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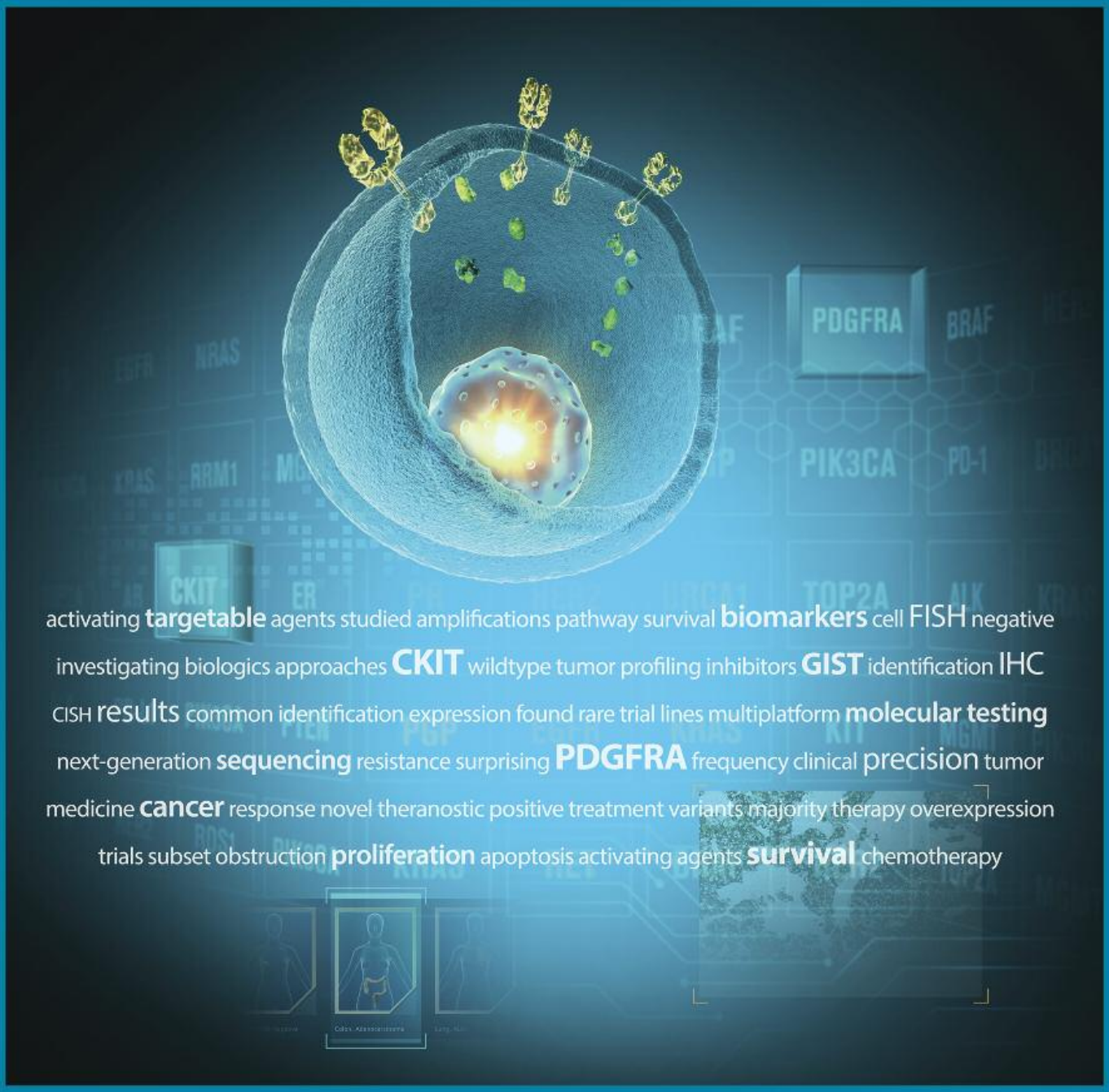
Biomarker Analysis Targets GIST Mutations, Drug Sensitivity

Gastroenterologist's New Role in GIST Care

Case Report: Neoadjuvant Therapy



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
In this artist's conceptual interpretation, a gastrointestinal stromal tumor (GIST) is shown attached to the gastric wall, center. As the text suggests, mutations associated with GIST, such as PDGFRA and c-KIT float along the fringe and in the text, all representative of findings obtained through biomarker analysis and facilitated by a multiplatform approach designed to identify these biomarkers as well as protein expression. (Image courtesy of Caris Life Sciences.)

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Editor's Memo

Is There a Toolkit for GIST? Yes, and It's Getting Better All the Time

If there were such a thing as a "toolkit" for making the diagnosis of gastrointestinal stromal tumor (GIST), you might finds many of its components in this issue of *The GIST Cancer Journal*. These are the technologies, biomarkers, modalities, devices, and various methods that are part of a broader armamentarium we now have available to diagnose GIST sooner and with more accuracy. And this "toolkit" is expanding all the time, giving us—compared to an earlier period of diagnosis—quantum leaps in recognizing the early signs of a tumor and assessing its malignant potential and risk for progression. The significant advances are not only exciting in themselves, they have ushered in what might be considered a new era in the diagnosis of a disease often elusive to the team within the continuum of care.

As one of our articles points out, these technological milestones are having a direct impact on the practice of gastroenterologists, frequently the first clinician to suspect GIST. Techniques such as fine-needle aspiration and capsule endoscopy are among the contributing factors expanding the role of the gastroenterologist in diagnosing GIST. According to one analysis cited in our review, gastroenterologists have a striking opportunity to capitalize on the unique position that these specialists hold in the patient care continuum. The gastroenterologist is evolving from a "pure" diagnostician to an endoscopic surgeon, a geneticist, a nutritionist, an immunologist and chemotherapist, and palliative care physician. In his review, David Kerman, MD, addresses how the new technologies are being incorporated into an algorithm for early diagnosis.

These modalities provide greater ability to evaluate submucosal lesions of the GI tract, including enhanced sonographic features that can more easily allow one to differentiate certain types of submucosal lesions, including potential GIST. Addressing this evolution of care, some authors have called GIST a model of multidisciplinary work in oncology, involving the integrated participation of several specialties, oncologists, gastroenterologists, pathologists, endoscopists and many more providers. If GIST is indeed this model, it becomes more imperative for all the members of the team to work closely, coordinate their roles, share as much knowledge as possible from the progress notes, and collaborate their efforts.

Yet the toolkit is expanding in other areas as well, including the molecular level where enhanced knowledge about biomarkers is contributing to a better understanding of GIST and its potential treatment. For example, it is widely believed that GISTs respond poorly to chemotherapeutic agents commonly used to treat mesenchymal malignancies. This notion, however, is mainly based on clinical studies that were carried out before the characterization of the KIT/

(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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List all authors, including mailing address, titles and affiliations, phone, fax, and email. Please note corresponding author.

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.

