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New Insights Into GIST Epidemiology and Risk of Additional Cancers

Tracking the Trials and Progress of Drugs in the Pipeline

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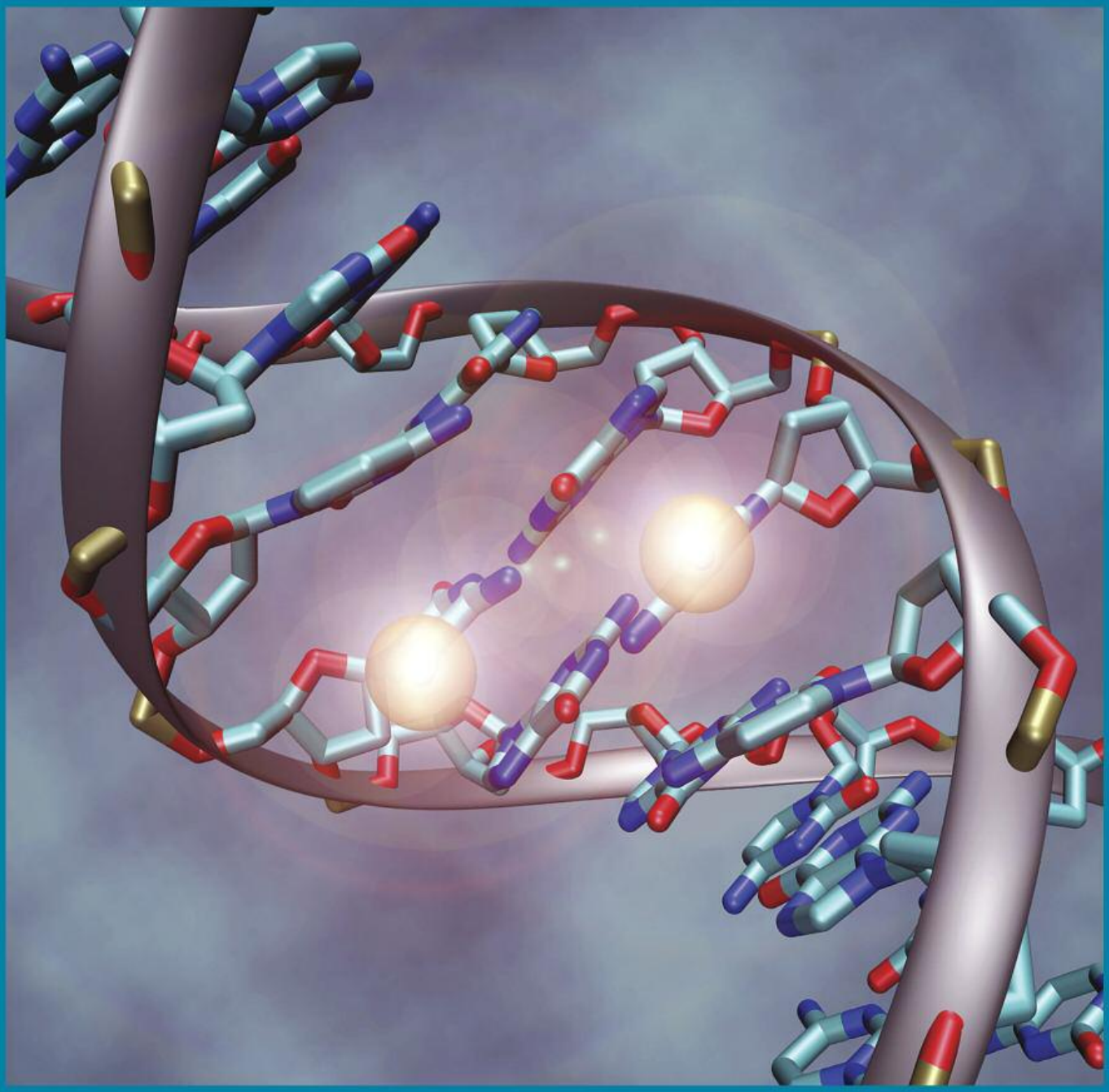

An Educational Service for Medical Oncologists, Gastroenterologists and other GIST Care Providers

SUTENT® IN TOUCH
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SUTENT IN TOUCH: Connecting your patients to our Certified Oncology Nurses to help support them during treatment.

SUTENT IN TOUCH PROVIDES:

Certified Oncology Nurses (CONs) —Trained to support your SUTENT patients, these nurses provide timely information, including tips to help manage certain adverse reactions.

Tools to Keep Patients on Track —Throughout treatment, patients receive calls, e-mails, and mailings timed to align with their treatment schedule.

YOUR PATIENTS CAN ENROLL BY:

- **Returning the business reply card in the SUTENT Patient Resource Kit**
- **Visiting SUTENT.com/in-touch-program**
- **Calling 1-877-5-SUTENT (1-877-578-8368)**

SUTENT® (sunitinib malate) is indicated for the treatment of advanced renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate, and progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.

Important Safety Information

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported.

Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

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- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Given the potential for serious adverse reactions (ARs) in nursing infants, a decision should be made whether to discontinue nursing or SUTENT.
- Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.
- SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsades de Pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.
- Hypertension may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.
- There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS).
- Hemorrhagic events, including tumor-related hemorrhage such as pulmonary hemorrhage, have occurred. Some of these events were fatal. Perform serial complete blood counts (CBCs) and physical examinations.
- Cases of tumor lysis syndrome (TLS) have been reported primarily in patients with high tumor burden. Monitor these patients closely and treat as clinically indicated.
- Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients who received SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.
- Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose-reduce if 24-hour urine protein is ≥3 g; discontinue SUTENT in cases of nephrotic syndrome or repeat episodes of urine protein ≥3 g despite dose reductions.
- Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, treatment must not be re-started.
- Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.
- Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, and treat per standard medical practice.
- SUTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness or require hospitalization. Reductions in blood glucose levels may be worse in patients with diabetes. Check blood glucose levels regularly during and after discontinuation of SUTENT. Assess whether antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.
- Osteonecrosis of the jaw (ONJ) has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving bisphosphonates.
- Cases of impaired wound healing have been reported. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures.
- Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.
- CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.
- Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St. John's Wort.
- The most common ARs occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%). The most common grade 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) were fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%).
- The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) included lymphocytes (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytes (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%).
- The most common ARs occurring in ≥20% of patients with GIST and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (40% vs 27%), anorexia (33% vs 29%), skin discoloration (30% vs 23%), mucositis/stomatitis (29% vs 18%), asthenia (22% vs 11%), altered taste (21% vs 12%), and constipation (20% vs 14%). The most common grade 3/4 ARs (occurring in ≥4% of patients with GIST receiving SUTENT vs placebo) were asthenia (5% vs 3%), hand-foot syndrome (4% vs 3%), diarrhea (4% vs 0%), and hypertension (4% vs 0%).
- The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with GIST receiving SUTENT vs placebo) included lipase (10% vs 7%), neutrophils (10% vs 0%), amylase (5% vs 3%), and platelets (5% vs 0%).
- The most common ARs occurring in ≥20% of patients with advanced pNET and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (59% vs 39%), stomatitis/oral syndromes (48% vs 18%), nausea (45% vs 29%), abdominal pain (39% vs 34%), vomiting (34% vs 31%), asthenia (34% vs 27%), fatigue (33% vs 27%), hair color changes (29% vs 1%), hypertension (27% vs 5%), hand-foot syndrome (23% vs 2%), bleeding events (22% vs 10%), epistaxis (21% vs 5%), and dysgeusia (21% vs 5%). The most commonly reported grade 3/4 ARs (occurring in ≥5% of patients with advanced pNET receiving SUTENT vs placebo) were hypertension (10% vs 1%), hand-foot syndrome (6% vs 0%), stomatitis/oral syndromes (6% vs 0%), abdominal pain (5% vs 10%), fatigue (5% vs 9%), asthenia (5% vs 4%), and diarrhea (5% vs 2%).
- The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with advanced pNET receiving SUTENT vs placebo) included decreased neutrophils (16% vs 0%), increased glucose (12% vs 18%), increased alkaline phosphatase (10% vs 11%), decreased phosphorus (7% vs 5%), decreased lymphocytes (7% vs 4%), increased creatinine (5% vs 5%), increased lipase (5% vs 4%), increased AST (5% vs 3%), and decreased platelets (5% vs 0%).

Please see full Prescribing Information, including Boxed Warning, attached.

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  Printed in USA/June 2015

References: 1. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2009;27(22):3584-3590. **2.** Clinical Trials website. SU011248 versus interferon-alfa as first-line systemic therapy for patients with metastatic renal cell carcinoma. https://clinicaltrials.gov/ct2/show/results/NCT00083889. Accessed May 20, 2015. **3.** Data on file. Pfizer Inc, New York, NY.

SUTENT® (SUNITINIB MALATE) CAPSULES, ORAL

Brief Summary of Prescribing Information

WARNING: HEPATOTOXICITY
Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. *[See Warnings and Precautions]*

INDICATION AND USAGE: SUTENT is indicated for the treatment of advanced renal cell carcinoma (RCC).

DOSAGE AND ADMINISTRATION

Recommended Dose. The recommended dose of SUTENT for advanced RCC is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.

Dose Modification. Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability.

A dose reduction for SUTENT to a minimum of 37.5 mg daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor.

A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Safety in patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN has not been established.

Pregnancy. SUTENT can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Cardiovascular Events. In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline. Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving interferon-α (IFN-α).

In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

QT Interval Prolongation and Torsade de Pointes. SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered *[see Dosage and Administration]*.

