Advances in Hematology
Part 2
ION Solutions Educational Programs

2017 Meeting Schedule

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All ION Solutions meeting materials are archived on iononline.com. Visit the website to view slides and videos from past meetings.

Registration will be available approximately 60 days prior to each event. To register, visit www.iononline.com.

*Meeting dates subject to change.*
Myriad is ION’s Preferred Partner for Best-In-Class Hereditary Cancer Testing & Services

Myriad provides a suite of solutions to allow you to confidently manage your patient’s comprehensive cancer risk based on your practice’s needs.

Preferred Partner Services

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- Practice-specific test ordering processes
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Myriad myRisk® hereditary cancer panel identifies patients at an elevated risk for cancer by analyzing 28 clinically significant genes associated with 8 important cancer sites.

The myRisk report includes the genetic test result and a comprehensive summary of medical society guidelines to inform your treatment decisions and optimize care.

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In this issue of Oncologistics, Dr. Lucio Gordan, director of Quality and Medical Informatics for Florida Cancer Specialists and Research Institute, delivers the second in a two-article series of the most significant presentations or abstracts presented at the 58th annual meeting of the American Society of Hematology (ASH). See page six for data in plasma cell dyscrasias, myeloproliferative neoplasms and myelodysplasia.

The Republican House of Representatives passed the American Health Care Act (AHCA) on May 4. It advanced to the Senate, where Republican Senators had their own vision of healthcare and began working on their own bill, the Better Care Reconciliation Act of 2017. On page 20, we explore how the AHCA will affect coverage and access for the estimated almost 15 million people living with cancer in the U.S.

At ION Solutions, we believe there is value in community oncology. As healthcare delivery evolves, we remain a steadfast partner to support community oncology practices with creative GPO partnering and contracting, educational events, practice advocacy and practice management resources to enable your practice to improve operational efficiency, financial performance and quality of care.

Thank you for your continued partnership,
Mark Santos
President, ION GPO
This is part two of the most salient presentations or abstracts presented at the American Society of Hematology in December 2016. This is written from one busy clinician to another, practicing hematology and oncology in the community setting. Part II focuses on plasma cell dyscrasias, myeloproliferative neoplasms and myelodysplasia. If you missed Part I, please see the spring 2017 issue of Oncologistics.
IFM Phase II Study: Carfilzomib, Revlimid, Dexamethasone (Krd) Induction and Consolidation Followed by Lenalidomide

**Authors:** Roussel M, et al. ASH 2016.abstract 1142

**Title:** Frontline Therapy with Carfilzomib, Lenalidomide and Dexamethasone (Krd) Induction Followed By Autologous Stem Cell Transplantation, KRd Consolidation and Lenalidomide Maintenance in Newly Diagnosed Multiple Myeloma (NDMM) Patients: Primary Results of the Intergroupe Francophone Du MyéLome (IFM) KRd Phase II Study

**Study Design:** This was an open-label multicentric single-arm study involving 46 patients younger than 65 years of age with newly diagnosed symptomatic multiple myeloma. Patients received induction chemotherapy with carfilzomib 36 mg/m² IV days 1, 2, 8, 9, 15, 16 plus lenalidomide 25 mg days 1-21, dexamethasone 20 mg days 1-2, 8-9, 15-16, 22-23. Subsequently, patients underwent consolidation peripheral blood stem cell harvesting with cyclophosphamide followed by high dose melphalan 200 mg/m² and autologous stem cell transplant (ASCT), then consolidation with carfilzomib 36 mg/m² IV days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg days 1-21, dexamethasone 20 mg days 1-2, 8-9, 15-16, 22-23 (cycles 5-8). Then patients were treated with maintenance lenalidomide 10 mg days 1-21 for 13 cycles.

**Objectives:** Primary endpoint was stringent complete remission at end of consolidation. The secondary endpoints included evaluation of minimal residual disease for patients who achieved greater than very good partial remission, progression-free survival and overall response at different times during the study.

**Results:** The overall response at the end of consolidation for 46 patients was 89%. Stringent CR 57%, MRD with flow cytometry 70%, MRD with Next-Generation Sequencing (NGS) 68%. Progression of disease was seen in only 1 patient (2%). Estimated 2 year progression-free survival is 91%. Two deaths were observed during the study, 1 during autologous stem cell transplant (ASCT) and 1 during followup.

**Toxicities:** Serious toxicities were seen in 30 out of 45 patients. Heart failure, pulmonary embolism, venous thrombosis, intracardiac thrombosis, superficial thrombosis, cardiac arrhythmias, hypertension were seen in 24 out of 45 patients.

**Conclusions:** This treatment protocol is very active with 70% of patients achieving negative MRD by Next-Gen Sequencing at the end of consolidation. Time to response appeared quicker with KRd regimen as opposed to VRD (bortezomib, lenalidomide, dexamethasone). This induction and treatment schema should be further evaluated.