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Editor's Memo *(continued from page 47)*

PDGFRA driver mutations in GIST and the introduction of specific diagnostic markers, such as KIT immunohistochemistry. The new avenue of investigation, as reflected in data presented at two ASCO scientific sessions earlier this year, confirms that a subgroup of GIST patients, including those that lack activating mutations in cKIT/PDGFRA and those harboring cKIT/ PDGFRA resistance mutations, are in great need of therapy options outside of the standard of care. Many of these patients, however, can be identified through new biomarker analysis.

Recognition of these biomarkers can be helpful in identifying drug sensitivities in GIST patients whose mutational status may be uncertain and therefore needs to be determined. Results from the evaluation of this technique suggest that chemotherapeutic agents may be reconsidered in the treatment setting because of sensitivities observed in recently presented data. I am not saying that TKI therapy is no longer the cornerstone of therapy, but perhaps we need to begin thinking of alternative strategies in subsets of patients. These biomarkers, part of that expanding toolkit we now have available, can make a difference in our ability to diagnose GIST sooner and treat it more effectively.

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

Identifying Drug Sensitivities of GIST With Mutational Analysis to Optimize Treatment Approaches

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Anyone looking for the next quantum leap in therapy for GIST should take note of new findings in biomarker analysis. Data emerging over the last year point toward new treatment opportunities as platforms have explored molecular subtypes and suggested targets guided by tumor profiling.

Major strides in biomarker analysis in gastrointestinal stromal tumors (GIST) could open new avenues of treatment beyond conventional approaches. Significant advances in the identification of biomarkers and a rediscovered interest in the potential use of agents previously thought to be generally ineffective are encouraging signs of progress in efforts to find drug sensitivities for GIST. Although GIST tumors are largely defined by KIT and PDGFRA mutations and are targetable with tyrosine kinase inhibitors (TKIs), the majority of these tumors become TKI-resistant. Since resistance mutations inevitably emerge in patients with KIT And PDGFRA mutations, novel therapy approaches are needed for patients who have stopped responding to TKIs.

In addition, treatment standards for the GIST population lacking cKIT or PDGFRA activating mutations (10-15% of GIST patients) are also needed. There is considerable interest in new findings, particularly the results of a recent study that demonstrated the surprising sensitivity of GIST cell lines and TKI-resistant GIST patient-derived xenograft models to non-targeted FDA-approved, chemotherapeutic agents.[1] It is known from a number of studies that resistance to kinase inhibitors is mainly caused by secondary mutations of the driver oncogenic kinase.[2,3] Treatment strategies that do not focus on kinase inhibitors may therefore be advantageous, but have remained largely unexplored in GISTs.

It is widely believed that GISTs respond poorly to chemotherapeutic agents commonly used to treat mesenchymal malignancies.[4,5] This notion, however, is mainly based on clinical studies that were carried out before the characterization of the KIT/PDGFRA driver mutations in GIST and the introduction of specific diagnostic markers, such as KIT immunohistochemistry. The new avenue of investigation, as reflected in data presented at two ASCO scientific sessions earlier this year confirm that a subgroup of GIST patients, including those that lack activating mutations in cKIT/PDGFRA and those harboring cKIT/PDGFRA resistance mutations, are in great need of therapy options outside of the standard of care.

Typical first-line treatment for GIST is the tyrosine kinase inhibitor (TKI) imatininb mesylate (Gleevec).[6]The TKI, sunitinib mesylate, (Sutent) is used as second-line treatment for patients who cannot tolerate or have disease refractory to imatinib.[7] Response to TKI therapy varies. Some patients are resistant to TKI therapy from the outset due to the molecular nature of their primary disease, whereas others respond initially and then acquire resistance. The notion that earlier chemotherapeutic agents could be effective in some patients with GIST built momentum in the study by Boichuk et al.[1]Taking into account that GISTs and intraabdominal leiomyosarcomas (LMS) are histopathologically very similar, it is possible that earlier clinical trials included gastrointestinal leiomyosarcomas,[5] a tumor entity that is known to be highly resistant to chemotherapy. Therefore, Boichuk et al concluded, a reassessment of the response of GISTs to chemotherapeutic agents is warranted. Additional support for this notion stems from the fact that histone H2AX, a component of the DNA damage and repair machinery, has recently been found to play a role in GIST cell viability and apoptosis.[8,9]

The findings from this study raised important considerations for therapy.[1] Boichuk et al performed a compound screen of FDA-approved chemotherapeutic agents in GIST cell lines. Unexpectedly, GIST cells were highly sensitive to drugs targeting gene transcription or inhibiting topoisomerase II.

Two compounds, mithramycin A and mitoxantrone, were chosen for further investigation and proved to be active in

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Key words: PDGFRA, c-KIT, biomarker analysis, multiplatform, GIST mutations.

Editor's note: **This poster was presented at the ASCO Gastrointestinal Symposium earlier this year. It delineates how a multiplatform approach of identifying potential therapeutic options for GIST patients who become resistant to TKI therapy or are cKIT/PDGFRA wildtype may yield therapeutic options beyond tyrosine kinase inhibitors.**

both imatinib-sensitive and imatinib-resistant GIST cell lines, patient-derived primary GIST cells, and 2 xenograft mouse models. Mechanistically, this activity can be explained by cellular dependence on oncogenically activated KIT, which is substantially downregulated on the transcriptional level by mithramycin A, as well as high expression levels of topoisomerase II and/or downregulation of topoisomerase I, which sensitize GIST cells to mitoxantrone-induced DNA damage. In another report, Edris et al showed that unbiased drug screens can identify novel and unexpected drug sen-

Molecularly-guided therapeutic options beyond

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Abstract

Background: GISTs are characterized by KIT/PDGFRA mutations. A range of multi-targeted tyrosine kinase inhibitors (TKIs) are available for treatment, however, resistance mechanisms inevitably emerge. Recent data (Boichuk, et al 2014) suggests the potential efficacy of various cytotoxic therapies that were identified as being able to effectively kill TKI-responsive and -resistant GIST cells. We sought to investigate the theranostic markers associated with non-TKI therapy options for their potential role in treatment of GIST.

Methods: 147 GIST cases were evaluated. A multiplatform approach of biomarker testing was used and included a combination of sequencing (NGS, Sanger), protein expression (IHC) and gene amplification (ISH).