Hypertension. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

Of patients receiving SUTENT for treatment-naïve RCC, 127/375 patients (34%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 50/375 treatment-naïve RCC patients (13%) on SUTENT compared to 1/360 patients (<1%) on IFN-α. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-naïve RCC study. Four treatment-naïve RCC patients, including one with malignant hypertension, discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 32/375 treatment-naïve RCC patients (9%) on SUTENT and 3/360 patients (1%) on IFN-α.

Hemorrhagic Events. Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In patients receiving SUTENT in a clinical trial for treatment-naïve RCC, 140/375 patients (37%) had bleeding events compared with 35/360 patients (10%) receiving IFN-α. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. Most events in RCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naïve patient.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Cases of pulmonary hemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with SUTENT. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Tumor Lysis Syndrome (TLS). Cases of TLS, some fatal, have occurred in patients treated with SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

Thrombotic Microangiopathy. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

Proteinuria. Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalyses during treatment, with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose reduce for 24-hour urine protein ≥ 3 grams. Discontinue SUTENT for patients with nephrotic syndrome or repeat episodes of urine protein ≥ 3 grams despite dose reductions. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

Dermatologic Toxicities. Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of SJS, TEN, or EM (e.g., progressive skin rash often with blisters or mucosal lesions) are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, SUTENT treatment must not be re-started.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with SUTENT, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

Thyroid Dysfunction. Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, on SUTENT treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Hypothyroidism was reported as an adverse reaction in sixty-one patients (16%) on SUTENT in the treatment-naïve RCC study and in three patients (1%) in the IFN-α arm.

Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

Hypoglycemia. SUTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness, or require hospitalization. Hypoglycemia has occurred in clinical trials in 2% of the patients treated with SUTENT for RCC. Reductions in blood glucose levels may be worse in diabetic patients. Check blood glucose levels regularly during and after discontinuation of treatment with SUTENT. Assess if anti-diabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Osteonecrosis of the Jaw (ONJ). ONJ has been observed in clinical trials and has been reported in post-marketing experience in patients treated with SUTENT. Concomitant exposure to other risk factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw.

Wound Healing. Cases of impaired wound healing have been reported during SUTENT therapy. Temporary interruption of SUTENT therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Adrenal Function. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation.
None of these patients were reported to have clinical evidence of adrenal insufficiency.

Laboratory Tests. CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 660 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of gastrointestinal stromal tumor (GIST), an active-controlled trial (n=375) for the treatment of RCC or a placebo-controlled trial (n=83) for the treatment of pancreatic neuroendocrine tumors (pNET). The RCC patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.

The most common adverse reactions (≥20%) in patients with GIST, RCC or pNET are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in *Warnings and Precautions*. Other adverse reactions occurring in RCC studies are described below.

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 rates observed in practice.

Adverse Reactions in the Treatment-Naïve RCC Study. The as-treated patient population for the treatment-naïve RCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4 - 46.1) for SUTENT treatment and 4.1 months (range: 0.1 - 45.6) for IFN-α treatment. Dose interruptions occurred in 202 patients (54%) on SUTENT and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on SUTENT and 98 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for SUTENT and 24% for IFN-α. Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 77% versus 55% of patients on SUTENT versus IFN-α, respectively.

The following table compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-α.

Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α*

	SUTENT (n=375)		IFN-α (n=360)	
Adverse Reaction, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any	372 (99)	290 (77)	355 (99)	197 (55)
Constitutional				
Fatigue	233 (62)	55 (15)	202 (56)	54 (15)
Asthenia	96 (26)	42 (11)	81 (22)	21 (6)
Fever	84 (22)	3 (1)	134 (37)	1 (<1)
Weight decreased	60 (16)	1 (<1)	60 (17)	3 (1)
Chills	53 (14)	3 (1)	111 (31)	0 (0)
Chest Pain	50 (13)	7 (2)	24 (7)	3 (1)
Influenza like illness	18 (5)	0 (0)	54 (15)	1 (<1)
Gastrointestinal				
Diarrhea	246 (66)	37 (10)	76 (21)	1 (<1)
Nausea	216 (58)	21 (6)	147 (41)	6 (2)
Mucositis/stomatitis	178 (47)	13 (3)	19 (5)	2 (<1)
Vomiting	148 (39)	19 (5)	62 (17)	4 (1)
Dyspepsia	128 (34)	8 (2)	16 (4)	0 (0)
Abdominal pain[c]	113 (30)	20 (5)	42 (12)	5 (1)
Constipation	85 (23)	4 (1)	49 (14)	1 (<1)
Dry mouth	50 (13)	0 (0)	27 (7)	1 (<1)
GERD/reflux esophagitis	47 (12)	1 (<1)	3 (1)	0 (0)
Flatulence	52 (14)	0 (0)	8 (2)	0 (0)
Oral pain	54 (14)	2 (<1)	2 (1)	0 (0)
Glossodynia	40 (11)	0 (0)	2 (1)	0 (0)
Hemorrhoids	38 (10)	0 (0)	6 (2)	0 (0)
Cardiac				
Hypertension	127 (34)	50 (13)	13 (4)	1 (<1)
Edema, peripheral	91 (24)	7 (2)	17 (5)	2 (1)
Ejection fraction decreased	61 (16)	10 (3)	19 (5)	6 (2)
Dermatology				
Rash	109 (29)	6 (2)	39 (11)	1 (<1)
Hand-foot syndrome	108 (29)	32 (8)	3 (1)	0 (0)
Skin discoloration/ yellow skin	94 (25)	1 (<1)	0 (0)	0 (0)
Dry skin	85 (23)	1 (<1)	26 (7)	0 (0)
Hair color changes	75 (20)	0 (0)	1 (<1)	0 (0)
Pruritus	44 (12)	1 (<1)	24 (7)	1 (<1)

Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α* (cont'd)

Adverse Reaction, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	All Grades	Grade 3/4[a]	All Grades	Grade 3/4[b]
Neurology				
Altered taste[d]	178 (47)	1 (<1)	54 (15)	0 (0)
Headache	86 (23)	4 (1)	69 (19)	0 (0)
Dizziness	43 (11)	2 (<1)	50 (14)	2 (1)
Musculoskeletal				
Back pain	105 (28)	19 (5)	52 (14)	7 (2)
Arthralgia	111 (30)	10 (3)	69 (19)	4 (1)
Pain in extremity/ limb discomfort	150 (40)	19 (5)	107 (30)	7 (2)
Endocrine				
Hypothyroidism	61 (16)	6 (2)	3 (1)	0 (0)
Respiratory				
Cough	100 (27)	3 (1)	51 (14)	1 (<1)
Dyspnea	99 (26)	24 (6)	71 (20)	15 (4)
Nasopharyngitis	54 (14)	0 (0)	8 (2)	0 (0)
Oropharyngeal Pain	51 (14)	2 (<1)	9 (2)	0 (0)
Upper respiratory tract infection	43 (11)	2 (<1)	9 (2)	0 (0)
Metabolism/Nutrition				
Anorexia[e]	182 (48)	11 (3)	153 (42)	7 (2)
Hemorrhage/Bleeding				
Bleeding, all sites	140 (37)	16 (4)[f]	35 (10)	3 (1)
Psychiatric				
Insomnia	57 (15)	3 (<1)	37 (10)	0 (0)
Depression[g]	40 (11)	0 (0)	51 (14)	5 (1)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), dyspnea (<1%), asthenia (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%).
[b]Grade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%), abdominal pain (<1%) and depression (<1%).
[c]Includes flank pain
[d]Includes ageusia, hypogeusia and dysgeusia
[e]Includes decreased appetite
[f]Includes one patient with Grade 5 gastric hemorrhage
[g]Includes depressed mood

Treatment-emergent Grade 3/4 laboratory abnormalities are presented below.

Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve RCC Patients Who Received SUTENT or IFN-α

Laboratory Parameter, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	All Grades*	Grade 3/4*[a]	All Grades*	Grade 3/4*[b]
Gastrointestinal				
AST	211 (56)	6 (2)	136 (38)	8 (2)
ALT	192 (51)	10 (3)	144 (40)	9 (2)
Lipase	211 (56)	69 (18)	165 (46)	29 (8)
Alkaline phosphatase	171 (46)	7 (2)	132 (37)	6 (2)
Amylase	130 (35)	22 (6)	114 (32)	12 (3)
Total bilirubin	75 (20)	3 (1)	8 (2)	0 (0)
Indirect bilirubin	49 (13)	4 (1)	3 (1)	0 (0)
Renal/Metabolic				
Creatinine	262 (70)	2 (<1)	183 (51)	1 (<1)
Creatine kinase	183 (49)	9 (2)	40 (11)	4 (1)
Uric acid	173 (46)	54 (14)	119 (33)	29 (8)
Calcium decreased	156 (42)	4 (1)	145 (40)	4 (1)
Phosphorus	116 (31)	22 (6)	87 (24)	23 (6)
Albumin	106 (28)	4 (1)	72 (20)	0 (0)
Glucose increased	86 (23)	21 (6)	55 (15)	22 (6)
Sodium decreased	75 (20)	31 (8)	55 (15)	13 (4)
Glucose decreased	65 (17)	0 (0)	43 (12)	1 (<1)
Potassium increased	61 (16)	13 (3)	61 (17)	15 (4)
Calcium increased	50 (13)	2 (<1)	35 (10)	5 (1)
Potassium decreased	49 (13)	3 (1)	7 (2)	1 (<1)
Sodium increased	48 (13)	0 (0)	38 (10)	0 (0)
Hematology				
Neutrophils	289 (77)	65 (17)	178 (49)	31 (9)
Hemoglobin	298 (79)	29 (8)	250 (69)	18 (5)
Platelets	255 (68)	35 (9)	85 (24)	2 (1)
Lymphocytes	256 (68)	66 (18)	245 (68)	93 (26)
Leukocytes	293 (78)	29 (8)	202 (56)	8 (2)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (14%), lipase (3%), neutrophils (2%), lymphocytes (2%), hemoglobin (2%), platelets (1%), amylase (1%), ALT (<1%), creatine kinase (<1%), creatinine (<1%), glucose increased (<1%), calcium decreased (<1%), phosphorous (<1%), potassium increased (<1%), and sodium decreased (<1%).
[b]Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lymphocytes (2%), lipase (1%), neutrophils (1%), amylase (<1%), calcium increased (<1%), glucose decreased (<1%), potassium increased (<1%) and hemoglobin (<1%).