Phase III STaMINA Clinical Trial

**Authors:** Stadtmauer A E, et al. ASH 2016.LBA-1.

**Title:** Comparison of Autologous Hematopoietic Cell Transplant (autoHCT), Bortezomib, Lenalidomide (Len) and Dexamethasone (RVD) Consolidation with Len Maintenance (ACM), Tandem Autohct with Len Maintenance (TAM) and Autohct with Len Maintenance (AM) for Up-front Treatment of Patients with Multiple Myeloma (MM): Primary Results from the Randomized Phase III Trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 – StaMINA Trial)

**Study Design:** ASCT-eligible patients, 758 patients, 70 years of age or younger, symptomatic multiple myeloma, received systemic chemotherapy and underwent ASCT with melphalan 200 mg/m². Objectives: These patients randomized to undergo single agent ASCT followed by maintenance divided in 3 groups:

Group 1 = 257 patients received lenalidomide 10 mg per day for 3 cycles and then 15 mg per day

Group 2 = 254 patients received bortezomib 1.3 mg/m² IV days 1, 4, 8, 11 plus lenalidomide 15 mg days 1-15, dexamethasone 40 mg IV days 1, 8 15 in a 28-day cycle

Group 3 = 247 patients received tandem autologous stem cell transplant with melphalan 200 mg/m² IV then lenalidomide maintenance until disease progression at 10 mg per day for 3 cycles, then 15 mg p.o. q.daily

Primary endpoint was progression-free survival at 38 months.

**Results:** There was no difference in progression-free survival, overall survival at 38 months among the 3 arms. There was also no difference for patients who were high risk versus standard risk.

**Toxicities:** No difference in incidence of secondary malignancies among different groups in the first 38 months of analysis.
**Daratumumab In Less Refractory Multiple Myeloma: Improvement in MRD.**

**Authors:** Avet-Loiseaw H, et al. ASH 2016.abstract 246

**Study Design:** Analysis of MRD in patients treated in POLLUX clinical trial with daratumumab plus Revlimid/dexamethasone versus Revlimid/dexamethasone alone as well as CASTOR study with daratumumab plus bortezomib/dexamethasone versus bortezomib/dexamethasone alone.

286 patients were in the POLLUX study and 251 patients in the CASTOR study.

**Results:** For all patients, 36.7% achieved MRD negativity or better in daratumumab plus Revlimid versus 8.2% Revlimid/dexamethasone alone in the POLLUX study. For all patients in the CASTOR study, 14.8% achieved better than 10-5 MRD negativity receiving daratumumab plus bortezomib/dexamethasone versus 3.2% in patients receiving bortezomib/dexamethasone alone. The benefit of daratumumab in achieving MRD negativity events accumulated and increased over time as the patients were followed and treated. In patients achieving complete remission or better, MRD negativity was doubled in patients receiving daratumumab/Revlimid/dexamethasone over Revlimid/dexamethasone alone in the POLLUX study. The benefit of daratumumab in achieving MRD negativity was valid with patients with high and standard cytogenetic risks, in both studies (POLLUX and CASTOR).

**Conclusions:** Patients achieving MRD negativity have 12-month progression-free survival greater than 90% regardless of what type of therapy is achieved. The addition of daratumumab to RD or VD brought significant improvement in progression-free survival, even in patients with MRD positivity. High risk patients were able to achieve MRD negativity with daratumumab and no patients achieving MRD negativity converted to MRD positivity while on daratumumab. Daratumumab added to RD or VD improved progression-free survival remarkably.

**Phase II Pembrolizumab, Pomalidomide, Dexamethasone For Relapsed Refractory Multiple Myeloma**

**Author:** Badros A Z, et al. ASH 2016.abstract 490

**Study Design:** 48 patients with relapsed refractory multiple myeloma, status post without lines of therapy, performance ECOG of 0 or 1 with adequate organ function and no active autoimmune disorder or history of treatment for severe autoimmune disease. Received pembrolizumab 200 mg IV on days 1, 14 plus pomalidomide 4 mg days 1-21, dexamethasone 40 mg p.o. days 1, 7, 14 and 21 every 28 days. Responders at 24 months were kept on pembrolizumab 20 mg IV monthly and previous same doses of pomalidomide dexamethasone.

**Results:** Overall response rate was 65% for all patients. Overall response rate was 68% for patients refractory to 2 classes of antimyeloma therapy. Overall response rate was 56% for patients with high risk cytogenetics. Median duration of response was 16 months, median progression-free survival 17.4 months and median overall survival was not reached. Progression-free survival appeared to be longer in low risk patients. Very good partial remission or better was high in patients with positive expression of PD-L1.

**Toxicities:** Grade 3 neutropenia occurred in greater than 30% of patients. Anemia, hyperglycemia occurred in 20% to 30% of patients (grade 3). Hypothyroid, pneumonitis, adrenal insufficiency, hepatitis was noted as well. Pneumonitis was seen in 12% of patients, hypothyroid 10%.

**Conclusions:** Additional pembrolizumab to standard therapy in multiple myeloma, either refractory, relapsed setting, warrants further studies.

**Myelodysplasia**

**Authors:** Garcia-Manero G et al. ASH 2016.abstract 244

**Study Design:** Open label, nonrandomized phase II trial with 6 treatment cohorts. The patients were 18 years of age or older with MDS with performance status ECOG 2 or less with adequate organ function.

