 or 5-fluorouracil (FU)/leucovorin (LV) after first-line treatment with 6 cycles of panitumumab plus modified FOLFOX6 administered in 2-week cycles.<sup>2,3</sup> The modified FOLFOX6 regimen consisted of 6 cycles of oxaliplatin (85 mg/m<sup>2</sup>) and LV (200 mg/m<sup>2</sup>), administered on the first day of the treatment cycle.

A 400-mg bolus of 5-FU was administered on day 1, followed by a 2400-mg infusion on days 1 to 3. Panitumumab at 6 mg/kg was also administered on day 1. Patients had wild-type *KRAS* and *NRAS*, and they had measurable lesions based on RECIST 1.1. Patients had not received prior chemotherapy, including adjuvant oxaliplatin. They had an ECOG performance status of 0 or 1.

The study randomly assigned patients with no signs of progressive disease to treatment after the sixth cycle of induction therapy. The primary endpoint was the PFS rate at 9 months after randomization. The

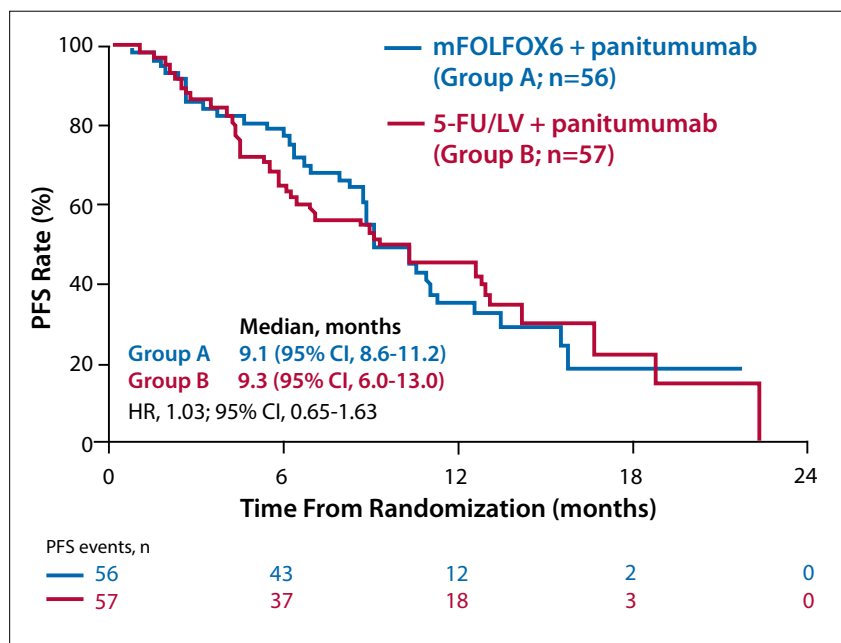
threshold PFS rate was defined as 30%. The expected PFS rate was set at 50%, with a 90% power and a 1-sided alpha value of 0.10.

The trial randomly assigned 56 patients to modified FOLFOX6 and 57 patients to 5-FU/LV. Patients had a mean age of approximately 67 years, and one-fourth were ages 70 years and older. Most tumors were located in the colon, and approximately three-fourths were left-sided. Approximately 53% of patients had 2 or more metastatic sites.

The trial met its primary endpoint in both arms. The 9-month PFS was 46.4% (80% CI, 38.1%-54.9%; *P*=.0037) in the modified

### ABSTRACT SUMMARY Impact of Primary Tumor Location on Outcomes in Patients With Metastatic Colorectal Cancer Undergoing First-Line Panitumumab + FOLFIRI Treatment

A single-arm, open-label, phase 2 study retrospectively evaluated first-line panitumumab plus FOLFIRI every 2 weeks in patients with metastatic colorectal cancer and wild-type *KRAS* (Abstract 820). The primary tumor was located on the left in 45 patients and on the right in 7 patients. In comparison with the patients with right-sided tumors, those with left-sided tumors had a longer median PFS (11.2 vs 7.2 months), and were more likely to experience early tumor shrinkage exceeding 30% (53% vs 29%). The ORR was 60% in patients with left-sided tumors vs 57% in patients with right-sided tumors. The median duration of response was 13.2 months (95% CI, 9.3-47.7 months) vs 14.3 months (95% CI, 3.5-17.3 months), respectively. The median PFS was 11.2 months (95% CI, 7.6-17.0 months) in the patients with left-sided tumors vs 7.2 months (95% CI, 1.1-19.1 months) in those with right-sided tumors.