Venous Thromboembolic Events. Thirteen (3%) patients receiving SUTENT for treatment-naïve RCC had venous thromboembolic events reported. Seven (2%) of these patients had pulmonary embolism, one was Grade 2 and six were Grade 4, and six (2%) patients had DVT, including three Grade 3. One patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption occurred in two patients with pulmonary embolism and one with DVT. In treatment-naïve RCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolism, all Grade 4.

Reversible Posterior Leukoencephalopathy Syndrome. There have been reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Pancreatic and Hepatic Function. If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve RCC compared to 1 (<1%) patient receiving IFN-α. Hepatotoxicity was observed in patients receiving SUTENT *[See Boxed Warning and Warnings and Precautions]*.

Post-marketing Experience. The following adverse reactions have been identified during post-approval use of SUTENT. 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.

Blood and lymphatic system disorders: hemorrhage associated with thrombocytopenia*. Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Gastrointestinal disorders: esophagitis.

Hepatobiliary disorders: cholecystitis, particularly acalculous cholecystitis.

Immune system disorders: hypersensitivity reactions, including angioedema.

Infections and infestations: serious infection (with or without neutropenia)*; necrotizing fasciitis, including of the perineum*. The infections most commonly observed with sunitinib treatment include respiratory, urinary tract, skin infections and sepsis/septic shock.

Musculoskeletal and connective tissue disorders: fistula formation, sometimes associated with tumor necrosis and/or regression*; myopathy and/or rhabdomyolysis with or without acute renal failure*. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Renal and urinary disorders: renal impairment and/or failure*; proteinuria; rare cases of nephrotic syndrome. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome.

Respiratory disorders: pulmonary embolism*.

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, including positive dechallenges; erythema multiforme and Stevens-Johnson syndrome.

Vascular disorders: arterial thromboembolic events*. The most frequent events included cerebrovascular accident, transient ischemic attack and cerebral infarction.

*including some fatalities

DRUG INTERACTIONS

CYP3A4 Inhibitors. Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors *[see Dosage and Administration]*.

CYP3A4 Inducers. CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers *[see Dosage and Administration]*.

In Vitro Studies of CYP Inhibition and Induction. *In vitro* studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category D *[see Warnings and Precautions]*.
Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at doses ≥1 mg/kg/day but no maternal reproductive toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). At the high dose of 3 mg/kg/day, reduced body weights were observed at birth and persisted for offspring of both sexes during the pre-weaning period and in males during post-weaning period. No other developmental toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Nursing Mothers. Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether this drug or its primary active metabolite are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SUTENT, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use. The safety and efficacy of SUTENT in pediatric patients have not been established.

Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were >0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

Geriatric Use. Of 825 GIST and RCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

Hepatic Impairment. No dose adjustment to the starting dose is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

Renal Impairment. No adjustment to the starting dose is required when administering SUTENT to patients with mild, moderate, and severe renal impairment. Subsequent dose modifications should be based on safety and tolerability *[see Dose Modification]*. In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to subjects with normal renal function, the sunitinib exposure is 47% lower in subjects with ESRD on hemodialysis. Therefore, the subsequent doses may be increased gradually up to 2 fold based on safety and tolerability.

OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT, or without adverse reactions. A case of intentional overdose involving the ingestion of 1,500 mg of SUTENT in an attempted suicide was reported without adverse reaction. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility. The carcinogenic potential of sunitinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. There were similar positive findings in both species. In rasH2 transgenic mice gastroduodenal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiosarcomas were observed at doses of ≥25 mg/kg/day following daily dose administration of sunitinib in studies of 1- or 6-months duration. No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day. Similarly, in a 2-year rat carcinogenicity study, administration of sunitinib in 28-day cycles followed by

7-day dose-free periods resulted in findings of duodenal carcinoma at doses as low as 1 mg/kg/day (approximately 0.9 times the AUC in patients given the RDD of 50 mg/day). At the high dose of 3 mg/kg/day (approximately 7.8 times the AUC in patients at the RDD of 50 mg/day) the incidence of duodenal tumors was increased and was accompanied by findings of gastric mucous cell hyperplasia and by an increased incidence of pheochromocytoma and hyperplasia of the adrenal medulla. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (≥ 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (≥ 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6 mg/kg dose produced a mean AUC that was ≥ 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was ≥ 5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10 mg/kg/day dose produced a mean AUC that was ≥ 25.8 times the AUC in patients administered the RDD).

PATIENT COUNSELING INFORMATION

Gastrointestinal Disorders. Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring inpatients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

Skin Effects. Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet. Severe dermatologic toxicities including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported. Patients should be advised to immediately inform their healthcare provider if severe dermatologic reactions occur.

Other Common Events. Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Osteonecrosis of the Jaw. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients being treated with SUTENT, who have previously received or are receiving bisphosphonates, invasive dental procedures should be avoided, if possible.

Hypoglycemia. Patients should be advised of the signs, symptoms, and risks associated with hypoglycemia that may occur during treatment with SUTENT. Hypoglycemia may be more severe in patients with diabetes taking antidiabetic medications. Severe hypoglycemia including loss of consciousness or requiring hospitalization has been reported. Patients should be advised to immediately inform their healthcare provider if severe signs or symptoms of hypoglycemia occur.

Thrombotic Microangiopathy. Thrombotic microangiopathy leading to renal insufficiency and neurologic abnormalities was observed in patients who received SUTENT as monotherapy or in combination with bevacizumab. Patients should be advised that signs and symptoms of thrombotic microangiopathy may occur during treatment with SUTENT. Patients should be advised to immediately inform their healthcare provider if signs and symptoms of thrombotic microangiopathy occur.

Proteinuria. Proteinuria and nephrotic syndrome has been reported. Patients should be advised that urinalysis will be performed prior to starting as well as during treatment with SUTENT. In cases with impact to renal function, treatment with SUTENT may be interrupted or discontinued.

Concomitant Medications. Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Drug Interactions]*.

Rx only Revised: April 2015

Editorial Mission
The GIST Cancer Journal is intended to serve as a comprehensive and authoritative resource of scientifically valid information for physicians and allied health care professionals regarding advances in the diagnosis and treatment of gastrointestinal stromal tumors. Editorial content focuses on the impact of translational research in oncology and gastroenterology relating specifically to GIST. As the official medical journal of the Life Raft Group, it also provides a forum for GIST patient advocacy. *The GIST Cancer Journal* is circulated to all medical oncologists and other selected medical professionals, and is available to members of the GIST community upon request

The Life Raft Group
The mission of the Life Raft Group is to ensure the survival of GIST patients through a comprehensive approach connecting individual patients' needs, the worldwide community of GIST advocates and the global health and research environment. To do this, the group focuses on three key areas: research, patient support and education, and advocacy. (For additional information, please see Page 15.)

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About the cover
Illustration of a DNA molecule methylated at the two center cytosines with implications for SDH-deficient GIST. Hypermethylation indicates a gene that is over-methylated and is not able to be expressed normally. SDHC is part of the SDH complex which requires normal expression of all components in order for the complex to function. This means that the SDH complex is not able to function normally in these patients. A disrupted SDH complex leads to disrupted cell metabolism and to cell growth and blood vessel growth and has been identified as a cause of tumorgenesis in a number of cancers. *Artwork by Christoph Bock (Max Planck Institute for Informatics).*

Table of Contents

Editor's Memo

Epidemiology of GIST: "Peeling Away Layers of the Onion" with Population-Based Studies

New information presented at the 2015 meeting of the American Society of Clinical Oncology (ASCO) offers an intriguing and revealing portrait of how the epidemiology of gastrointestinal stromal tumor (GIST) is evolving. Between 1991 and 2011, according to Lin and Radvin, more than a doubling of the incidence of gastric sarcoma (GS) was observed with a concurrent rapid change in GIST - most in localized disease and a dramatic improvement in its outcome. The overall incidence of GS increased from 1991 to 2011 from 2.9 (standard error [SE] 0.4) to 6.6 (SE 0.6) cases per million per year. The histologic subtypes have changed over this time interval with leiomyosarcoma being initially the leading GS subtype with an incidence from 2.3 (SE 0.4) decreasing to 0.1 (SE 0.1). The incidence of gastric GIST increased from 0.1 (SE 0.1) to 6.3 (SE 0.6) representing 95% of all GS cases in 2011.

These figures are remarkable in the sense that as recently as 2006, authors were expressing their disappointment about how the epidemiology of GIST was poorly understood. They were calling for more accurate information to delineate the disease, identify the groups and settings where it most likely is diagnosed, and ultimately, suggest clinical implications. The data presented at ASCO represents another effort to "peel away the layers of the onion." Until recently, that so-called onion was largely an enigma, with the epidemiology of GIST lagging far behind the efforts in other cancers, such as colorectal, where a population-based study from SEER data was published as early as 2009.