There were 3 cohorts for hypomethylating agent failure. Cohort 1 was the nivolumab 3 mg/kg IV q.2 weeks (15 patients). Cohort 2 was ipilimumab 3 mg/kg IV q.3 weeks (n=18). Cohort 3 was nivolumab 3 mg/kg IV q.2 weeks plus ipilimumab 2 mg/kg q.4 weeks.

Treatment-naive cohorts included: cohort 4 = azacitidine 75 units/m2 IV x5 days q.4 weeks plus nivolumab 3 mg/kg IV on day 6 and day 20 (n=21). Cohort 5 included azacitidine 75 mg/m2 IV x5 days every 4 weeks plus ipilimumab 3 mg/kg on day 6. Cohort 6 was azacitidine 75 mg/m2 IV x5 days every 4 weeks plus nivolumab 3 mg/kg IV on day 6, day 20 plus ipilimumab 2 mg/kg IV on day 6.

**Results:** A total of 54 patients were treated. 62% were male. Bone marrow blasts, the average was 7%. 55% had a higher IPSS risk category.
With a short followup, i.e. median 3 cycles, nivolumab and ipilimumab were well tolerated as single agents or with azacitidine. There were approximately 30% overall response with ipilimumab single agent in patients who had failed HMA therapy. However, nivolumab as single agent did not show activity. Of note, 65% overall response rate was noted in patients who were previously untreated, who received azacitidine in combination with immunotherapy.

**Toxicities:** No unusual toxicity signals were noted.

**Conclusion:** Further studies are recommended to analyze the utility of ipilimumab and/or nivolumab in combination with hypomethylating agents or others in patients with myelodysplasia.

**Combination of Ruxolitinib Plus Azacitidine in Patients with Myelofibrosis**

**Authors:** Daver N, et al. ASH 2017.abstract 1127.

**Title:** Ruxolitinib (RUX) in Combination with 5-Azacytidine (AZA) As Therapy for Patients (pts) with Myelofibrosis (MF)

**Study Design:** Open label, nonrandomized phase II study. 44 patients newly diagnosed or with relapsed, refractory intermediate 1 risk, intermediate 2 risk or high risk myelofibrosis, previously untreated with ruxolitinib or 5- azacitidine, received 3 courses of ruxolitinib 15-20 mg p.o. b.i.d., i.e. 1-3 months of therapy, then followed by ruxolitinib 15-20 mg p.o. b.i.d. plus 5-azacitidine 25 mg/m2 IV daily days 1-5.

**Study Objectives:** Objective response rate defined as CR, PR and clinical improvement.

**Results:** Overall response was 69%. Clinical improvement as far as splenomegaly was 55%. There was 48% splenomegaly reduction by 50% at week 24. There was 79% splenomegaly reduction by 50% for the duration of this study. Improvement in bone marrow fibrosis was noted. Tolerability was acceptable and the degree of cytopenias was not necessarily worse as compared to ruxolitinib alone.

**Conclusion:** Further studies are recommended as far as the use of ruxolitinib plus 5-azacitidine in patients with myelofibrosis.

**Myelodysplasia**

**Title:** A Randomized Phase II Study of Low-Dose Decitabine Versus Azacitidine in Patients with Low- or Intermediate-1- Risk Myelodysplastic Syndromes: A Report on Behalf of the MDS Clinical Research Consortium

**Authors:** Jabbour E J, et al. ASH 2016.abstract 226.

**Study Design:** Adult patients with de novo secondary low or intermediated 1 IPSS risk MDS including CMML, status post ECOG 0-3 with adequate organ function and no prior HMA therapy. 113 patients were randomized to receive either decitabine 20 mg/m2 IV days 1-3 every 4 weeks (73 patients) or azacitidine 75 mg/m2 IV or sub cu days 1-3 q.4 weeks (40 patients). Randomization was done by bayesian adaptive design. Median followup of this study was 20 months.

**Objective:** The primary point of study was overall improvement rate including complete remission, partial remission, marrow complete remission or hematological improvement. Secondary endpoints were safety, cytogenetic response, transfusion dependence, event-free survival and overall survival.

**Results:** Overall response rate was 70% for patients receiving decitabine versus 49% patients receiving azacitidine. PRP value was 0.03 in favor of decitabine. Complete cytogenetic response plus partial cytogenetic response was seen in 61% of patients receiving decitabine versus 25% of patients receiving azacitidine with P value of 0.02. The stronger predictors of response were bone marrow blasts of 5% or more, CMML diagnosis, IPSS intermediate 1 risk.

**Toxicities:** Toxicities were as expected for this class of drugs. Cycle delays were noted more often at nearly 40% of the decitabine arm versus 20% azacitidine arm. Dose reductions are more often at 12% in decitabine arm versus 5% of patients receiving azacitidine.

**Conclusion:** Both low dose, hypomethylating agents showed activity. Overall response was 60% with 1 year event-free survival of 65% and 1 year overall survival of 85% for this patient population. As stated, decitabine showed a better overall response rate of 70% versus 49%, especially in patients with higher number of blasts in the bone marrow. Further studies are necessary to compare low dose decitabine, azacitidine which shortened duration of therapy, standard azacitidine versus best supportive care only in patients with low risk MDS.