Results: Multidrug resistance phenotype was found in 52-68% (PGP, MRP1). Tubulin-binding agents (taxanes, vinca alkaloids) may be of potential use due to the high frequency of low TUBB3 expression (72% or 39/54). Anthracyclines and topoisomerase inhibitors may be of potential benefit in 1/3 of patients based on expression of TOPO2A (32% or 32/99) and TOPO1 (34% or 37/110). Cytotoxic agents used in non-GIST solid tumors, may also be considered, based on high frequency of low expression of MGMT (47% or 57/122), TS (70% or 76/109) and RRM1 (79% or 88/111). PTEN was intact (positive expression) in the majority of GIST (87%). Nine patients were examined for PD1/PDL1: 56% exhibited positive tumor infiltrating lymphocytes and 33% exhibited PDL1 tumor expression. Only one amplification event was observed: cMET (0/53), HER2 (0/69), EGFR (0/16), PIK3CA (0/1) and TOP2A (1/11). Mutational screening using a hot spot cancer panel (and Sanger sequencing for some genes) resulted in the detection of variants in only 10 genes, excluding KIT (97/132) and PDGFRA (5/55). Variants were detected in the following genes, in decreasing order of frequency: RB1, APC and JAK3 (2/55; 2/55; 2/57), PIK3CA (2/69) and ABL1, cMET, EGFR, KDR, VHL and BRAF (1/55, 1/57, 1/57, 1/57, 1/52, 1/78).

Conclusions: A multi-platform approach of theranostic biomarkers identified therapies beyond TKIs for GIST. Various cytotoxics and non-KIT/PDGFRA targeted therapies were identified based on protein expression or gene variations.

*Data is updated to include an additional 67 GIST patients

Background

Prior to the identification of the molecular drivers, cKIT and PDGFRA, in GIST, clinical management of GIST was similar to other soft tissue sarcomas, which included surgery and conventional chemotherapies such as doxorubicin. Standard treatment for GIST now includes a repertoire of small-molecule tyrosine kinase inhibitors (TKIs), including imatinib, sunitinib and regorafenib. As with other targeted approaches, the acquisition of resistance mutations inevitably emerge, and novel approaches are needed for patients who have stopped responding to TKIs. Further, treatment standards for the GIST population lacking cKIT or PDGFRA activating mutations (10-13% of GIST patients) are also needed.

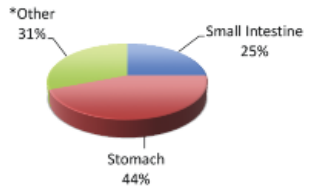
Interestingly, a recent study (Boichuk, et al. 2014, Cancer Res) demonstrates the surprising sensitivity of GIST cell lines and patient-derived GIST xenograft models to non-targeted FDA-approved, chemotherapeutic agents. Here, we explore the non-cKIT and non-PDGFRA aberrations that occur in GIST tumors to uncover potential treatment strategies that include conventional chemotherapy.

Methods

Two hundred fourteen GIST cases referred to Caris Life Sciences from 2009 through 2014 were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (next-generation sequencing [NGS] or Sanger), protein expression (immunohistochemistry) and gene amplification (CISH or FISH).

Results

Tumor Attributes and Patient Demographics



*other includes patients with confirmed history of GIST, with tumor sites in abdominal soft tissues, peritoneum, retroperitoneum, colon or rectum, esophagus or unknown primary tumor site

Figure 1. Primary Tumor Location. 214 GIST were studied and grouped according to primary tumor site location.

Specimen Site	% (n)
Mesentery, Omentum, Peritoneum, Retroperitoneum	28% (31/109)
Liver	20% (22/109)
Other (bone, chest wall, kidney, mediastinum, spleen, vulva, etc.)	17% (18/109)
Abdomen, NOS	15% (16/109)
Pelvis, NOS	13% (14/109)
Connective tissues, soft tissues	9% (10/109)
Colon	5% (5/109)
Pancreas	3% (3/109)

Table 1. Specimen site for profiling. 51% of specimens profiled were from sites other than the primary tumor site listed, suggestive of metastatic (local and distant) disease.

Patient Demographics: 54% male; 46% female, mean age of 61

sitivities in GISTs caused by the underlying biologic alterations of the tumor.[10]

The latest data to emerge, extending the line of investigation by Boichuk et al, come from posters presented at the two ASCO meetings: the 2015 ASCO Gastrointestinal Cancer Symposium in San Francisco and the 2015 ASCO Scientific Sessions in Chicago.[11,12] At the San Francisco meeting our team of researchers used Caris Molecular Intelligence®("CMI"), a multi-technology platform that combines next-generation gene sequencing, immunohistochemistry, in situ hybridization (fluorescence and chromogenic), and polymerase chain reaction methods, to analyze 147 GIST specimens for patterns of protein and gene alterations. In addition to the biomarker assays, the CMI offering includes review and analysis of the relevant medical literature for reported associations between the GIST biomarkers detected and various approved or investigational agents.

The evidence presented in the poster session demonstrated that the relative frequency of GIST tumors found to

TKIs for Gastrointestinal Stromal Tumors (GIST)

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Results (contd.)

Boichuk, S. et al. (Cancer Res 74:1200-1213) explored the sensitivity of GIST cells to various FDA-approved chemotherapeutic agents by performing a compound screen using the NCI/NIH Approved Oncology Drugs Set II. Using a pre-defined drug response score, they identified a number of chemotherapeutic agents that had high antitumor activity. We assessed the frequency distributions of GIST patients' protein expression and gene copy number data that associate with several chemotherapies. Agents highlighted in green below were shown to have antitumor effects on GIST cells in Boichuk's study.

Predictive Biomarker (n/total)	% in favor of Response to Rx (based on mechanism)	Therapy	Drug Class
RRM1_low (127/166)	76.50%	gemcitabine	DNA synthesis inhibitor
TUBB3_low (45/62))/ TUB3 (6/80)	72.60%/7.50%	paclitaxel, vinorelbine	Microtubule poison
TS_low (119/165)	72.10%	pemetrexed	Antimetabolite
PD-1 (10/16)/PD-L1 (5/16)	62.50%/31.30%	*nivolumab	Immunomodulatory agent
TOPO1 (77/166)	46.40%	topotecan	Topoisomerase inhibitor
ERCC1_low (49/110)	45.0%	cisplatin	Crosslinking agent
MGMT_low (72/175)	41.10%	temozolomide	Alkylating agent
TOP2A (44/154)/TOP2A FISH(1/11)	28.60%/9.0%	doxorubicin	Topoisomerase inhibitor
EGFR (3/11)	27.3%	*cetuximab	monoclonal antibody
SPARC (60/347)	19.90%	*nab-paclitaxel	Microtubule poison
PTEN_low (32/178)	18.00%	everolimus	Kinase inhibitor
PR (28/173)	16.20%	anti-hormonal therapy	others
Androgen Receptor (18/172)	10.5%	anti-hormonal therapy	others
EGFR FISH (1/38)	2.6%	erlotinib	Kinase inhibitor
Estrogen Receptor (4/173)	2.3%	anti-hormonal therapy	others
cMET (1/78)	1.3%	*tivantinib	Kinase inhibitor
ALK FISH (0/8), cMET ISH (0/57), HER2 (0/173), HER2 ISH (0/79)	0.0%	*crizotinib, *tivantinib, *trastuzumab	Kinase inhibitor, monoclonal antibody

*drugs were not included in the compound library

Table 2. Frequency distribution of protein and gene copy number changes. All biomarkers above are tested by immunohistochemistry (protein levels), unless indicated by "ISH" (gene copy status by in situ hybridization). Percent frequencies represent data collected from CMI database; highlighted rows correspond to drugs that effectively inhibit GIST cells in Boichuk's study.