**Figure 9.** Progression-free survival among patients treated with mFOLFOX6 plus panitumumab or 5-FU/LV plus panitumumab. A month was defined as 28 days. LV, leucovorin; mFOLFOX6, 6 cycles of oxaliplatin (85 mg/m<sup>2</sup>) and leucovorin (200 mg/m<sup>2</sup>), administered on day 1; 5-FU/LV, 5-fluorouracil plus leucovorin; PFS, progression-free survival. Adapted from Nakamura M et al. ASCO GI abstract 729. *J Clin Oncol.* 2018; 36(suppl 4S).<sup>3</sup>

FOLFOX6 arm vs 47.4% (95% CI, 39.1%-55.8%) in the 5-FU/LV arm ( $P=.$ 0021). The median PFS was 9.1

months (95% CI, 8.6-11.2 months) in the mFOLFOX6 arm and 9.3 months (95% CI, 6.0-13.0 months) in the

5-FU/LV arm (Figure 9). The ORR was 80.4% (95% CI, 68.0%-88.8%) vs 87.7% (95% CI, 76.4%-94.2%), respectively.

No grade 3/4 peripheral neuropathy was observed in either arm. Peripheral sensory neuropathy of any grade occurred in 5.4% of the mFOLFOX6 arm vs 5.6% of the 5-FU/LV arm. Peripheral motor neuropathy of any grade was observed in 0% vs 1.9% of patients, respectively. Peripheral neuropathy of any grade occurred in 14.3% vs 11.1% of patients, and grade 2 peripheral neuropathy was observed in 10.7% vs 1.9%.

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## Highlights in Metastatic Colorectal Cancer From the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium: Commentary

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**S**tudies at the 2018 American Society of Clinical Oncology Gastrointestinal Cancers (ASCO GI) symposium provided new insights into the management of colorectal cancer. Interesting new analyses were presented on nivolumab; atezolizumab plus cobimetinib;

regorafenib; binimetinib, encorafenib, and cetuximab; oxaliplatin; and other treatments.

### Nivolumab With or Without Ipilimumab

The CheckMate 142 study evaluated nivolumab with or without

ipilimumab in patients with metastatic colorectal cancer and mismatch repair-deficient microsatellite instability (MSI) in a later-line setting.<sup>1,2</sup> This nonrandomized study had 2 cohorts: in one, 119 patients received a combination of nivolumab and ipilimumab,<sup>2</sup> and in the other, 74 patients received

nivolumab as a single agent.<sup>1</sup> Earlier data from this study, published in 2017, showed an overall response rate of 32% at 12.0 months of follow-up among patients treated with single-agent nivolumab, given at 3 mg/kg every 2 weeks.<sup>3</sup> A question was raised about the durability of these responses.

At the ASCO GI meeting, Dr Michael Overman provided an update for the monotherapy cohort, with a longer median follow-up of 21 months.<sup>1</sup> There was a minimal increase in the response rate, to 34%. The rate of complete responses, however, increased from 3% to 9%. Longer follow-up with single-agent PD-1 antibodies suggested that the quality of the response may improve. The responses were durable. An intriguing observation is an apparent plateau in the rate of progression-free survival, starting at approximately 9 months, which reaches approximately 40% to 45%. The analysis showed that the better the overall responses, such as complete response or stable disease, the longer the overall survival. However, this finding is not unusual.

Dr Thierry André provided updated results for combination therapy.<sup>2</sup> Nivolumab at 3 mg was given every 3 weeks with ipilimumab at 1 mg for the first 4 doses.<sup>2</sup> Nivolumab at 3 mg was continued every 2 weeks. It is important to mention that ipilimumab was discontinued after the first 4 doses. In this analysis, the median follow-up was 13 months. The overall response rate with the combination was 55% (vs 31% with the single agent). This response rate is remarkable. The plateau for progression-free survival was at approximately 70%, which was 20% to 25% higher than that for nivolumab alone. As mentioned, the combination regimen used a short course of ipilimumab at a lower dose than that seen in other trials. The side effects, particularly grade 3/4 events, were manageable. Ipilimumab is a CTLA-4 antibody, and more toxic than the programmed death 1 (PD-1)

antibody nivolumab. There were more autoimmune events with ipilimumab than nivolumab. However, at the schedule used in this trial, ipilimumab was well-tolerated.

With longer follow-up, the combination of nivolumab and ipilimumab may emerge as one of the best treatments for patients with colorectal cancer that has high MSI and is mismatch repair-deficient. It will be interesting to see how this combination works in earlier lines of treatment, particularly as compared with pembrolizumab. Nivolumab, as well as pembrolizumab, is approved for patients with mismatch repair deficient colorectal cancer. The combination of nivolumab plus ipilimumab is not yet approved.

### Atezolizumab Plus Cobimetinib

Dr Johanna Bendell presented a study of atezolizumab and cobimetinib in metastatic colorectal cancer.<sup>4</sup> Approximately 4% to 5% of patients with advanced disease are mismatch repair-deficient, and these patients are highly responsive to immunotherapy. The remaining 95% of patients with mismatch repair-proficient or microsatellite-stable tumors do not respond to immunotherapy. A goal in colorectal cancer would be to make these initially nonimmunogenic tumors immunogenic, so that these patients could benefit from immunotherapy.