Dr. Lucio Gordan, is the director of Quality and Medical Informatics for Florida Cancer Specialists and Research Institute.
STIVARGA® (regorafenib): NOW APPROVED
FOR PATIENTS WITH HEPATOCellular CARCINOMA (HCC)
PREVIOUSLY TREATED WITH NEXAVAR® (sorafenib)

Pivotal phase III RESORCE trial defines a new treatment plan in HCC that involves use of STIVARGA directly after progression on NEXAVAR

RESORCE (REGorafenib after SORafenib in patients with hepatoCEllular carcinoma) was an international, multicenter, randomized (2:1), double-blind, placebo-controlled phase III trial that evaluated the efficacy and safety of STIVARGA in patients with Child-Pugh A and Barcelona Clinic Liver Cancer Stage Category B or C HCC, with documented disease progression following sorafenib (N=573). Patients who permanently discontinued sorafenib due to toxicity or were unable to tolerate sorafenib doses of 400 mg once daily were ineligible.

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

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 hepatocellular carcinoma (HCC), there was no increase in the incidence of fatal hepatic failure as compared to placebo.

Please see additional Important Safety Information and brief summary of full Prescribing Information, including the Boxed Warning, on the following pages.
Pivotal phase III RESORCE trial defines a new treatment plan in HCC that

Prescribing Information, including the Boxed Warning, on the following pages.

pattern of injury. In hepatocellular carcinoma (HCC), there was no increase in the

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STIVARGA-treated patients across all clinical trials. In most cases, liver dysfunction

• Monitor hepatic function prior to and during treatment.

WARNING: HEPATOTOXICITY

Important Safety Information

Indication

randomized (2:1), double-blind, placebo-controlled phase III trial that evaluated the efficacy and safety of STIVARGA

RESORCE (REgorafenib after SORafenib in patients with hepatoCEllular carcinoma) was an international, multicenter,

Severe drug-induced liver injury with fatal outcome occurred in

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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

caus ed an increased incidence of hypertension (31% vs. 6% in

HCC). 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% vs 0.2%) 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 isch Emic

ev ents 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 therapy. 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 HCC

(≥30%): The most frequently observed adverse drug reactions

(≥30%) in STIVARGA-treated patients vs placebo-treated patients

in HCC, respectively, were: pain (55% vs 44%), HFSR/PPE (51%

vs 7%), asthenia/fatigue (42% vs 33%), diarrhea (41% vs 15%),

hypertension (31% vs 6%), infection (31% vs 18%), decreased

appetite and food intake (31% vs 15%).

Reference: STIVARGA Prescribing Information. Whippany, N J: Bayer

HealthCare Pharmaceuticals, Inc; April 2017.

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.

You are encouraged to report negative side effects or quality

complaints of prescription drugs to the FDA.

Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
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 (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy.

1.2 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 placebo arm, fatal hepatic failure occurred in 0.4% of patients in the placebo arm. In the 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 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 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 (3.3%) and systemic fungal infections (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 palmoplantar 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 (1.8% vs 0.4% versus <1%) and Grade 4 HFSR (0.3% vs 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 all 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)].

1.4 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.

5.6 Hypertension

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 usually attributable to the cerebral angiography procedure, 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 harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Regorafenib was embryotoxic and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, renal, skeletal and neurobehavioral anomalies. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception to prevent pregnancy during treatment with STIVARGA and for 2 months after the final dose. Advise males to use condoms with female partners to prevent pregnancy or use effective contraceptive methods 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)]
• Dermatologic Toxicity [see Warnings and Precautions (5.5)]
• Cardiac Ischemia and Infarction [see Warnings and Precautions (5.6)]
• Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [see Warnings and Precautions (5.7)]

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) 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; 61% men) with previously-treated metastatic colorectal cancer (CRC) received STIVARGA as a single agent at the dose of 160 mg orally 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.

Table 1: Adverse drug reactions reported in ≥10% of patients treated with STIVARGA in CORRECT and reported more commonly than in patients receiving placebo

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>STIVARGA (N=500)</th>
<th>Placebo (N=253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>64%</td>
<td>15%</td>
</tr>
<tr>
<td>Pain</td>
<td>59%</td>
<td>9%</td>
</tr>
<tr>
<td>Fever</td>
<td>28%</td>
<td>2%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite and food intake</td>
<td>47%</td>
<td>5%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFSR/PPE</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Rash</td>
<td>26%</td>
<td>6%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43%</td>
<td>8%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>33%</td>
<td>4%</td>
</tr>
<tr>
<td>Infectious and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>31%</td>
<td>9%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>30%</td>
<td>8%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>21%</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphonia</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
<td>1%</td>
</tr>
</tbody>
</table>

- Adverse reactions graded according to National Cancer Institute Common Toxicity for Adverse Events version 3.0 (NCI CTCAE v3.0).
- The term rash represents reports of events of drug eruption, rash, erethymatous rash, generalized rash, macular rash, maculopapular rash, papular rash, and pruritic rash.
- Fatal outcomes observed.