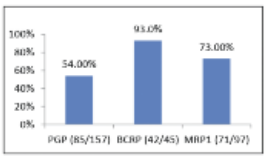

Figure 2. Multidrug Resistance (MDR) Phenotype – majority of GIST patients exhibit overexpression of ABC transporters which are drug efflux pumps.

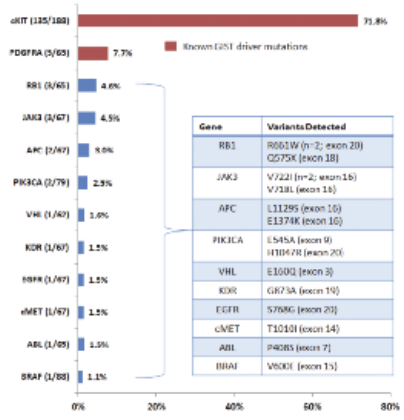

Figure 3. Mutational analysis in up to 188 GIST patients. Data demonstrates that beyond cKIT and PDGFRA, there is limited success at identifying a targetable gene through sequencing platforms.

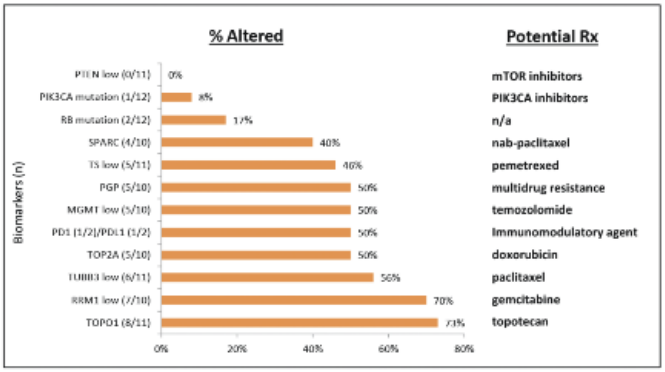

Figure 4. Notable biomarker alterations in cKIT and PDGFRA wildtype GIST patients. Multiplatform profiling including IHC, ISH and NGS platforms revealed several potential therapeutic options based on expression status of multiple predictive biomarkers. Importantly, NGS identified only 2 alterations and ISH did not identify any alterations. Data suggests potential therapeutic options based on protein expression status for cKIT/PDGFRA wildtype GIST patients.

Conclusions

- A multiplatform approach of identifying potential therapeutic options for GIST patients who become resistant to TKI therapy or are cKIT/PDGFRA wildtype may yield therapeutic options beyond tyrosine kinase inhibitors.
- Our data demonstrate GIST patients exhibit high frequency of low RRM1, low TUBB3, low TS and high TOP2A protein expression. These frequencies suggest the potential utility of cytotoxic agents that include DNA synthesis inhibitors, microtubule poisons, antimetabolites and topoisomerase inhibitors.
- GIST patients frequently exhibit high levels of drug efflux pumps, demonstrating the potential role for multidrug resistance, which lends support for the added benefit of identifying treatment options through molecular profiling.
- Mutational platforms offer limited value in detecting targetable genes outside of cKIT and PDGFRA. Non-cKIT/PDGFRA targetable mutants are rare events (e.g. BRAF V600E)
- Protein expression offers the most value for cKIT and PDGFRA wildtype patients (10-13% of GIST population), identifying multiple ,potential treatment choices based on expression status of predictive biomarkers (TOPO1, TUBB3, etc.)

References

1. Boichuk, S., A. Duensing, et al. (2014). "Unbiased Compound Screening Identifies Unexpected Drug Sensitivities and Novel Treatment Options for Gastrointestinal Stromal Tumors." Cancer Res 74(4): 1200-1213.

Insights on Tumor Profiling: Finding the Elusive but Pivotal Piece of the GIST Puzzle With Patterns of Biomarker Expression

Two scientific sessions earlier this year explored biomarker analysis for gastrointestinal stromal tumors (GIST). These sessions, sponsored by the American Society of Clinical Oncology (ASCO) provided exciting information on how such analysis could facilitate more effective identification of therapeutic targets in the disease. In this interview with The GIST Cancer Journal*, two researchers from Caris Life Sciences, Phoenix, Arizona, offered their perspectives on the role of biomarker analysis in clinical decision making and what looms on the horizon to use analytic techniques to optimize treatment choices. The interview features comments by Sandeep K. Reddy, MD, Chief Medical Officer at Caris Life Sciences, and Rebecca Feldman, PhD, Research Scientist and Molecular Science Liaison.*

Q. How is biomarker analysis moving beyond earlier approaches to delineate the heterogeneous nature of gastrointestinal stromal tumors (GIST)?

Dr Reddy: The Caris multiplatform approach picks up mutations in PDGFRA and KIT, but also looks at additional abnormal protein expression. The analysis picks up the variance in PDGFRA as part of identifying the primary resistance to imatinib. At Caris, we want to understand the underlining biology of the tumor in order to provide actionable information to help the oncologist create a more informed treatment decision.

Q. What are the key treatment issues arising from biomarker analysis?

Dr Reddy: Imatinib has been the standard of treatment for a long time and KIT/PDGFRA analysis is widely considered routine, but now we have the second generation TKIs. The real issue actually is how to treat or think about the resistant GIST, perhaps KIT/PDGFRA negative tumors that lack more common molecular features. Patients are already having this done, but the real question concerns patients who are phenotypically negative and who can benefit from having additional molecular analysis routinely and how we can target clinical trials for them.

Dr Feldman: We test for all of the "hot spots" of KIT and PDGFRA mutations. The platform detects the primary activating mutations and the secondary resistant mutations. We cover all of the important areas for c-KIT and PDGFRA analysis. The information we presented at two ASCO sessions included one that focused on TKI-resistant and rare GISTs lacking the active mutations in cKIT and PDGFRA patients, and one that looked at molecular profiling of GIST as a whole disease.

Q. How then, could treatment options be expanded if TKI resistance is a problem? Do the findings in TKI-resistant patients suggest an opportunity to reconsider some overlooked strategies in the light of new data?

Dr Feldman: Perhaps some of the traditional chemotherapies could be revisited, particularly in the right setting. And the right setting would be for those rare or resistant GISTs. The rationale for doing that is based on the fact that many of the chemotherapy trials that were performed with GIST predated the identification of c-KIT and PDGFRA as driver mutations. So there are a lot of patients who should not have been treated with chemotherapies who were being treated. Therefore, the response rates were really low but at the time there were also a lot of misdiagnoses, a sizeable number of leiomyosarcomas were being included in those studies. So those are very chemotherapy-resistant cancers that were included in the studies.