In 2016, a study combining a MEK inhibitor, cobimetinib, with atezolizumab, a programmed death ligand 1 (PD-L1) antibody, showed interesting responses in a phase 1/1b cohort of 20 patients.<sup>5</sup> The idea of combining a MEK inhibitor with a PD-L1 antibody is intriguing from a preclinical perspective. There is a higher influx of T cells in the context of MEK inhibition, where there is higher expression of MLH1 and MHC antigens. There is more immunogenicity in these cancers and in preclinical models. Among the 20 patients in the phase 1/1b cohort, 4 responded to cobimetinib and atezolizumab. The sample size was small, but the data

were still intriguing because some of the responses were seen in patients with documented MSI cancers. For a few patients, the MSI status was unknown. These positive results led to an extension of this cohort, which now includes 84 patients.

At the ASCO GI meeting, Dr Bendell presented updated data for these patients.<sup>4</sup> Unfortunately, the response rate attenuated. With the addition of 64 patients, only 3 more responses were seen. Therefore, enthusiasm for the combination of cobimetinib and atezolizumab was dampened. The phase 1/1b results also led to the phase 3 COTEZO IMblaze370 trial (A Study to Investigate Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy Versus Regorafenib in Participants With Metastatic Colorectal Adenocarcinoma), which randomly assigned patients to cobimetinib plus atezolizumab, single-agent atezolizumab, or regorafenib in the later-line setting.<sup>6</sup> Results are expected in mid-2018. This registration study is targeting survival as the primary endpoint. It will be interesting to see whether results from the phase 1/1b study are maintained in the phase 3 study, possibly establishing a new standard of care.

### Regorafenib

Several studies shed new light on the use of regorafenib. This therapy was approved for metastatic colorectal cancer in 2012, based on results from the CORRECT trial (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy).<sup>7</sup> There have been some concerns regarding the toxicity of regorafenib when it is used at the standard starting dose of 160 mg (4 tablets). The side effects of regorafenib, in particular hand-foot skin reaction and fatigue, arise early in the treatment course. It was postulated that starting with a lower dose that is gradually raised could mitigate some of the early side effects. This question was evaluated in the phase 3 ReDOS trial (Regorafenib Dose Optimization

Study), which was presented by Dr Tanios Bekaii-Saab at the ASCO GI symposium.<sup>8</sup> The study randomly assigned 123 patients who were candidates for regorafenib to the package insert dose of 160 mg/day or an escalated dose that started at 80 mg/day for the first week and then increased to 120 mg/day and 160 mg/day in a weekly escalation schema. The primary endpoint was those patients who completed 2 cycles, which led them to the response evaluation by imaging, and then initiated the third cycle, which captured a composite endpoint of efficacy and toxicity. Patients would go beyond the scan only if they had been able to tolerate the treatment and could continue it, and also showed some efficacy (stable disease or better).

The primary endpoint was reached. In the standard-dosing arm of 160 mg/day, only 24% of patients started cycle 3 vs 43% of patients in the escalated dose arm ( $P=.0281$ ). This highly significant difference allowed patients in the escalated-dose arm to receive a longer duration of therapy. Interestingly, the secondary endpoint of overall survival showed a strong trend toward improvement, at 5.9 months with the standard dose vs 9.0 months with the escalated dose. The overall survival of 5.9 months is comparable with that in previous studies that established regorafenib as a standard-of-care later-line therapy. It is intriguing that modification of the dosing schedule to make regorafenib more tolerable and allow longer treatment might also contribute to better outcomes. It will be interesting to see how this strategy will be adopted into clinical practice, and whether it will be included in guidelines.

The REVERCE trial was an interesting study from Japan that evaluated sequencing of regorafenib and an epidermal growth factor receptor (EGFR) antibody in patients with *KRAS* wild-type tumors.<sup>9</sup> During the development of regorafenib, the CONCUR study

(Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) compared regorafenib vs placebo in a fairly heavily pretreated patient population in Asia.<sup>10</sup> Many of the patients had received treatment with biologic agents. Among patients in the CONCUR study who were less heavily pretreated, regorafenib had better efficacy than that seen in the Western CORRECT trial.<sup>7</sup>

The REVERCE study compared regorafenib followed by cetuximab vs cetuximab followed by regorafenib in approximately 100 patients.<sup>9</sup> Overall survival favored the regorafenib-first approach, at a median of 17.4 months, compared with 11.6 months with cetuximab first (hazard ratio, 0.61;  $P=.029$ ). This improvement was surprising. Breaking it down, progression-free survival was similar after the first phase of treatment with regorafenib or cetuximab. In the second phase of treatment, after patients switched therapy, cetuximab was more active than regorafenib. This finding supported previous observations that EGFR antibodies maintain their efficacy after several lines of therapy. In the United States, many physicians reserve EGFR antibodies for a later time point, and do not use them early enough, particularly with regard to the skin toxicities that can occur with these agents (and which are seen more frequently than with the vascular endothelial growth factor inhibitors, such as bevacizumab).