Table 2 provides laboratory abnormalities observed in CORRECT.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>STIVARGA (N=500)</th>
<th>Placebo (N=253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>79%</td>
<td>5%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>41%</td>
<td>2%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>54%</td>
<td>9%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>59%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>30%</td>
<td>7%</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>45%</td>
<td>10%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>65%</td>
<td>5%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45%</td>
<td>5%</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>84%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Adverse reactions graded according to NCI CTCAE v4.0.
- The term rash represents reports of events of rash, erethymatous rash, macular rash, maculopapular rash, papular rash, and pruritic rash.
- Fatal outcomes observed.
- Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

Table 4 provides laboratory abnormalities observed in GRID.
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 1. Adverse reactions requiring dose modification (interruption or discontinuation) were reported in 10.4% of STIVARGA-treated patients compared to ≤ 1% in placebo patients. The most common adverse reactions requiring dose modification/interruption were fatigue (5.1%) and diarrhea (5.3%). Adverse reactions that resulted in treatment discontinuation were reported in 1.6% of patients receiving STIVARGA and 0.7% in patients receiving placebo. Of the patients receiving STIVARGA, 15% were exposed to STIVARGA for greater than or equal to 12 months and 14% were exposed to STIVARGA for greater than or equal 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 who had their dose reduced. The 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 ≤ 1% 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 receiving RESORCE.

#### Table 5: Adverse reactions reported in ≥10% of patients treated with STIVARGA in RESORCE and reported more commonly than in patients receiving placebo

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>STIVARGA (N=374)</th>
<th>Placebo (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td></td>
<td>All %</td>
<td>≤ 3 %</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>HFSR/PPES</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>55</td>
<td>9</td>
</tr>
<tr>
<td>Asthenia/Fatigue</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Fever</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasticity</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite and food intake</td>
<td>31</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight loss</td>
<td>13</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasticity</td>
<td>10</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>STIVARGA (N=374)</th>
<th>Placebo (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>63</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>68</td>
<td>16</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>23</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>70</td>
<td>32</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>59</td>
<td>3 - d</td>
</tr>
<tr>
<td>Investigations</td>
<td>Increased Lipase</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

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

b NCI CTCAE v4.0.

c Based on urine protein-creatinine ratio data.

d No Grade 4 denoted in NCI CTCAE v4.0.
clinical exposure based on AUC). At doses ≥ 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, and dental malformations in the epiphyseal growth plate and dilitation 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 rabbits at the recommended dose). At doses of ≥ 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 fetal growth including missing kidney/urinary, small, deformed, and malpositioned kidney; and hydrenephrosis. 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 3-month 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 thinning 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 <ULN and AST > ULN, or total bilirubin > ULN to <1.5 times ULN) or moderate (total bilirubin >1.5 to <3 times ULN and any AST) hepatic impairment. [see Clinical Pharmacology (12.3)]. STIVARGA is not recommended for use in patients with severe hepatic impairment (total bilirubin >3x ULN) as STIVARGA has not been studied in this population.

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 overdosage. 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 abnormalities in the epididymal duct, epididymal sperm, and epididymal tissue. In male rats at doses similar to those in humans 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 33% 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 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 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 their 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)].

Drug Interactions
• 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)].

Dosage 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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Whippany, NJ 07981 USA
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67083068S
Practice Profile: Central Georgia Cancer Care

With changing regulations and seeing the move to quality care reimbursements, the oncologists at Central Georgia Cancer Care in Macon, Ga., and specifically one of the founders - Dr. Frederick Schnell - realized they had to change to keep up with the times. The practice worked diligently to become part of the Oncology Care Model program. Under the program the practice “committed to providing enhanced services to Medicare beneficiaries such as care coordination, navigation and national treatment guidelines for care.”

As Practice Administrator Louis Woessner notes, “The one constant in this practice is change.” In the four decades of practice, oncologists, clinicians and staff have had to adjust processes to stay profitable and be a source for cancer patients in the middle Georgia community. Some of the staff has been with the practice since its inception in the late 1970s.

Dr. Schnell and his partners routinely addressed changes in oncology care. One of which was bringing clinical research trials to patients for additional options in treatment. Central Georgia Cancer Care has offered the trials since 1985. The practice is involved with anywhere from 15 – 40 trials each year.

Not long before Woessner joined the practice of eight physicians, five mid-level providers and approximately 80 staff, Central Georgia Cancer Care signed on to be a member of Innovation Cancer. The practice has anywhere from 3,000 – 3,500 patient visits per month. Business Coaching has helped them with an external look at their processes and reporting, helping them to make improvements and efficiently use the data reporting systems like InfoDive and Protocol Analyzer. Both of those solutions were new to the practice in the past year.
The practice management believes that information and data is knowledge, and while it can be overwhelming at times, the reports from that data can make their jobs much easier.

Central Georgia Cancer Care knew their reports and reporting systems were good, but have been able to improve and identify reimbursement issues with GapFinder analysis.

In the past few years, Central Georgia Cancer Care revamped how they help patients. Their two locations had either a financial counselor or a nurse navigator to help the patients. Now they have combined those services so patients have a more streamlined continuum of care. Protocol Analyzer helps to create an estimate of treatment cost and the patient’s responsibility so the navigator can help ensure that co-pays and health and general wellness needs, including transportation, are met.

Woessner also credits Business Coaching with tightening up drug inventory management and validating those processes and procedures that the practice was already doing correctly.