The need for a population-based study in GIST was plainly evident because single, institution-based reports have been plentiful but limited in their scope and ability to spot trends on a national basis. As Jason Sicklick, MD notes in his report in this issue of *The GIST Cancer Journal*, we relied upon the results of several descriptive, single-institution case series to determine the likelihood that patients with sporadic GISTs develop synchronous or metachronous malignancies. These studies qualitatively characterized cancer associations, but the findings were unsatisfying in their variability. Population-based studies take advantage of the growing repository of data to make new associations, draw novel conclusions and possibly shift thinking about the histology and mechanics of diseases like GIST. Dr Sicklick's review, derived from the first population-based, epidemiologic study of histologically confirmed disease is

(continued on next page)

The GIST Cancer Journal Author Guidelines

Scope of Manuscripts
The GIST Cancer Journal considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Original contributions based on original, basic, clinical, translational, epidemiological, or prevention studies relating to gastrointestinal stromal cancer that are well documented, novel, and significant.
- Letters to the Editor on timely and relevant subjects pertaining to the diagnosis and treatment of gastrointestinal stromal tumor.
- Clinical case studies.

Manuscript Submission
Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Jonathan C. Trent, MD, PhD at jtrent@med.miami.edu. Please provide in a word processing program. Images should be submitted electronically as well.

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Peer Review and Editing
Manuscripts will be peer reviewed. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with American Medical Association (AMA) style. Authors whose manuscripts are not initially accepted may have the opportunity to revise the manuscript based on recommendations from peer reviewers and at the discretion of the Editor-in-Chief.

Conflict of Interest
The GIST Cancer Journal policy requires that authors reveal to the Editor-in-Chief any relationships that they believe could be construed as resulting in an actual, potential, or apparent conflict of interest with regard to the manuscript submitted for review. Authors must disclose this information in the covering letter accompanying their submission.

Manuscript Preparation
Length: Full-length manuscripts should not exceed 4000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally 4-5 figures and 2-3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a legend for all abbreviations. Manuscripts should not contain an abstract but an introduction is recommended.

Spacing: One space after periods. Manuscripts should be double spaced.

References
All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style.

Example:
Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest*. 2001;119:818-823.

Copyright

Editor's Memo *(continued from page 27)*

part of what we hope will become a broader initiative in epidemiology to provide a robust representation of GIST in the era of immunohistochemical diagnoses. The report helps to debunk some of the misconceptions about the epidemiology that have persisted because the earlier, institution-based data did view data through the lens of the SEER findings. By doing so, the new information gives us a more precise estimate of histologic subtypes in the era of histology coding.

To what can we attribute the difference between the new epidemiologic associations and the old? The underlying biology of the disease has not changed; perhaps the use of imatinib and the advent of advanced diagnostic techniques and pathologic evaluation have contributed to the new associations observed. The answer to this question awaits further study. However, there are practical implications apparent in this setting. As clinicians, we need to be aware of the possibility of increased cancers at many anatomic sites and how such identification is related to screening, prevention, earlier diagnosis, and potential mechanisms. Ultimately, these associations may allow us to change clinical care and start thinking about GIST in a new way.

Jonathan C. Trent, MD, PhD
Editor-in-Chief

Population-Based Study Provides Insight into GIST Epidemiology and Risk of Additional Cancers

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Although we have not completely deciphered the epidemiology of gastrointestinal stromal tumor (GIST) and additional cancers, our new population based study uses modern data collection resources to suss out significant temporal and disease associations between GIST and other cancers.[1] Expanding upon the publications from several single institution studies, we broadened the data set and casted a wider net to build upon these important earlier studies.[2-6]

Until recently, we relied upon the results of several descriptive, single-institution case series to determine the likelihood that patients with sporadic GISTs develop synchronous or metachronous malignancies.[2-6] These studies qualitatively characterized cancer associations, but the findings were unsatisfying in their variability. For example, in a review by Agaimy and colleagues that included 4,813 patients,[4] the frequency of additional malignancies varied from 4.5% to 33% in patients with GIST. There have been other large studies that added to this body of literature.[7] For example, single or multiple institution studies have demonstrated associations between GIST and desmoids[6] acute myeloid leukemia[5] and other gastrointestinal malignancies found incidentally.[8] While a hereditary etiology has been attributed to approximately 5% of all GIST cases associated with multiple benign and malignant tumors,[9] we attempted to quantify the frequency and temporal relationships of GIST to other cancer histologies in the remaining 95% of GIST patients without known hereditary GIST syndromes. These single-institution studies were helpful but they did not provide the broad-based characterizations.

In his Editorial in the journal, *Cancer*, Dr. Stratakis, Scientific Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, wrote that it is a "different world out there for clinical oncology, one that changes every day because of the availability of large patient cohorts and the advances of modern genetics."[9] Population-based studies take advantage of the growing repository of data to make new associations, draw novel conclusions and possibly shift thinking about the histology and mechanics of diseases like GIST. In our recently published study,[1] we utilized population-level data in the United States in order to define demographic, clinical characteristics, and temporal factors associated with increased probability of developing additional malignancies. From data culled from the Surveillance, Epidemiology, and End Results (SEER) database, we identified further evidence supporting the existence of nonrandom associations between GIST and other malignancies. Our work builds on the foundation created by these studies with the hypothesis that greater insight could be gained into possible associations between GIST and other primary tumors with a national cancer database inquiry. Aside from the impact the findings may have on understanding GIST from a purely epidemiological perspective, the associations have important clinical implications for future cancer screening and treatment strategies.[1]

Key Findings

The key findings emerging from this study include the following:

- One-in-5.8 patients with GIST will develop additional malignancies before and after their diagnosis.
- When compared to the United States population, people

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Key words: GIST, epidemiology, population-based studies, SEER database, associated malignancies, additional cancers.

with GIST had a 44% increased prevalence of cancers occurring before a GIST diagnosis and a 66% higher incidence of developing cancers after diagnosis.

- Patients with GIST are more likely to develop many cancers, including other sarcomas, non-Hodgkin's lymphoma, carcinoid tumors, melanoma, colorectal, esophageal, pancreatic, hepatobiliary, non-small cell lung, prostate and renal cell cancers.
- Non-Hispanic patients had a higher incidence of other cancers before a GIST diagnosis.
- Patients with tumors smaller than 10 cm had a higher probability of a second cancer than patients with larger tumors.
- Patients with tumors smaller than 2 cm had the greatest likelihood of developing additional malignancies, both before and after diagnosis.
- Patients diagnosed with GIST may warrant consideration for additional screenings based on the other cancers that they are most susceptible to develop.

Methodology

The findings in the population-based study were derived from data in the National Cancer Institute's SEER database.[10] The database consists of 18 regional cancer registries spanning the U.S. that gather data on incident cancer diagnoses nationwide, including GIST diagnosed between 2001 and 2011 (**Table**). To exclude the likelihood of a diagnosis of hereditary GIST, patients diagnosed under the age of 20 years were not considered. Standardized prevalence ratios (SPRs), defined as the number of observed cases of additional cancers divided by the number of expected cases, were utilized to estimate cancer occurrence before GIST. Standardized incidence ratios (SIRs), defined similarly, were utilized to estimate cancer occurrence after GIST. We then calculated SPRs and SIRs for any additional cancers, as well as site-specific cancers. If these ratios exceeded 1.0, they were considered an increase in prevalence or incidence with respect to the general population.

Most Commonly Associated Malignancies

Among the cancers with significantly increased occurrence *both before and after* the GIST diagnosis were sarcomas, neuroendocrine tumors, colorectal adenocarcinoma, and non-Hodgkin's lymphoma. The malignancies with an elevated prevalence *only before* GIST were esophageal adenocarcinoma, melanoma, and prostate adenocarcinoma. The malignancies significantly elevated *only after* GISTs included small bowel adenocarcinoma, papillary thyroid cancer, renal cell carcinoma, gastric adenocarcinoma, hepatobiliary adenocarcinoma, pancreatic adenocarcinoma, non-small cell lung cancer and transitional cell carcinoma of the bladder (**Figure**).

Effect of Demographics and Tumor Characteristics

Ethnicity and tumor size appear to affect the risk of developing additional cancers. Our findings demonstrated an elevated prevalence of other cancers before GIST among non-Hispanic versus Hispanic patients. Tumor size also emerged as a significant factor. Patients with primary GISTs of 10 cm or less had higher probabilities of second cancers than patients with GISTs more than 10 cm. Furthermore, patients with tumors 2 cm or less had the highest likelihood of having associated cancers before and after GIST diagnosis.

Table. Demographic and Clinical Characteristics of the GIST Cohort (n=56112)

Characteristic	No.	%
Age at GIST diagnosis		
20-39 y	325	5.3
40-49 y	739	12.1
50-59 y	1289	21.1
60-69 y	1553	25.4
70-79 y	1398	22.9
80 y	808	13.2
Sex		
Female	2860	46.8
Male	3252	53.2
Race		
White/unknown	4320	70.7
Black	1079	17.7
Other	713	11.7
Ethnicity		
Hispanic	560	9.2
Non-Hispanic/unknown	5552	90.8
Year of diagnosis		
2001	408	6.7
2002	522	8.5
2003	505	8.3
2004	521	8.5
2005	531	8.7
2006	494	8.1
2007	517	8.5
2008	577	9.4
2009	604	9.9
2010	730	11.9
2011	703	11.5
GIST location		
Esophagus	33	0.5
Stomach	3368	55.1
Small intestine	1762	28.8
Colorectal	343	5.6
Hepatobiliary	5	0.1
Pancreas	23	0.4
Retroperitoneum	57	0.9
Peritoneum, omentum, and mesentery	126	2.1
Other digestive organs	384	6.3
GIST size		
2 cm	430	7.0
>2, 5 cm	1351	22.1
>5, 10 cm	1847	30.2
>10 cm	1478	24.2
Unknown	1006	16.5

Abbreviation: GIST, gastrointestinal stromal tumor.