### **Binimetinib, Encorafenib, and Cetuximab**

The ongoing phase 3 BEACON study (Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA)/Irinotecan (FOLFIRI)/Cetuximab With a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients With *BRAF* V600E-Mutant Metastatic Colorectal Cancer) is evaluating

whether the addition of binimetinib, a MEK inhibitor, improves outcome when added to the BRAF inhibitor encorafenib and the EGFR inhibitor cetuximab in the second-line or third-line setting.<sup>11</sup> This study was underappreciated at the ASCO GI symposium. The study population consists of patients with *BRAF*<sup>V600</sup> mutant colorectal cancer. The control arm consists of irinotecan-based therapies, such as 5-fluorouracil, LV, and irinotecan (FOLFIRI) or irinotecan plus cetuximab.

Hopefully, the results of this trial will lead to a new standard of care. Among patients with the *BRAF*<sup>V600</sup> mutation, the standard of care regimen of irinotecan and cetuximab does not work well.<sup>12</sup> The BEACON study will accrue approximately 200 patients in each arm, and it is being used as a registration study for the US Food and Drug Administration. To confirm the safety of the triplet combination of binimetinib, encorafenib, and cetuximab, the study conducted a safety lead-in phase including 30 patients, 29 of whom had tumors with the *BRAF*<sup>V600</sup> mutation. (Enrollment of a patient who did not have the *BRAF*<sup>V600</sup> mutation was an oversight by the investigators.) Safety and efficacy data for these 29 patients were presented at the ASCO GI symposium. Patients with *BRAF*<sup>V600</sup> immune tumors have a poor prognosis, with a median survival of approximately 5 to 6 months. Few responses to treatment are seen. In the safety lead-in phase of the BEACON trial, none of the patients treated with the triplet therapy developed progressive disease. The response rate was more than 45%, and the median progression-free survival was 8 months. These data are very intriguing. Several of the patients continue to receive therapy more than a year after initiation of treatment, which is impressive in this setting. I am hopeful that this regimen will emerge as a standard of care.

These results are reminiscent of

those from the randomized SWOG 1406 study, which Dr Scott Kopetz presented at the 2017 ASCO GI symposium.<sup>12</sup> This study combined a BRAF inhibitor, vemurafenib, with the standard chemotherapies cetuximab and irinotecan. The use of an EGFR inhibitor in this setting, where BRAF is also inhibited, is mainly to block a feedback loop in which the MAP kinase pathway is inhibited by the BRAF inhibitor. The cancer cells try to reactivate the MAP kinase pathway by increasing agents of the signaling. This is where EGFR antibodies have a role. The efficacy data of the SWOG 1406 trial do not match the efficacy seen in the safety lead-in phase of the BEACON study.

### Oxaliplatin

The randomized phase 2 SAPPHERE study (Safety and Efficacy Study of mFOLFOX6 + Panitumumab Combination Therapy and 5-FU/LV + Panitumumab Combination Therapy in Patients With Chemotherapy-Naïve Unresectable Advanced Recurrent Colorectal Carcinoma) examined the duration of oxaliplatin-based therapy in patients with *KRAS* wild-type cancers who are first treated with FOLFOX plus panitumumab.<sup>13</sup> The study randomly assigned 114 patients to modified FOLFOX plus panitumumab, with oxaliplatin discontinued after 6 cycles (meaning after 12 weeks of therapy), or to continuation of the modified FOLFOX plus panitumumab combination regimen for another 6 cycles. The idea behind the study was to evaluate whether the combination of panitumumab plus fluorouracil/leucovorin without oxaliplatin is as effective in maintain-

ing the response achieved in the early phase of the induction treatment with the combination therapy.

Interestingly, when oxaliplatin was omitted from therapy after 6 cycles, there was no decrease in progression-free survival. In a Kaplan-Meier analysis, the progression-free survival curves almost completely overlapped. Therefore, it is safe to eliminate oxaliplatin from treatment. It is possible to maintain response with a combination of fluorouracil, leucovorin, and panitumumab in patients with *RAS* wild-type tumors. This finding is important because it allows us to potentially use oxaliplatin later and not treat patients to neurotoxicity, which is very much in line with the induction-maintenance approach,<sup>14</sup> which we have been using for patients treated with FOLFOX/CAPOX plus bevacizumab.

### Disclosure

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