In addition to the Business Coaching service from Innovation Cancer, Central Georgia Cancer Care takes advantage of the different educational services – from webinars on new reports out of InfoDive or marketing webinars and information which they forward to their local marketing agency.

With change being constant, Central Georgia Cancer Care is not sitting still. They realize the need to consistently attract new patients and will embark on a marketing campaign. The campaign will draw attention to cancer patients having a choice to be treated in a community setting. Woessner credits the caring and dedicated staff who are willing to adjust and make a difference in their patient’s care.

Central Georgia Cancer Care’s goal is “to provide premier oncology care and ensure the greatest level of patient satisfaction.”
4 Reasons You Should Consider an Innovation Cancer Business Coach

The primary benefit of Innovation Cancer membership is access to an expert Business Coach – leveraging their knowledge and expertise to help your practice drive success.

1. You are in the business of helping cancer patients.

You and your staff went to school to learn how to help patients through their cancer journey. Your focus was on finding the best treatments and understanding how to make your patient’s journey the easiest possible. Medical students and health-related majors in college typically do not take marketing, finance and accounting courses. A business coach will review your business operations and highlight where you can maximize your profitability – from changing the terms on your accounts receivable to reviewing your payer contracts to managing your drug inventory costs. The business coach looks at the “business” of your practice.

2. The reporting tools at your dispense can be daunting.

ION Solutions offers you many tools to help with financial reporting and finding those gaps. With so many tools, you could spend hours trying to find and analyze what is important to your own practice. Maybe your practice has two or three locations and you can only anecdotally determine how one location is doing over another. Or in a single location practice, maybe you need to understand how practitioners are benchmarked against others in similar practices regionally or nationwide. A business coach can help interpret that data to create meaningful and actionable tasks for your practice’s success.

3. You need to project next year’s growth.

Do you know where your patients are coming from? Are some referrals coming from a physician you’ve never spoken with? How does that physician know about you? With InfoDive, you can measure and determine your best referral sources. A business coach can take that data and help you create a plan for outreach – whether it’s through direct contact or marketing campaigns. The coach can put you in touch with the right resources to decide what is best for your practice – and how you can build stronger relationships with your referring practices.

4. That second set of eyes is important.

A business coach is an outside set of eyes looking at your business. The coaches—all who have years of experience as practice administrators and/or business consulting—have the knowledge to look at everything: drug inventory, billing and reimbursement methods, aligning staff needs within the practice for better efficiency, even looking at maximizing payer contracts. That objective “second set of eyes” will help you identify ways to maintain and grow profitability.

To learn more about how an Innovation Cancer business coach can help, please contact your ION Solutions strategic account manager or email info@innovationcancer.com

The business coaching received through Innovation Cancer provided our practice with an overview of our current practices, both financial and clinical, including what we are doing well and areas where we could do better. Our business coach was able to bring expertise and additional value by providing ideas on how to expand the use of available tools to optimize our processes.

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Tracie Whitley, RN, BSN, OCN
Practice Manager, Regional Medical Oncology Center
Your number one priority is the health of your patients. With the changing healthcare landscape, our number one priority is the business health of your practice.

Dedicated exclusively to the viability of community oncology, ION Solutions provides contracting, technology, education and advocacy support that ensures you have the tools to run your practice both efficiently and effectively. With the practice support of ION Solutions, you can navigate this changing environment and focus on providing quality care for your patients.

To learn how ION Solutions enables community oncology practices to improve operational efficiency, financial performance and quality of care, contact your Strategic Account Manager or visit IONonline.com.

To experience ION Solutions advocacy support, visit ourcommunitycounts.org.
How Would Cancer Patients Fare under the American Health Care Act?

By Scott Shields

Background

President Donald Trump was elected and Republicans maintained their majority in Congress in no small part due to their campaign promises to repeal and replace the Affordable Care Act (ACA). During the past few months, Republicans have learned that it can be easier to be united opposing a law than it is to find common ground in drafting an alternative.

After some back and forth, the Republican House of Representatives passed the American Health Care Act (AHCA) on May 4. It advanced to the Senate, where Republican Senators had their own vision of healthcare and began working on their own bill, the Better Care Reconciliation Act of 2017.

At press time, the Senate had just released a discussion draft of the Better Care Reconciliation Act, but had not voted. Should the bill pass the Senate, the two chambers of Congress would likely meet in conference to hash out the differences, vote on the resulting legislation and present to President Trump to sign it into law.

In the meantime, it is instructive to explore how the AHCA – the most complete bill of the House and Senate versions of healthcare reform – will affect coverage and access for the estimated almost 15 million people living with cancer in the U.S. (as of 2014).

In the short term, the most critical sections of the AHCA for cancer patients are the consumer protections. The ACA added many consumer protections that benefited cancer patients, so comparing the two pieces of legislation offers a quick thumbnail sketch of how the AHCA may affect cancer patients.
Insurance Coverage

The Congressional Budget Office (CBO) estimated that, in 2018, 14 million more people would be uninsured under the AHCA than under current law, increasing to a total of 23 million uninsured people after 10 years. Many of the newly uninsured will be cancer patients who then will be scrambling to pay for their treatments.