Temporal Relationships

Analyzing the data for a temporal relationship, we found that the maximum increase in associated neoplasms occurred

Site	Observed	Expected	SPR/SIR (95% CI)
Cancers before GIST			
Esophageal adenocarcinoma	13	1.1	12.0 (6.40-20.6)
Bladder adenocarcinoma	3	0.4	7.51 (1.66-22.0)
Sarcoma	32	6.1	5.24 (3.58-7.39)
Neuroendocrine	20	5.6	3.56 (2.17-5.50)
Non-Hodgkin lymphoma	34	20.2	1.69 (1.17-2.35)
Colorectal adenocarcinoma	81	53.7	1.51 (1.20-1.88)
Melanoma	38	25.9	1.46 (1.04-2.01)
Prostate adenocarcinoma	184	153.9	1.20 (1.03-1.38)
All sites	*703*	*488*	*1.44 (1.33-1.55)*
Cancers after GIST			
Ovarian carcinoma	2	0.2	8.72 (1.06-31.5)
Small bowel adenocarcinoma	3	0.5	5.89 (1.22-17.2)
Other female GU*	6	1.0	6.00 (2.20-13.1)
Papillary thyroid cancer	16	3.1	5.16 (2.95-8.38)
Neuroendocrine	18	3.8	4.79 (2.84-7.56)
Renal cell carcinoma	35	7.8	4.46 (3.11-6.21)
Sarcoma	15	3.7	4.02 (2.25-6.64)
Hepatobiliary adenocarcinoma**	8	2.6	3.10 (1.34-6.10)
Gastric adenocarcinoma	14	5.2	2.70 (1.48-4.54)
Colorectal adenocarcinoma	71	32.8	2.16 (1.69-2.73)
Pancreatic adenocarcinoma	13	6.4	2.03 (1.08-3.47)
Uterine adenocarcinoma	12	6.1	1.96 (1.01-3.43)
Non-Hodgkin lymphoma	22	12.5	1.76 (1.11-2.67)
Non-small cell lung cancer	61	35.1	1.74 (1.33-2.23)
Bladder transitional cell carcinoma	27	16.4	1.65 (1.09-2.40)
All sites	*505*	*304*	*1.66 (1.52-1.81)*

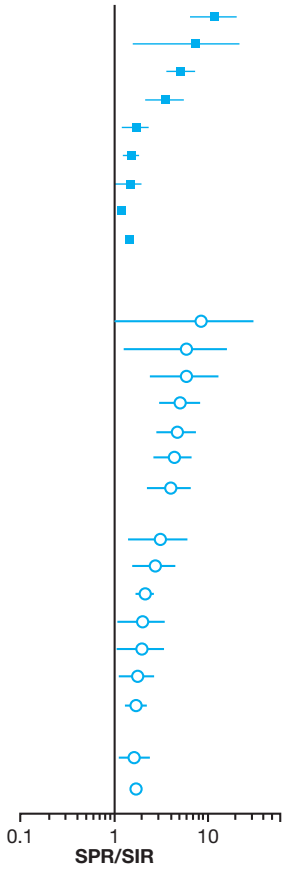

Figure. Cancer development before and after the diagnosis of GIST. The occurrence of each cancer before the diagnosis of GIST is reported with the SPR (solid squares), and the occurrence after the diagnosis of GIST is reported as the SIR (white circles). Horizontal lines illustrate associated 95% CIs. Only cancers with statistically significantly elevated SPRs and SIRs (*P*<.05) and more than 1 reported case within the cohort are included. *Other female GU includes vulvar cancer (n=54), vaginal cancer (n=51), fallopian tube cancer (n=52), and not otherwise specified (n=51). **Hepatobiliary adenocarcinoma includes liver adenocarcinoma (n=52), intrahepatic cholangiocarcinoma (n=51), extrahepatic cholangiocarcinoma (n=51), and ampullary adenocarcinoma (n=54). CI indicates confidence interval; GIST, gastrointestinal stromal tumor; GU, genitourinary; SIR, standardized incidence ratio; SPR, standardized prevalence ratio.

within 1 year around the GIST diagnosis, likely representing a detection bias. The median latency period from the diagnosis of the first cancer to was 3.6 years. In contrast, the median time from the diagnosis of GIST to diagnosis of a subsequent cancer was 10 months.

Convergent and Divergent Observations

As the first population-based study with current SEER coding to quantify the occurrence of specific malignancies before and after GISTs, we confirmed some of the results confirmed previous studies and refuted many earlier findings. We also identified several novel associations and most importantly, offered a rigorous statistical analysis supporting nonrandom associations between GIST and other malignancies. In several respects the study begins to hone in on where and when the increased occurrence of other cancers are likely to occur—identifying the anatomic site, histologic subtype and temporal association with a GIST diagnosis.

We corroborated several trends observed in these earlier studies. For example, we confirmed that 17.1% of GIST patients developed additional cancers; and the anatomic sites of additional malignancies were roughly similar to earlier data. Agaimy et al. previously reported second cancers in 13% of GIST patients on average with an elevated risk of melanoma, as well as gastrointestinal, lung, and prostate cancers.[4] Subsequently Trent and colleagues at MD Andersen Cancer Center reported second neoplasms in 20.3% of GIST patient.[3] Thus, our population-based frequency falls in the middle of these two reports.

But our population-based results diverged with regard to several malignancies identified in association with GIST. We failed to identify a significantly elevated risk of breast cancer or leukemias within GIST patients, while noting differences in the temporal relationships for several additional cancers associated with GIST. Finally, we added several new cancers to the list that may be associated with GIST, including non-Hodgkin's lymphoma, as well as thyroid, gastric, small intestine, colorectal, pancreatic, hepatobiliary, bladder, uterine, and ovarian cancers.

Limitations

While we have expanded our understanding of additional cancers in patients with GIST, our study has several limitations. The most important being a lack of tumor genomic studies to correlate with the identified patients with multiple tumors.[1,9] In his editorial, Dr. Stratakis alludes to a number of genetic possibilities that could underlie the biologic basis of the associations observed, but these are speculative. To address this, the group at Memorial Sloan- Kettering Cancer Center recently evaluated 260 GISTs. In their study, 50 (19%) patients had at least one additional primary malignancy. Patients who developed other malignancies after GIST more often had KIT exon 11 mutations and increased mitotic rate in the GISTs.[11] Nevertheless, the genetic "fingerprint" is an intriguing issue needing further elucidation.

In addition, there are several other limitations to all studies utilizing administrative databases including:

- Misdiagnosis and miscoding errors in SEER.
- Inclusion of potential hereditary syndrome patients as there was no direct way of identifying them.
- Detection bias of additional cancers in patients with one cancer.
- Lack of non-melanoma skin cancers and myeloproliferative disorders in SEER.[7]

Practical Considerations

Despite the study's limitations, the significant associations between GISTs and many cancers should prompt a renewed focus on cancer screening guidelines in subsets of GIST patients. The increased incidence of post-GIST gastric, small bowel, and colorectal adenocarcinoma, as well as neuroendocrine-carcinoid tumors, is reason to consider more aggressively employing upper and lower endoscopies among symptomatic patients. It may also be a good opportunity to re-evaluate the current guidelines of the National Comprehensive Cancer Network with regard to chest imaging—currently recommending such imaging only during the staging workup of GIST.[12] But, GIST patients are at an increased risk of non-small cell lung cancer. While it remains to be determined, perhaps GIST patients with a smoking history may be at an even higher risk. Thus, more consideration may be warranted for the use of chest CT to monitor certain GIST patients at higher risk.[13] A higher risk for genitourinary malignancies was also noted and highlights a potential need for increased index of suspicion for bladder, renal, and uterine cancers when hematuria or vaginal bleeding is observed following a GIST diagnosis. Finally, attention should be paid to the risk for malignancy in the lymph nodes, in light of our understanding that GIST rarely metastasizes to this site. Because of a higher risk for non-Hodgkin's lymphoma, new lymphadenopathy should prompt consideration of additional workup.

"Population-based studies take advantage of the growing repository of data to make new associations, draw novel conclusions and possibly shift thinking about the histology and mechanics of diseases like GIST."

Future Directions

One of the key areas still to be elucidated remains the potential mechanisms underlying the additional cancers; many hypotheses have been proposed, but the exact mechanism(s) remain to be determined. Among the candidates are age, sex, possible hereditary syndromes, spontaneous germline mutations, infection, exposure to environmental risks and toxic chemicals, treatment-related toxicities, and a detection bias associated with surveillance after an initial cancer.

Conclusion

In conclusion, for the first time, our recent population-based study quantifies the occurrence of specific cancers before and after GIST diagnosis, as well as provides the rates of histologically distinct malignancies associated with GIST. The epidemiological findings of increased cancers at many anatomic sites raise important issues related to screening, prevention, earlier diagnosis, and potential mechanisms. Ultimately, these associations may us allow to change clinical care and start thinking about GIST in a new way.

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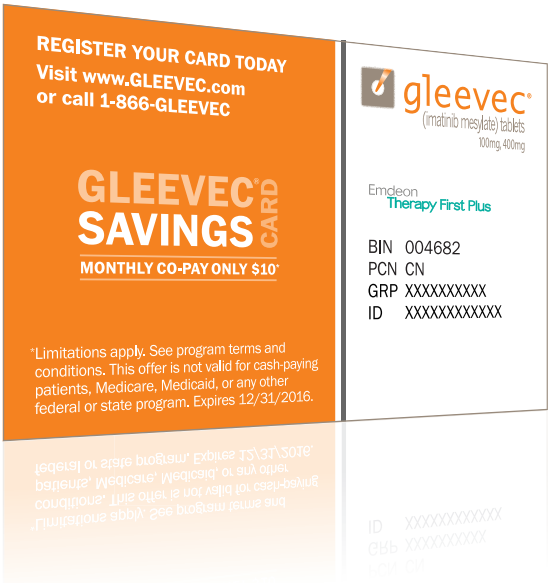

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Tracking the Trials and Progress of Drugs in the Pipeline: New Directions in Novel Treatments and Identification of Pathways

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Most gastrointestinal stromal tumors (GISTs) are caused by activating mutations of the *KIT* or *PDGFRA* (platelet-derived growth factor receptor alpha) receptor tyrosine kinase gene.[1-3] Imatinib treatment is and remains the cornerstone of therapy, but complete remissions are rare and up to 50% of patients with GIST develop resistance during the course of the first two years of systemic treatment.[4,5] This is why novel therapies to mitigate the occurrence of resistance (usually driven by secondary mutations in *KIT* or *PDGFRA*) and/or stabilize the disease are urgently needed. In addition, studying new therapeutic concepts can reveal more about the biology of the disease itself and what targets may help to optimize treatment in the future. This article will review current clinical trials for new therapeutic agents in GIST providing a glimpse of how the landscape of treatment is evolving and how this goal may be met.