Q. To what extent is protein expression an essential part of the analysis of biomarkers?

Dr Feldman: It is a major part of the analysis, and it is reflected in the 13 biomarkers highlighted in the presentation at the ASCO meeting. As a case in point, consider the use of Taxanes in the setting of GIST. There are three biomarkers that the platform tests for that could help predict a response to this agent. An appropriate avenue moving forward would be a clinical trial to determine if these biomarkers could predict response to various therapies.

Q. What percentage of GIST patients would benefit from application of the platform, perhaps as a screening tool?

Dr Reddy: Anybody who has suspected GIST would have benefit because it would certainly rule in GIST. If we detect a c-KIT or PDGFRA mutation, that's going to be helpful in terms of a confirmatory diagnosis.

Q. What might be important implications for guiding therapy in view of obtaining biomarkers suggestive of imatinib resistance or other molecular findings?

Dr Reddy: Even if you are treating a patient with imatinib, it would be helpful to know that your patient is at higher likelihood of *early* progression. That might change the way you follow the patient. For example, you may want to do that CT a little bit earlier. There is value to obtaining biomarker analysis for every patient, not just the 10-15% of patients who lack KIT/PDGFRA mutations. The key issue is how the information is used by the clinician.

Q. Looking ahead, what are some of the gaps in our knowledge about biomarkers in GIST and what is needed to more effectively optimize clinical decision making?

Dr Reddy: There are a couple of things we will be looking for. One is to collect outcome data. Much of the data we have been looking at involves alterations at the genomic and proteomic levels. We are working with our centers of excellence partners to obtain outcome data so that when we see what we think is a drug target, strategies can be tailored to address that target. And then, do patients actually benefit from that therapy? At the end of the day, we might find a lot of interesting targets but if people do not improve, there is no actual clinical benefit, then the target is not meaningful. That is the key thing we are looking at—obtaining that outcome piece, focusing on end points of progression-free survival and overall survival.

Dr Feldman: To continue with that line of thinking, it would be particularly interesting to go back and follow the patients who were double Wild-type or TKI-resistant and review how the treating physician treated that patient and see if we can find a correlation with the biomarkers that we tested and what treatment they actually chose. This would be a retrospective analysis of how those patients were treated. This would definitely be the next step in the analysis. ■

express low levels of DNA repair genes may have implications for use of cytotoxic therapies for other solid tumors as well. Perhaps this approach could have merit in treating patients with GIST that progress despite TKI therapy or patients whose tumor does not have a KIT or PDGFRA mutation. Furthermore, through its comprehensive literature review, CMI identified some cytotoxic agents as potential treatments for GIST based on its reported effectiveness at killing TKI-responsive and TKI-resistant GIST cells.[11]

The conclusions from our study are:

- A multiplatform approach may yield therapeutic options beyond tyrosine kinase inhibitors by identifying potential therapeutic options for GIST patients who have become resistant to TKI therapy or are cKIT/PDGFRA Wild-type.
- Our data demonstrates that GIST patients exhibit high frequency of low RRM1, low TUBB3, low TS and high TOP2A protein expression, suggesting the potential utility of cytotoxic agents that include DNA synthesis inhibitors, microtubule poisons, antimetabolites and topoisomerase inhibitors.
- GIST patients frequently exhibit high levels of drug efflux pumps, demonstrating the potential role for multidrug resistance, which further supports the benefit of molecular profiling of identifying additional treatment options.
- Single-platform gene mutation analysis offers limited value in detecting targetable genes outside of cKIT and PDGFRA. Non-cKIT/PDGFRA targetable mutants are rare events (eg, BRAF V600E).
- Protein expression offers the most value for cKIT and PDGFRA Wild-type patients (10-13% of GIST population), identifying multiple potential treatments.

The study underscored the heterogeneous nature of GIST. According to study investigators, CMI demonstrated that at least half the tumors (52% to 68%) expressed one or more proteins known to confer multidrug resistance (P-glycoprotein, multidrug resistance protein 1, or both).

Approximately three-quarters of tumors (72%) expressed low levels of tubulin beta 3 (TUBB3), which the investigators said suggests agents that bind tubulins such as taxanes (eg, paclitaxel and docetaxel) or vinca alkaloids (eg, vincristine, vinblastine, and vinorelbine), may be active in a large proportion of GIST patients. Expression of topoisomerase enzymes 1 and 2A was detected in 34% and 32% of specimens, respectively. Thus, tumors in one-third of patients may respond to treatment with anthracyclines or topoisomerase inhibitors such as topotecan, irinotecan, etoposide or doxorubicin.

Table. Molecular Subsets of GIST

Mutations at
- *KIT* exon 9, 11, 13, 14, 17, or 18
- *PDGFRA D842V* or non-D842V

KIT and PDGFRA wild-type with mutations at
- *NF1*
- *BRAF V600E*
- *KRAS* or *NRAS*
- *SDHB* or *SDHC*
- Overexpression of IGF1R

Nine GIST specimens were analyzed for expression of the programmed cell death protein 1 (PD-1) and the PD-1 ligand (PD-L1). Of these samples, 56% expressed positive tumor-infiltrating lymphocytes and 33% expressed PD-L1 in tumor tissue. Two PD-1 inhibitors have been approved thus far in the United States, both for melanoma: pembrolizumab in September 2014 and nivolumab in December 2014. Many other PD-1 and PD-L1 immunotherapies are in development, and the Caris investigators said these immune checkpoint inhibitors may represent viable options for patients with TKI-resistant GIST.

In an abstract and poster presented at the 2015 ASCO Scientific Sessions our team further explored the value of biomarker analysis in a different subset of patients.[12] Double (KIT/PDGFRA) Wild-type (D-WT) GISTs represent a rare subset of GIST patients in need of treatment options. We investigated a commercial database of theranostic biomarkers for the identification of novel therapy options for GIST; 217 GIST cases were evaluated for D-WT and TKI-R. Nineteen D-WT and 24 TKI-R GIST patients were identified, a multi-

Editor's note: **This poster was presented at the scientific sessions of the 2015 ASCO meeting. It suggests how a multiplatform approach identifies preclinical data and predictive biomarker expression distribution that supports "re-visiting" chemotherapy options in a selected population of GIST patients.**

platform approach of biomarker testing was used and included a combination of sequencing (NGS, Sanger), protein expression (IHC) and gene amplification (ISH) in these patients.

Mutational screening revealed variants in 6/47 genes (excluding cKIT and PDGFRA), most of which are potentially targetable with therapies currently available, or in clinical trials: PIK3CA, ABL, cMET, JAK3, RB1, and VHL. ABL and JAK3 mutations were exclusively found in the TKI-R subgroup. PD-1 positive tumor infiltrating lymphocytes were

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Identification of therapy options for Rare and

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Abstract (No. 10539)

Background: GISTs are predominantly defined by KIT/PDGFRA mutations which are targetable with a range of kinase inhibitors, however the majority become TKI-resistant (TKI-R). Double (KIT/PDGFRA) wildtype (D-WT) GISTs represent a rare subset of GIST patients in need of treatment options. We investigated a commercial database of theranostic biomarkers for the identification of novel therapy options for GIST.