Verdict: ACA > AHCA

Medicaid

The AHCA will cut Medicaid spending by $834 million, which would affect low- and moderate-income Americans. It would replace the current system of an unlimited spending ceiling with a fixed “per-capita cap,” with each state having a fixed amount of federal spending each year. States would be responsible for 100 percent of Medicaid costs above the per-capita cap, unlike the current system in which the federal government contributes a “match” with no spending limit.

Under the new system, states will probably have to reorganize and reallocate their spending, perhaps along the lines of Oregon’s Medicaid program, which rations benefits.

Verdict: ACA > AHCA

Changes in Insurance Costs

Under the ACA, subsidies are tied to the person’s income and to the cost of insurance where they live. Under the AHCA, people will still receive subsidies in the insurance exchanges, but the amount would be tied to a person’s age.

VERDICT:
For Younger / Higher Income / Living in Area with Lower Premiums: AHCA > ACA
For Older / Lower Income / Living in Area with Higher Premiums: ACA > AHCA

Verdict: ACA > AHCA

Insurance Mandate

Unlike the ACA, the AHCA does not require qualifying Americans to purchase health insurance or pay a tax penalty. However, the AHCA would charge anyone who foregoes health insurance for more than two months a 30 percent premium surcharge on any new plans.

This provision would neither advantage nor disadvantage cancer patients. Virtually every diagnosed cancer patient would prefer to have insurance coverage, so a mandate to purchase insurance is immaterial.

VERDICT: AHCA = ACA

Guaranteed Coverage

The ACA offered tremendous protections to Americans with pre-existing medical conditions, including cancer. The ACA prohibited insurers from denying health insurance to people with pre-existing medical conditions. Additionally, the ACA could not charge people with pre-existing conditions more for health insurance, and the law eliminated insurers from imposing annual or lifetime limits on insurance costs. These protections provided cancer patients with a sense of security they had not had before, given the high cost of cancer treatment.

The ACA also required all insurers “essential health benefits,” a package of benefits that includes emergency room visits, prescription drugs, mental health services and preventive care and screenings – all important to treating and surviving cancer.

The AHCA would retain the ACA’s pre-existing-condition exclusion clause; however, it would allow states to seek waivers from several consumer protections, including essential health benefits. Due to how the ACA is written, insurance benefits that are not part of the essential health benefits are subject to annual and lifetime limits. Cancer patients in states that seek waivers from essential health benefits may run into pre-ACA problems, such as not having prescription-drug coverage, or reaching annual or lifetime limits of healthcare costs.

VERDICT: ACA > AHCA
Table 1. Summary - Which Health Insurance Law is Better for Cancer Patients?

<table>
<thead>
<tr>
<th>Provision</th>
<th>Is ACA or AHCA Better for Cancer Patients</th>
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<tbody>
<tr>
<td>Insurance Coverage</td>
<td>ACA</td>
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<tr>
<td>Medicaid Enrollment</td>
<td>ACA</td>
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<tr>
<td>Changes in Insurance Cost</td>
<td>Depends</td>
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<tr>
<td>Individual Mandate</td>
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<tr>
<td>Guaranteed Coverage</td>
<td>ACA</td>
</tr>
<tr>
<td>Summary</td>
<td>3 ACA, 0 AHCA</td>
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</tbody>
</table>

**Conclusion**

By almost every measure, the ACA offers far greater protection and benefits to cancer patients than the AHCA but the AHCA is still evolving. Some would say that it is possible the ACA may eventually strain the federal government’s financial resources, whereas the AHCA may place the country on a stronger fiscal footing, thus allowing more cancer patients to be treated further into the future.

Nevertheless, should a patient be diagnosed with cancer today, he or she would undeniably be better off with the ACA being the prevailing healthcare law, given the greater number of Americans who would have health insurance and the better protections offered by that health insurance.

Scott Shields is the associate director of Health Policy with Xcenda.

Taking a Deeper Dive into MIPS

The information for this article was taken from a webinar, “Diving Into the Details of MIPS”, presented by the Quality Reporting Engagement Group. If you have any questions, send an email to insidesales@iononline.com or call 877-570-8721 x2.

Understanding who is Eligible and Registration Methods

As patients look to the Internet to make healthcare decisions, particularly on the quality of a physician or practice, CMS has designed a website to help consumers make informed choices about care they receive through Medicare. The site, www.medicare.gov/physiciancompare/, will indicate - by a green check mark next to the name - if quality performance scores are posted. The information for that data will be taken from reporting under the Quality Payment Program.

This year, physicians and practices are faced with reporting health data to CMS for the Quality Payment Program under two tracks – the Merit-based Incentive Payment System (MIPS) and Advanced Alternative Payment Models (APMs). In May, practices are receiving a letter from CMS (acknowledged by their taxpayer identification number) letting the practice know whether or not clinicians in their group must participate in MIPS in 2017, or whether they are exempt. The eligibility is calculated by CMS using both historical data and claims data. With the changes in the final rulings, CMS is protecting more small and independent practices where approximately 225,000 more clinicians will meet the low-volume thresholds.

It is important for practices to understand where their clinicians are categorized for this year, and to make sure they look at all clinicians.