Phase I Studies: Preclinical Implications to "First-in-Man"

The following group of studies evaluates agents in the Phase I setting for GIST patients that merit attention. Although the primary goal of these studies is not to test efficacy of the new treatment, if the drug is active towards GIST, it is expected to see an effect towards growth stabilization even in these early phase trials.

A number of new initiatives have focused on developing agents that effectively inhibit specific KIT/PDGFRA mutations. This not only encompasses mutations that are currently not targeted by FDA-approved treatments (such as the *PDGFRA* D842V mutation), but also secondary *KIT*/*PDGFRA* mutations that are mainly seen in tyrosine kinase inhibitor (TKI)-resistant GISTs.

PLX9486 (Plexxikon Inc., Berkeley, CA) is such a compound that is designed to block mutated KIT signaling. By combining this agent with **PLX3397**, a novel oral small molecule that potently and selectively inhibits not mutated (i.e., wildtype) KIT (as well as the CSF-1R and mutant FLT3 kinases), the investigators hope to block most aberrant KIT signaling in GIST with the goal to stop the tumor from progressing. In addition, it is known that CSF1R and KIT regulate key components of the tumor microenvironment (macrophages, osteoclasts, mast cells) thereby possibly providing an additional anti-cancer effect. A Phase I study has been initiated and is designed to test PLX9486 (alone or in combination with PLX3397) in patients with types of advanced solid tumors including GIST (NCT02401815; https://clinicaltrials.gov/ct2/show/NCT02401815).[6] Previous studies of PLX3397 in patients with other tumor entities, some of them already in Phase II, have shown favorable results.[7]

BLU-285 (Blueprint Medicines, Cambridge, MA) is another orally available agent that was developed to specifically target the mutant forms of *KIT* and *PDGFRA*.[8] It potently and selectively inhibits the *PDGFRA* D842V mutant as well as exon 17-mutated *KIT*. While *PDGFRA* D842V mutations are overall rare (occurring in only about 5% of GIST patients) they encompass almost two-thirds of all *PDGFRA* mutations that are found in GIST.[9] Importantly, *PDGFRA* D842V mutant GISTs are insensitive to imatinib, sunitinib and regorafenib impeding the therapeutic management of GIST patients with this mutation once their tumor is progressing. In addition, BLU-285 potently inhibits *KIT* D816V, a mutation that is seen with increasing frequency in TKI-resistant GIST patients and leads to disease progression. Preclinical data on BLU-285, and its potential value in treatment-resistant GIST were presented at the 2015 American Association for Cancer Research Annual Meeting in April.[10] BLU-285 showed significant anti-tumor activity in treatment-resistant *KIT* mutations *in vitro* and led to complete tumor regression in a patient-derived mouse model of GIST that is refractory to treatment with imatinib. According to their website, Blueprint Medicines will file an Investigational New Drug (IND) Application and is planning a Phase I clinical trial of BLU-285 in mid-2015.[10]

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Key words: GIST, novel treatments, KIT and PDGFRA mutations, MEK inhibitor, cllinical trials, SURE Trial, PAZOGIST, CYCLIGIST.

A different approach to tackle secondary *KIT* mutations occurring in patients with TKI-resistant GIST is taken in the "**SURE Trial**" (NCT02164240; https://clinicaltrials.gov/show/NCT02164240).[11] This study is based on the knowledge that the current, FDA-approved second- and third-line treatments for GIST, sunitinib and regorafenib, have largely opposing activity profiles against the commonly occurring secondary *KIT* mutations that confer imatinib resistance. Because different metastatic lesions within one patient can harbor different resistance mutations, using sunitinib and regorafenib in combination could theoretically be able to suppress the growth of a larger number of lesions. However, both drugs share a very similar profile of adverse effects and a high toxicity is therefore anticipated if using them in conjunction. Through a number of preclinical studies, the optimal length of treatment (as well as washout before tumor cell regrowth) was determined. The resulting protocol consists of three days of sunitinib alternating with four days of throughout each 28-day cycle.[12] This trial combines existing, FDA-approved drugs based on their mechanism of action in a pre-clinically well-validated validated fashion. This approach has great potential and may change the way that we approach clinical trial design in the future.

A number of current trials are testing new substances in conjunction with imatinib. Several of them are using inhibitors of direct downstream pathways of KIT. One promising study is using the MEK inhibitor **MEK162** in combination with imatinib mesylate in patients with advanced gastrointestinal stromal tumor (GIST; NCT01991379; https://clinicaltrials.gov/show/NCT01991379).[13] This study is based on the finding that MEK/MAPK signaling activates ETV1, a lineage-specific survival factor for GIST and its precursor interstitial cells of Cajal.[14] In preclinical models, inhibition of MEK with MEK162 (binimetinib; Novartis, Basel, Switzerland; Array BioPharma, Boulder, CO), synergized with imatinib in destabilizing ETV1 protein and suppressed GIST formation and progression.[15] Promising results were reported of the Phase I portion of the study at the 2015 ASCO Annual Meeting that included patients with imatinib-resistant advanced GIST.[16] An ensuing Phase II portion of the study will include patients with untreated GIST.

In addition to the MEK/MAPK signaling pathway downstream of KIT, the PI3K/AKT pathway has been noted for its importance in GIST cell survival.[17] Preclinical studies of various orally available PI3K inhibitors in various *in vivo* GIST models have shown a significant anti-tumor effect, especially when used in combination with imatinib.[18] Based on these studies, dose-finding Phase I clinical trials for two of these compounds, both in combination with imatinib, are currently recruiting:

- A dose-finding study of a combination of **imatinib** and **BKM120 (buparlisib**; Novartis) in the treatment of 3rd Line GIST patients (NCT01468688; https://clinicaltrials.gov/show/NCT01468688).[19]
- A dose-finding study of a combination of **imatinib** and **BYL719 (alpelisib**; Novartis) in the treatment of 3rd Line GIST patients (NCT01735968; https://clinicaltrials.gov/show/NCT01735968).[20]

While buparlisib (BKM120) is a pan-PI3K inhibitor, alpelisib (BYL719) is a selective inhibitor of the PI3K catalytic p110a subunit.[21,22] Importantly, both compounds do not significantly inhibit the downstream kinase mTOR, which is known to provide a negative feedback loop causing reactivation of the PI3K and the MAPK pathways.

While all previously mentioned studies focus on strategies that use small molecule inhibitors to abrogate KIT/PDGFRA kinase and downstream signaling, there are a few conceptually different trials that are based on entirely different strategies.

LOP628 (Novartis) is a humanized monoclonal antibody that is targeted against the KIT receptor. Linked to the antibody is the cytotoxic agent maytansine that inhibits the assembly of microtubules, molecules that are necessary for cell division. The proposed mechanism of action this so-called "antibody-drug conjugate" (ADC) requires two steps.[23] First, the monoclonal antibody portion of LOP628 targets and binds to the cell surface receptor KIT that is expressed on all GIST cells. This is followed by internalization of the LOP628-KIT complex and binding of the maytansine portion of LOP628 to the tubulin molecules inside the cell thereby inhibiting cell division and hence tumor growth. A similar concept has been FDA-approved for treating HER2-positive metastatic breast cancer using an anti-HER2 antibody (trastuzumab, Herceptin®) conjugated to the cytotoxic maytansinoid DM1 (trastuzumab emtansine).[24] This therapeutic concept has a great potential, especially in GIST, because most GIST are still dependent on activated KIT signaling, even when they are resistant to TKIs. LOP628 can only bind to KIT-expressing cells, yet its activity is not hampered by the existence of secondary resistance mutations (NCT02221505; https://clinicaltrials.gov/show/ NCT02221505).[25]

Another antibody-based study that is currently accruing GIST patients is based yet on another concept. This trial is testing the monoclonal antibody **ipilimumab** (Bristol-Myers Squibb, New York, NY) in combination with **dasatinib**. Ipililumab is an agent that is directed against the cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), a protein receptor expressed on T cells that functions as an immune checkpoint to downregulate the immune system. Inhibition of CTLA4 can re-activate the known anti-tumor activities of cytotoxic T cells. In a recent study it was noted that the immune system contributes substantially to the antitumor effects of imatinib.[26] Moreover, augmenting the immune system with a CTLA4 inhibitor significantly enhanced the effect of imatinib treatment. The current trial is testing a similar combination approach using dasatinib to achieve blockade of KIT signaling in combination with ipililumab (NCT01643278; https://clinicaltrials.gov/ct2/show/study/NCT01643278).[27]

While all above-mentioned studies are directed towards adult, KIT/PDGFRA-mutant GIST, there have virtually been no clinical trials specifically directed towards pediatric-type, KIT/PDGFRA-wildtype GIST. In the past few years, it has become clear that most of these tumors are characterized by a deficiency in succinate dehydrogenase (SDH) family proteins.[28] SDH family proteins are localized in the mitochon-

drial membrane and function as important enzymes in the citric acid cycle. Loss of SDH function leads to the accumulation of succinate and eventually contributes to a tumorigenic, pseudohypoxic state through overexpression of HIF1-alpha. **CB-839** (Calithera Biosciences, South San Francisco, CA) is an orally bioavailable inhibitor of glutaminase.[29] Studies indicate that glutamine metabolism is important in the synthesis of succinate. Hence, inhibition of glutaminase could be an effective treatment for SDH-deficient GIST through reduction of succinate levels in the tumor cells. An open-label Phase I evaluation of CB-839 in patients with advanced solid tumors is currently recruiting (NCT02071862; https://www.clinicaltrials.gov/ct2/show/ NCT02071862).[30] After a dose escalation study enrolling patients with locally-advanced, metastatic and/or refractory solid tumors, the study will be expanded to accrue patients of specifically selected tumor entities, such as SDH-deficient GIST. This is the first attempt to specifically target this patient population based on the well-defined molecular characteristics of their tumors.