Methods: 217 GIST cases were evaluated for D-WT and TKI-R. A multiplatform approach of biomarker testing was used and included a combination of sequencing (NGS, Sanger), protein expression (IHC) and gene amplification (ISH).

Results: D-WT (n=15) and TKI-R (n= 23) (including 7 with resistance mutations in the absence of a primary, activating KIT mutation and 4 PDGFRA D842V) were studied for additional targetable alterations. IHC and ISH tests revealed no overexpression or amplification in cMET, EGFR, or HER2. PTEN was intact (positive expression) in the majority of GISTs (92.9% (13/14) D-WT; 100% (19/19) TKI-R). Mutational screening revealed variants in 6/47 genes (excluding cKIT and PDGFRA), most of which are potentially targetable with therapies currently available, or in clinical trials: PIK3CA, ABL, cMET, JAK3, RB1, and VHL. ABL and JAK3 mutations were exclusively found in the TKI-R subgroup. PD-1 positive tumor infiltrating lymphocytes were found in 33% (1/3 D-WT) and 60% (3/5 TKI-R), while PD-L1 tumor expression was found in 67% (2/3 D-WT) and 40% (2/5 TKI-R). Although chemotherapy has historically elicited poor responses in GIST (non-selected patient trials), we observed a high frequency of low expression of predictive markers for gemcitabine (RRM1) and paclitaxel (TUBB3) (77%, 90%; 57%, 73% for D-WT and TKI-R, respectively) and high frequency of TOPO1 overexpression for irinotecan (57%, 32% in D-WT and TKI-R, respectively) which were recently shown to be cytotoxic in TKI-R GIST cell lines (Boichuk, 2014).

Conclusions: A multiplatform approach of theranostic biomarkers identified non-cKIT/PDGFRA therapy options for rare and resistant GIST. Opportunities for investigating new targetable agents and potentially re-visiting cytotoxics with biomarker guidance in these subpopulations are warranted.

Background

- Prior to the identification of the molecular drivers, cKIT and PDGFRA, in GIST, clinical management was similar to other soft tissue sarcomas, which included conventional chemotherapies such as doxorubicin.
- Standard treatment for GIST now includes a repertoire of small-molecule inhibitors including imatinib, sunitinib and regorafenib. As with other targeted approaches, the acquisition of resistance mutations inevitably emerge, and novel therapy approaches are needed for patients who have stopped responding to TKIs.
- In addition, treatment standards for the GIST population lacking cKIT or PDGFRA activating mutations (10-15% of GIST patients) are also needed.
- Interestingly, a recent study[3] demonstrated the surprising sensitivity of GIST cell lines and TKI-R GIST patient-derived xenograft models to non-targeted FDA-approved, chemotherapeutic agents.

Methods

** An additional 5 patients have been identified since the submission of the abstract and included in this analysis*

Two hundred seventeen GIST cases referred to Caris Life Sciences from 2009 – 2015 were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (next-generation sequencing [NGS, 47 genes, hot spot] or Sanger), protein expression (immunohistochemistry or IHC) and gene amplification (CISH or FISH).

Patients included in this study were those exhibiting wildtype cKIT and PDGFRA genotypes (D-WT) and cKIT/PDGFRA variants associated with resistance to TKI therapy.

Results

A

	D-WT (n=19)	TKI-R (n=24)
Esophagus	(1/19) 5%	(0/24) 0%
Stomach	(6/19) 32%	(6/24) 25%
Small Intestine	(6/19) 32%	(6/24) 25%
Colorectum	(1/19) 5%	(1/24) 4%
Other (abdominal soft tissues, peritoneum, GI Tract, nos)	(5/19) 26%	(11/24) 46%

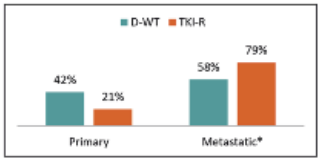
B

Mean Age (years): 57 (D-WT), 62 (TKI-R)

C

	cKIT	PDGFRA
Secondary Mutation Present	11 (554_K558del); 17 (Y823D)	WT
	11 (557_K558del); 13(V654A)	WT
	9 (502_Y503dup); 17 (D820E)	WT
	11 (V560D); 13 (V654A)	WT
	11 (V560D); 17 (D820G)	WT
	11 (557_V559delinsF); 13 (V654A)	WT
	11 (L576P); 17 (D820V/D816N)	WT
	11 (554_V560delinsVG); 17 (R815_K818delinsIE)	WT
	11 (552_k558del); 17 (Y823D)	WT
	11 (P551_V555del); 13 (V654A)	WT
	11 (W557R); 13 (H650dup)	WT
	11 (572_P573dup); 17 (D820Y)	WT
	11(S51_V555del); 17 (N822K)	WT
Resistance Mutation in Absence of Primary	17 (N822Y)	WT
	17 (N822K)	WT
	17 (N822K)	WT
	17 (N822K)	WT
	17 (Y823D)	WT
	17 (Y823D)	WT
	17 (D820G)	WT
PDGFRA Resistance Mutation	WT	18 (D842V)
	WT	18 (D842V)
	WT	18 (D842V)
	WT	18 (D842V)

Figure 1A-1C. Primary Tumor Attributes (e.g. site location, genotypes) and Patient Demographics. 1A. Primary tumor sites; most frequent sites were stomach/small intestine for D-WT and gastrointestinal tract, nos for TKI-R. 1B. Male gender and higher mean age associated with TKI-R subgroup. 1C. cKIT/PDGFRA genotypes for TKI-R subgroup.



*Metastatic sites included, for D-WT: abdomen (n=2), connective & soft tissues, chest wall, pelvis, liver (n=2), mesentery, adnexa, colon (n=2) and for TKI-R: abdomen (n=8), pelvis, connective & soft tissue, liver (n=3), omentum, pelvis (n=5), pancreas.