Some clinicians will be excluded from MIPS this year because they are enrolled in Medicare for the first time during this performance year; others because they see a low volume of Medicare patients (less or equal to $30K in Medicare Part B or 100 or fewer Medicare Part B patients) OR the clinician significantly participated in an Advanced APM and earned the status of QP – qualified participant. (NOTE: Those clinicians participating in an Advanced APM and earned the status ‘partial QP’ can choose whether or not to participate; but if not, will not receive a payment adjustment under the QPP)

In addition, there are special rules for non-patient facing providers (examples: pathology, diagnostic radiology, etc.), as well as physicians who are in designated rural areas. (More information on rules for the non-patient facing clinicians will be provided at a later date once CMS makes them available.)

Registration

The only two registration requirements for practices to participate in 2017 are Web Interface and CAHPS Survey. Clinicians who plan to participate in MIPS through any other submission mechanism do not need to register.

The place to register or check to see if your practice is already registered is at www.qpp.cms.gov – with a valid EIDM account and access to your PV-PQRS role. Previously registered groups under PQRS may be automatically registered under the Web Interface, and will need to cancel their registration if a different submission method is chosen. The deadline for registration is June 30.

Under the Web Interface for groups of 25+ clinicians, CMS has already pre-selected 15 quality measures that must be reported for a required number of patients for the year. If CMS has determined that your assigned beneficiaries are less than 248, your group will have to report on 100 percent of those beneficiaries. In addition, the Web Interface will satisfy only the Quality category. Practices and clinicians will be required to report 90 days of data for Advancing Care Information (ACI) and Improvement Activities (IA).
Under the CAHPS Survey (Consumer Assessment of Healthcare Providers and Systems), practices can elect to have the survey administered to their patients. A CMS-certified vendor will be required to administer that survey, but the list for certified vendors for 2017 has not been released. Practices interested in this method are advised to contact a vendor from the 2016 certified vendor list to see if they are asking to be certified for 2017. This survey will count toward the Quality category, and will also count as a high-weighted Improvement Activity.

**Non-Patient Facing Clinicians**

How do you determine a non-patient facing eligible clinician in your practice who still has to report for the Quality Payment Program under MIPS?

CMS is conducting eligibility determinations based on claims data from Sept. 1, 2015, through August 31, 2016, and another period from Sept. 1, 2016, through August 31, 2017. Non-patient facing clinicians who have been identified in the first period will not have their status change because of data in the second period – that will just be used to identify more who may have been missed during the first determination set. This information will be updated on the CMS website, https://qpp.cms.gov, at a later date.

Clinicians who bill 100 or fewer patient-facing encounters (claims that include E&M codes, surgical procedure codes and visit codes) will be considered non-patient facing. Groups are considered non-patient facing if more than 75 percent of those clinicians are determined non-patient facing. A group is defined as one that CMS would identify by a single tax identifier.

CMS will also use Medicare telehealth service claims in the determination. For a full list of those codes, visit: www.cms.gov/Medicare/Medicare-General-Information/Telehealth/Telehealth-Codes.html

How non-patient facing clinicians will participate in MIPS is slightly different than other clinicians. In addition to not having to report in the ACI (Advancing Care Information) category, they will have a re-weighted performance score with the Quality category set at 85 percent of the total. Groups that elect to report using the CAHPS survey for MIPS (Consumer Assessment of Healthcare Providers and Systems) will not have those non-patient facing clinicians as focal providers.

There are a number of specialty measure sets for clinicians under Pathology, Diagnostic Radiology, Anesthesiology, etc. that can be viewed at https://qpp.cms.gov/measures/quality. Many quality measures for non-patient facing clinicians will be able to be reported through qualified registries. It is also suggested that specialists contact their specialty society to see if they have compiled a suggested list of measures.

Non-patient-facing clinicians must also report on Improvement Activities (IA) as 15 percent of the total score. Requirements include one high-weighted activity or two medium-weighted activities.

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Learn more by viewing the “Diving Into the Details of MIPS” webinar. Go to www.iononline.com, click on Meetings and Webcasts and go to the Webcast Archives.
Shrinking margins have pushed independent specialty practices to place even greater focus on operational efficiency. In response, successful practices have turned to their GPO and distribution partner for customized inventory management, as well as integrated technologies and business consulting, to increase time with patients. Improving cash flow takes a streamlined workflow. It takes AmerisourceBergen.
“Just like any other morning, our Customer Service reps were busy on the phones taking orders when all of the sudden, the entire office began slowly filling up with smoke. Alarms started blaring and safety lights began flashing in this blinding white light. But once we learned it was a smoke event and not an actual fire, we did what we always do—we kept working. As the smoke got heavier, the CSR’s were lying on the floor where the air was still clear, taking orders on notepads! I was running from phone to phone, manually transferring calls so we could set up a make-shift call center in our distribution center across the parking lot. That is until the fireman began forcing us to get out of the building and chasing me through the cubicles. He may have been bigger, but I was faster! But what he didn’t realize is that just like him, we, too, work to help save lives every single day.”

Because at Oncology Supply, we believe a cancer patient needs a hero, too.

– C. Oldham
Customer Service Manager
Oncology Supply (16 years)