Phase 2 and Phase 3 Studies: Moving closer to FDA-approval

As many new agents and concepts are currently being tested in Phase I of Phase Ib/II clinical studies for GIST, as little are currently in active Phase II or Phase III studies. Many ongoing trials have just reached their primary endpoints during the course of the past months and have recently been reported.

Final results of a multicenter randomized phase II study (PAZOGIST) evaluating the efficacy of **pazopanib** (Votrient; GlaxoSmithKline, Brentford, UK), a broad-spectrum tyrosine kinase inhibitor with efficacy against KIT, FGFR, PDGFR and VEGFR were just reported at the 2015 Annual Meeting of ASCO in June.[31,32] 81 patients with resistant unresectable metastatic and/or locally advanced GIST were enrolled to either receive pazopanib plus best supportive care or best supportive care alone. An improvement in progression-free survival at four months in favor of pazopanib was seen. 36 out of 41 patients switched to pazopanib following investigator-assessed progressive disease. Hence, no difference in overall survival was found. It has to be noted that almost 75% of patients experienced fairly high grade (≥ 3) adverse events with hypertension being the most common. Further pharmacokinetic analyses are ongoing. However, it is not yet clear what the next steps with respect to further clinical trials are going to be.

Similarly, the results of a multicenter, open-label Phase II trial (DOVIGIST; NCT01478373) to evaluate safety and efficacy of **dovitinib** (Novartis), another investigational oral tyrosine kinase inhibitor, were reported at the ESMO Congress in November 2014.[33] Interestingly, this study set out to test dovitinib as an agent for second-line therapy in GIST patients who were intolerant to or no longer responsive to first-line imatinib. The disease control rate at 12 weeks was over 50%. However, dovitinib did not perform as well as sunitinib in this second-line setting. In view of these results it is therefore unclear whether there will be a follow-up Phase III study. Moreover, a study to evaluate dovitinib for patients with tumor pathway activations inhibited by dovitinib (SIGNATURE; NCT01831726; https://clinicaltrials.gov/ct2/show/NCT01831726), which includes GIST, is listed as ongoing, but not accruing on the clinicaltrials.gov website. The goal here was to select eligible patients via genomic profiling of their tumors (including KIT-mutant GIST).[34]

There are at least two agents that are currently being studied in active clinical trials, masitinib and palbociclib. **Masitinib mesylate** (AB Science, Paris, France) is an orally available tyrosine kinase inhibitor with greater *in vitro* activity and selectivity than imatinib against wild-type and juxtamembrane mutations of KIT.[35] It also effectively inhibits PDGFR and FGFR. The compound has already undergone several clinical trials to study its efficacy and safety in GIST. Most notably, a randomized Phase II study in imatinib-resistant advanced GIST studied efficacy and safety of masitinib *versus* sunitinib. This study apparently showed a longer survival in the masitinib treatment-arm with a better safety profile than sunitinib although the progression-free survival curves were similar. However, masitinib-treated patients could cross over to the sunitib treatment arm when experiencing progression, while patients in the control arm (sunitinib) were not offered masitinib. Hence, the difference in overall survival between the two arms could be due to the anti-tumor effects of sunitinib. This question is currently being studied in a follow-up Phase III study (NCT01694277; https://clinicaltrials.gov/ct2/show/NCT01694277).[36] Another Phase III study is being planned to test masitinib in the adjuvant setting. GIST patients with no evidence of disease after surgery, but with a high risk of recurrence will be treated with either masitinib or placebo (NCT02009423; https://clinicaltrials.gov/ct2/show/NCT02009423).[37] Furthermore, a Phase III study has been ongoing to evaluate the efficacy and safety of masitinib in the first-line setting for GIST (NCT00812240; https://clinicaltrials.gov/ct2/show/NCT00812240).[38]

Last, but not least, a new class of compounds – inhibitors of cyclin-dependent kinases – have made their way into Phase II clinical trials for GIST patients. **CYCLIGIST** is evaluating the efficacy and safety of PD-0332991 (palbociclib, Ibrance, Pfizer, New York, NY) in patients with advanced GIST who are refractory to imatinib and sunitinib (NCT01907607; https://clinicaltrials.gov/ct2/show/NCT019076 07).[39] Palbociclib is an orally available selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6. CDK4/6 are crucial promoters of the cell division cycle and oftentimes deregulated in cancer, including GIST. In fact, a recent publication by Bauer et al. showed that defects in the cell division cycle are amongst the most common aberrations in GIST besides *KIT*/*PDGFRA* mutations.[40] This ongoing study is assessing the antitumor activity of palbociclib in terms of non-progression at 16 weeks (after centralized review) in patients with documented disease progression while on therapy with imatinib and sunitinib for unresectable and/or metastatic GIST.

In summary, many novel therapeutic agents encompassing a multitude of novel therapeutic concepts are currently being evaluated in GIST and will hopefully make their way

to later stage clinical trials. As we review these most promising and potentially pivotal trials, a number of criteria tend to suggest how protocols should be designed to produce reliable results. They include the following:

- a well conceived strategy evaluating a molecularly targeted therapy in a well-selected patient cohort (specifically accruing GIST patients) with correlative biomarker confirmation
- preferably later phase trials that are based on earlier efficacy in GIST models (*in vitro* and *in vivo*)
- availability of enrollment at an established GIST treatment center and/or with an experienced GIST Primary Investigator
- a potential impact of the therapy on outcomes
- a determination or suggestion of how many patients will benefit
- a strategy as to what extent there is a limit on alternate options (i.e., whether the specific trial could limit patient access to future trials – such as treatment with an agent already being evaluated in another trial)

Many of the trials discussed above already incorporate these criteria. It seems like the future is going to look bright – we urgently need it.

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ASCO Highlights: Selected Abstracts

New treatment options propose strategies to circumvent TKI resistance

Although only three drugs have been approved for gastrointestinal stromal tumors (GISTs), results emerging from this year's meeting of the American Society of Clinical Oncology (ASCO) suggest how the spectrum of therapy could evolve, with efforts focused on overcoming resistance to tyrosine kinase inhibition (TKI). Ongoing trials using several TKIs, possibly in combination with imatinib, and another trial involving a MEK inhibitor, suggest new opportunities for prolonging progression-free survival and overall survival. Other abstracts presented at ASCO further delineate what to expect with the use of sunitinib after imatinib and how plasma sequencing (plasma seq) could be used as a novel approach to detect or monitor the spectrum of resistance mutations in GIST. The following abstracts were selected by Jonathan C. Trent, MD, Editor-in-Chief, for their relevance and potential impact. Results are briefly summarized.

Three vs. 1 year of adjuvant imatinib (IM) for operable high-risk GIST: The second planned analysis of the randomized SSGXVIII/AIO trial. *J Clin Oncol*. 33, 2015 (suppl; abstr 10505)**.**Heikki Joensuu, Mikael Eriksson, Kirsten Sundby Hall, et al.

Summary: Three years of adjuvant IM is recommended after surgery for patients (pts) with high-risk GIST with an IM-sensitive mutation. This recommendation is based on the findings from the SSGXVIII/AIO trial that compared 1 year (Arm A) to 3 years (Arm B) duration of administration of adjuvant IM. This abstract presents the second planned analysis of the trial based on a median follow-up time of 7.5 years; 400 patients were entered to this multicenter, open study between February 4, 2004, and September 29, 2008. In this second analysis, 171 recurrences and 68 deaths were detected. Patients assigned to 3 yearsrs of IM had longer RFS (HR 0.60, 95% CI 0.44 - 0.81; $P < 0.001$) and longer OS (HR 0.61, 95% CI 0.38 - 1.00; $P = 0.046$) than those assigned to 1 year of IM. The frequency of cardiac events (A, 10; B, 6) and the numbers of second cancers (A, 18; B, 23) were similar in the groups.
Conclusions: Three years of adjuvant IM resulted in superior RFS and OS as compared to 1 year of IM. Clinical trial information: NCT00116935.

Final results of the multicenter randomized phase II PAZOGIST trial evaluating the efficacy of pazopanib (P) plus best supportive care (BSC) *vs* BSC alone in resistant unresectable metastatic and/or locally advanced gastrointestinal stromal tumors (GIST). *J Clin Oncol*. 33, 2015 (suppl; abstr 10506) Jean-Yves Blay, Mathieu Molimard, Claire Cropet, et al.