Figure 2. Percent of profiling performed on primary or metastatic tumor specimens. Metastatic sites used for profiling are listed.

found in 33% (1/3 D-WT) and 60% (3/5 TKI-R), while PD-L1 tumor expression was found in 67% (2/3 D-WT) and 40% (2/5 TKI-R). Although chemotherapy has historically elicited poor responses in GIST (non-selected patient trials), we observed a high frequency of low expression of predictive markers for gemcitabine (RRM1) and paclitaxel (TUBB3) (77%, 90%; 57%, 73% for D-WT and TKI-R, respectively) and high frequency of TOPO1 overexpression for irinotecan (57%, 32% in D-WT and TKI-R, respectively) which were recently shown to be cytotoxic in TKI-R GIST cell lines.[1]

The conclusions reached by this study are:

- A subgroup of GIST patients, including those that lack activating mutations in cKIT/PDGFRA and those harboring cKIT/PDGFRA resistance mutations, are in great need of therapy options outside of the standard of care.
- Preclinical data and predictive biomarker expression distribution presented here, supports "re-visiting" chemotherapy options in a selected population of GIST patients
- IHC identified at least 1 therapy option (chemotherapy

Resistant Gastrointestinal Stromal Tumors (GIST)

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Results, continued

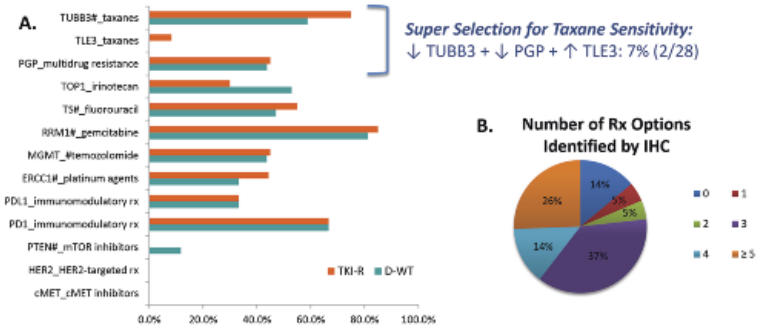

Figure 3A-3B. Protein Biomarkers and Therapy Identification by IHC. 3A. % positivity is shown, unless indicated by #, which are low/negative frequencies (low expression associates with favorable response). Select biomarkers are associated with responses to cytotoxic agents, which were shown to have anti-tumor effects on TKI-R GIST patient-derived xenografts[3]. Immunomodulatory therapies may be of interest as well, based on presence of PDL1 expression in tumor cells and presence of PD1+ TILs. The 2 GIST patients with loss of PTEN expression had normal PIK3CA/AKT genotype. 3B. Predictive biomarker assay by IHC identifies at least one therapy option in 86% of D-WT and TKI-R GIST patients.

** Note- Changes in gene copy number, assayed by *in situ* hybridization methods, were not detected in cMET (0/14, 0/9) or HER2 (0/16, 0/12) in either subgroup.

	ABL	ATM	cMET	JAK3	PIK3CA	RB1	RET	TP53	VHL
D-WT	0% (0/19)	5% (1/19)	5% (1/19)	0% (0/19)	5% (1/19)	11% (2/19)	5% (1/19)	5% (1/19)	0% (0/17)
TKI-R	7% (1/14)	0% (0/14)	0% (0/14)	21% (3/14)	7% (1/15)	0% (0/12)	0% (0/14)	0% (0/14)	8% (1/13)

Variants were not detected in the following genes, in either subgroup: AKT1, ALK, APC, BRAF, BRCA1, BRCA2, CDH1, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, HNF1A, HRAS, IDH1, JAK2, KDR, KRAS, MLH1, NOTCH1, NPM1, NRAS, PTEN, PTPN11, SMAD4, SMARCB1, SMO, STK11

Table 2. Variants detected by Next Generation Sequencing for D-WT and TKI-R GIST subgroups. PIK3CA is the only gene, out of the 47 tested, for which variants were detected in both subgroups. Variants in RB1 were detected in two patients in the D-WT subgroup, and JAK3 in three patients in the TKI-R subgroup. A minority of variants detected can be matched to therapies approved for other solid tumors, or therapies under investigation in clinical trials.

	Patient	cKIT	PDGFRA	Additional Gene Alterations and Potential Therapeutic Targets: Gene	Variant	Variant Classification/ Functional Significance	Therapeutic Approach
D-WT	1	WT	WT	ATM	D1815fs	Pathogenic, inactivating mutation	DNA-damaging agents, e.g. platinum agents, PARP inhibitors
				RET	Y791F	VUS, likely passenger role	n/a
	2	WT	WT	cMET	T1010I	VUS, weak oncogenic potential	n/a
	3	WT	WT	PIK3CA	E545A	Pathogenic, increased catalytic activity	PIK3CA-AKT-mTOR pathway inhibitors
	4	WT	WT	RB1	R661W	Pathogenic: Partial inactivation of Rb protein	n/a
	5	WT	WT	RB1	R661W		
	6	WT	WT	TP53	C277Y	Presumed Pathogenic	n/a
TKI-R	1	11(P551_V555del); 17 (N822K)	WT	VHL	E160Q	VUS, likely passenger role	n/a
	2	11(V560D); 17 (D820G)	WT	PIK3CA	H1047R	Pathogenic, increased catalytic activity	PIK3CA-AKT-mTOR pathway inhibitors
	3	17 (D820G)	WT	JAK3	V722I	VUS, gain of function variants, activating alleles in AML & AML	JAK3 inhibitors being tested for autoimmune diseases, unknown role in cancer
	4	WT	18 (D842V)	JAK3	V722I		
	5	WT	18 (D842V)	JAK3	V718L		
	6	WT	18 (D842V)	ABL1	P408S	VUS	n/a

Table 3. Clinical Implications of variants detected by Next-Generation Sequencing. Therapeutic targets identified by NGS are infrequent events. In D-WT GIST, pathogenic mutations in ATM, PIK3CA, RB1 and TP53 were detected, for which, only PIK3CA and ATM are considered targetable. The most frequently mutated gene in TKI-R GIST, JAK3, has unknown clinical implications in these patients.

Conclusions

- A subgroup of GIST patients, including those that lack activating mutations in cKIT/PDGFRA and those harboring cKIT/PDGFRA resistance mutations, are in great need of therapy options outside of the standard of care
- Preclinical data[3] and predictive biomarker expression distribution presented here, supports "re-visiting" chemotherapy options in a selected population of GIST patients
- IHC identified at least 1 therapy option (chemotherapy and/or targeted therapies not considered standard of care for GIST) in 86% of rare (D-WT) and resistant (TKI-R) GIST.
- Variants detected by NGS offer limited value in identification of targetable alterations. Of the 43 patients included in this study, 3 patients exhibited variants that can be targeted (PIK3CA, ATM).

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and/or targeted therapies not considered standard of care for GIST) in 86% of rare (D-WT) and resistant (TKI-R) GIST.

- Variants detected by NGS offer limited value in identification of targetable alterations. Of the 43 patients included in this study, 3 patients exhibited variants that can be targeted (PIK3CA, ATM).

Conclusion

Caris Molecular Intelligence, a multi-technology tumor-profiling platform that combines next-generation gene sequencing, immunohistochemistry, in situ hybridization (fluorescence and chromogenic), and polymerase chain reaction methods can identify patterns of protein and gene alterations in GIST. Recognition of these biomarkers can be helpful in identifying drug sensitivities in GIST patients whose mutational status may be uncertain and therefore needs to be determined. Results from the evaluation of this technique suggest that chemotherapeutic agents may be reconsidered in the treatment setting because of sensitivities observed in recently presented data.