Summary: Pazopanib (P) is effective in soft tissue sarcomas but has never been evaluated in a randomized setting in GIST. Eligible patients were randomized to receive P+ best supportive care (BSC) or BSC. Primary endpoint was Progression-Free Survival (PFS); 80 patients were planned to detect an improvement in the 4-month PFS rate (PFS-4m) from 15% (BSC) to 45% (P+BSC) with 5% two-sided and 80% power. Secondary objectives included Best Overall Response (BOR), Overall Survival (OS), safety and trough plasma P concentrations (Ct). From Apr 11 to Dec 13, 81 pts (P+BSC: 40, BSC: 41) were randomized. Arms were well balanced; median age: 63y (27-85), 70% males and 54% with ≥ 3 prior drugs. The intent-to-treat analysis based on investigator-assessed progressive disease (PD) showed an improved PFS with PFS-4m of 45.2% (95% CI 29.1-60.0) for P+BSC *vs* 17.6% (95% CI 7.8-30.8) for BSC;36 patients out of 41 switched to P following investigator-assessed PD (median P duration: 3.5 months (0.1-19), main reasons for discontinuation: PD (52.8%) and toxicity (22.3%)). Centrally-assessed BOR showed stable disease in 84.2% *vs* 70.7% and PD in 15.8% *vs* 26.8% of pts in P+BSC and BSC arms. Among all patients treated with P (n = 76), 72.4% experienced grade ≥ 3 related adverse events (AE) (hypertension: 36.8%), including 25% of related serious AE (pulmonary embolism, 9.2%). At the time of analysis, 29 *vs* 31 pts had died in the P+BSC and BSC arms (OS HR: 0.94, 0.56-1.56).
Conclusions: P combined with BSC improves PFS in advanced GIST resistant to imatinib and sunitinib. In the context of a high switch rate, no difference in OS was found. Further PK analyses are ongoing. Clinical trial information: NCT01323400

A phase Ib/II study of MEK162 (binimetinib [BINI]) in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST). *J Clin Oncol*. 33, 2015 (suppl; abstr 10507)Ping Chi, Li-Xuan Qin, Sandra P. D'Angelo, et al.

Summary: In preclinical models, MEK inhibition with BINI, synergizes with imatinib in destabilizing ETV1 protein and suppressing GIST tumorigenesis and progression. Combined MEK and KIT inhibition therefore represents a novel therapeutic approach for patients with GIST.
Methods: The phase Ib portion of the imatinib (400 mg daily) plus BINI was performed in patients with imatinib-resistant advanced GIST. A standard 3+3 dosing schema was utilized to determine the recommended phase II dose (RP2D) of this combination. Additional pts were enrolled on an expansion cohort at the RP2D. Imatinib 400 mg daily with BINI 45mg BID was established as the RP2D. Dose limiting toxicity (DLT) was asymptomatic grade 4 Creatinine Phosphokinase (CPK) elevation (1/6 pts at RP2D).. Of the 15 pts with evaluable CT scans, 5 pts (33%) had Choi PR; and 9 pts had RECIST SD at 8 weeks. Seven patients remain on trial at data cutoff (range 4-53 weeks). Median progression free survival is not reached.
Conclusions: BINI and imatinib combination is well-tolerated and has clinical activity in imatinib-refractory GIST. Phase II study is on-going in untreated GIST pts and a larger clinical trial in the imatinib-resistant GIST population is warranted. Clinical trial information: NCT01991379

Plasma sequencing to detect a multitude of secondary KIT resistance mutations in metastatic gastrointestinal stromal tumors (GIST). *J Clin Oncol*. 33, 2015 (suppl; abstr 10518) Sebastian Bauer, Thomas Herold, Thomas Mühlenberg, et al.

Summary: This study evaluated plasma sequencing (plasma

seq) as a novel approach to detect or monitor the spectrum of resistance mutations in GIST. It prospectively collected 30 plasma samples from 22 patients with metastatic GIST. Circulating free DNA (cf DNA) and tumor DNA were sequenced on an Illumina MiSeq platform using a custom designed targeted sequencing panel. Mutations with a percentage < 0.5% of total reads were excluded; the study detected 87 non-synonymous KIT mutations in plasma samples with various percentages of total reads (0.5-20% of cf-DNA). Primary mutations were found in 41% (all matching the tumor analysis), resistance mutations were seen in 86% of pts including patients responding to imatinib. Mutations in exon 17 were the most common resistance mutations. Resistance mutations detected in tumor samples were infrequently matched by plasma DNA. Notably, p53 mutations were detected in 77%, mutations of RAS or RAF in 59% of patients albeit at low levels. A comparator group of 19 plasma samples from pts with NSCLC harbored 6 low level KIT mutations at levels of 0.9% fc-DNA (median).
Conclusions: Plasma seq in patients with metastatic GIST detects a multitude of resistance mutations of KIT and other genes. Future validations should incorporate comprehensive sequencing of corresponding tumor tissue. Handling of plasma samples should be standardized in order to maximize the yield of mutant DNA. The clinical value of plasma seq should be tested in randomized trials.

Anti-tumor effects of dovitinib in patient-derived gastrointestinal stromal tumor (GIST) xenograft models. *J Clin Oncol*. 33, 2015 (suppl; abstr 10532) Yemarshet Kelemework Gebreyohannes, Thomas Van Looy, Agnieszka Wozniak, et al.
Summary: This study tested the efficacy of dovitinib which acts against VEGFR, FGFR, FLT3, PDGFRB and KIT, using patient-derived GIST xenograft models. NMRI *nu/nu* mice (n = 47) were transplanted bilaterally with the human GIST xenografts UZLX-GIST2 (*KIT* p.A502_Y503dup) or -GIST9 (*KIT* p.P577del+p.W557LfsX5+p.D820G) and were treated in 4 cohorts: control (untreated), imatinib (50 mg/kg/bid p.o.), imatinib (100 mg/kg/bid p.o.) and dovitinib (30 mg/kg/qd p.o.). After three weeks of treatment, dovitinib caused tumor volume reduction (to 37% of baseline) in UZLX-GIST2 and disease stabilization in -GIST9. It induced grade 2-3 HR in > 50% of tumors in both models. Compared to control, dovitinib reduced mitotic activity by 22.6 fold ($p < 0.0001$) in UZLX-GIST2, whereas no significant difference was observed in the other model. Results were confirmed by pHH3 and Ki67 stainings. Apoptotic activity was decreased in dovitinib treated UZLX-GIST2 tumors compared to control. MVD was reduced in both UZLX-GIST2 (1.6 fold; $p < 0.05$) and -GIST9 (1.3 fold; $p = 0.059$) under dovitinib. Furthermore, it partially inhibited KIT, AKT and 4EBP-1 phosphorylation in UZLX-GIST2.
Conclusions: Dovitinib showed anti-tumor efficacy in GIST xenograft models, with more pronounced effects in *KIT* exon 9 mutant disease. The decrease in MVD in both models suggested that the anti-tumor effects were at least partially mediated by the anti-angiogenic capacity of dovitinib. These results support ongoing and planned GIST trials (NCT01478373, 02268435, 01440959 and 01831726).

Ponatinib efficacy and safety in patients (pts) with advanced gastrointestinal stromal tumors (GIST) after tyrosine kinase inhibitor (TKI) failure: Results from a phase 2 study. *J Clin Oncol*. 33, 2015 (suppl; abstr 10535) Author(s): Michael C. Heinrich, Margaret von Mehren, George D. Demetri, et al.
Summary: The oral TKI ponatinib has potent pre-clinical activity against mutant KIT and PDGFRA, including clinically relevant mutants resistant to available TKIs. This phase 2, single-arm study (NCT01874665) evaluated efficacy and safety of ponatinib 45 mg qd in advanced GIST after TKI failure; N = 45. Cohorts were enrolled based on presence (A) or absence (B) of *KIT* exon 11 mutations. Primary endpoint was clinical benefit rate (CBR = CR + PR + SD) at 16 wk by modified RECIST 1.1 in Cohort A. Secondary endpoints include CBR (Cohort B and overall) and objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. At 10-mo median follow-up, 9 patients were ongoing; 15 discontinued for progressive disease per RECIST, 9 for AEs, and 12 for other reasons. Cohort A CBR was 37% (10/27); ORR 7% (2/27). Best responses: PR 2; SD 16. Median PFS/OS: 4.3 mo/15.0 mo. Cohort B CBR was 14% (2/14); ORR 0%. Best response: SD 6. Median PFS/OS: 2.0 mo/13.5 mo. Treatment-emergent AEs (TEAEs) in ≥40% of patients: rash 58%; fatigue 51%; constipation 42%; headache 42%; myalgia 40%. Serious TEAEs (other than disease progression) in ≥2 patients: abdominal pain 9%; pneumonia 7%; fatigue, nausea, small intestinal obstruction, vomiting, 4% each. Two deaths, from pneumonia and pulmonary embolism, were considered possibly ponatinib-related.
Conclusions: Ponatinib has clinical activity in advanced GIST patients after TKI failure, particularly patients with *KIT* exon 11 mutations. Clinical trial information NCT01874665

Treatment of advanced gastrointestinal stromal tumors (GIST): Are results of second-line sunitinib therapy related to duration of response of first-line imatinib? *J Clin Oncol*. 33, 2015 (suppl; abstr 10538)
Daniela Katz, Sari Greenberg-Dotan, Ilan Feldhamer, et al
Summary: Clinical trials have shown that clinical activity of SU after IM failure is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases. Only patients who progressed on second-line SU after receiving IM as first-line therapy, were included. A linear regression model were used to identify the relation between first-line IM duration of response (the independent variable) and duration of response of second line SU. We identified 31 consecutive patients with advanced GIST treated with IM and SU, consequently. There were 18 male and 13 female patients, with median age at the start of SU therapy 63.5 years (range: 34-85). Only 7% of patients (n = 3) received adjuvant IM therapy, prior to their metastatic disease. Median duration of response was 25.8 months (2.3-67.4) for IM and 5.2 months (0.8-32.7) for SU.
Conclusions: In our study, results of SU therapy in advanced GIST patients were found to positively relate with the duration of first line IM treatment. This relation may serve as a handy estimate for SU duration in the clinic. However, further studies in wider cohorts of patients are needed to confirm this observation. ■

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