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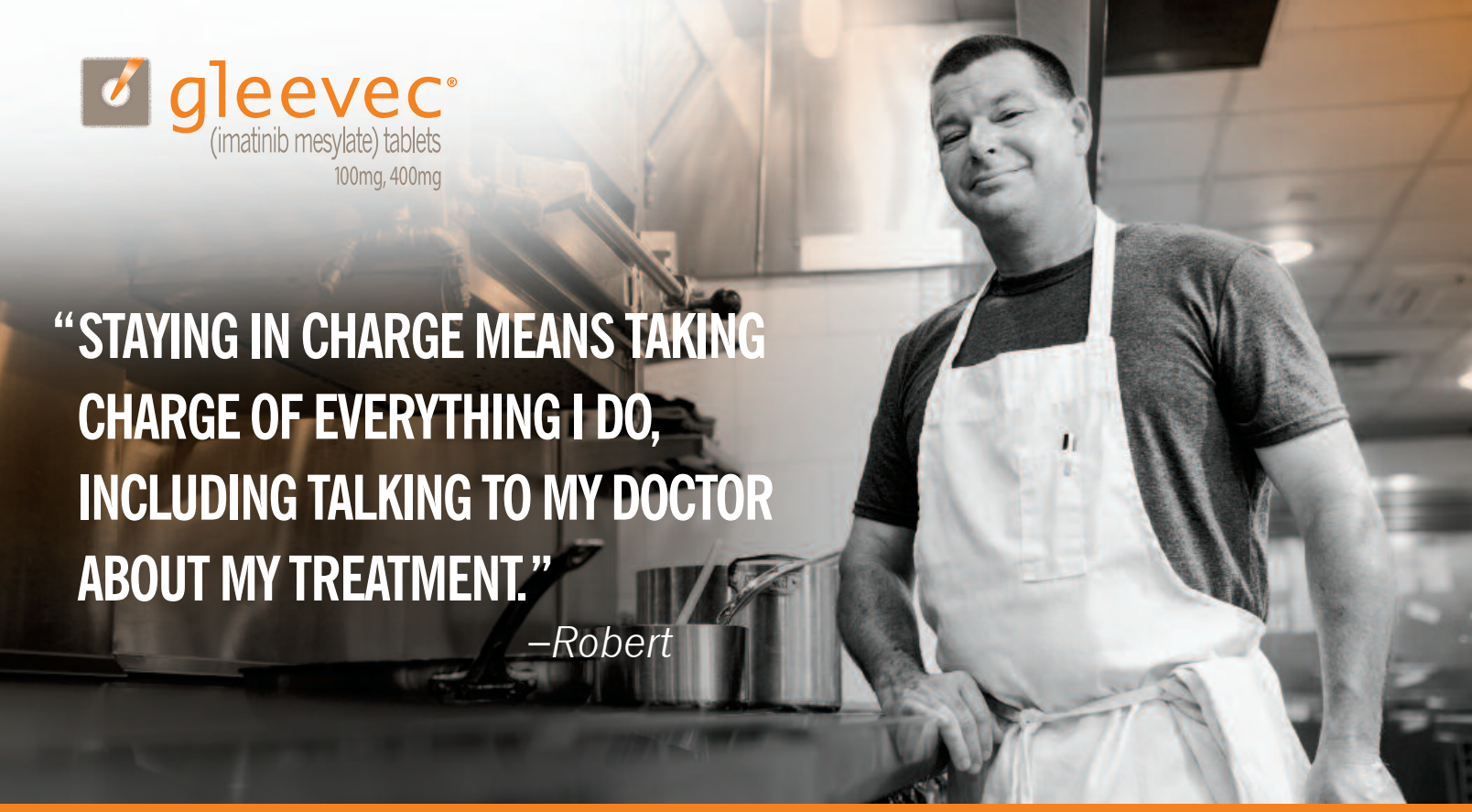

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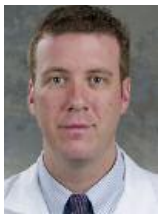
The Gastroenterologist and GIST: A Vital Member of the Team Becomes More of a 'Diagnostician' in the Continuum of Care



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Gastrointestinal stromal tumor (GIST) can present a formidable diagnostic challenge, and the first clinician to meet the challenge is likely to be the gastroenterologist. The diagnostic yield of imaging techniques has improved markedly, but there are still limitations associated with their use by the gastroenterologist. This report clarifies the options available and the relative merits of how they can be used in daily practice.

Advances in technology, advances in the understanding of biology of cancer, and the advent of improved and novel therapies are all contributing factors to the expanded role of the gastroenterologist in diagnosing gastrointestinal stromal tumors (GIST). Gastroenterologists have a unique opportunity to capitalize on the position that they hold in the patient care continuum. The gastroenterologist has evolved from a "pure" diagnostician to an endoscopic surgeon, geneticist, nutritionist, immunologist and chemotherapist, and palliative care physician.[1]

As the role of the gastroenterologist has expanded, so has the spectrum of diagnostic techniques available. There is an evolving need by both gastroenterologists and oncologists to adapt to the new thinking on diagnosing GIST through the use of various endoscopic tools available. These modalities provide greater ability to evaluate submucosal lesions of the GI tract, including enhanced endosonographic features that can more easily allow one to differentiate certain types of subepithelial lesions, including potential GIST. Addressing this evolution of care, some authors have called GIST a model of multidisciplinary work in oncology, involving the integrated participation of several specialties, oncologists, gastroenterologists, pathologists, and many more.[2]

Although not well defined as yet, an algorithm is beginning to emerge on incorporating a range of techniques, including endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), endoscopic/laparoscopic intragastric enucleation, device-assisted enteroscopy, and related procedures, including PillCam or capsule endoscopy. Most GISTs are discovered incidentally by the gastroenterologist, often because of GI bleeding or other symptoms alerting the clinician to a potential malignancy. GIST is unlikely to be identified definitively by a superficial biopsy and it remains for an advanced endoscopist to fully characterize the lesion and determine which layer of the stomach may be involved. Although GISTs may be found anywhere in the GI tract, they are most commonly encountered in the stomach.[3] GISTs are believed to originate from stem cell precursors to the interstitial cells of Cajal, which are involved in the regulation of gastrointestinal motility.[4]

Presentation

Population-based studies offer insights into the early signs of GIST. Approximately 70% of patients with GISTs were clinically symptomatic, according to one report.[5] The most common presenting symptoms are GI bleeding, and the others were abdominal pain or the presence of a palpable mass. However, small-sized GISTs are asymptomatic and incidentally discovered on endoscopy.[6]

As GIST is usually located in muscularis propria which cannot be obtained by routine endoscopic biopsy, endoscopic ultrasonography (EUS) is useful for further information. In EUS, gastric GIST typically appears as well demarcated, round, hypoechoic mass arising from fourth layer

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Key words: gastroenterologist, GIST, diagnosis, endoscopic ultrasonography, fine-needle aspiration, capsule endoscopy, enucleation, laparoscopic.

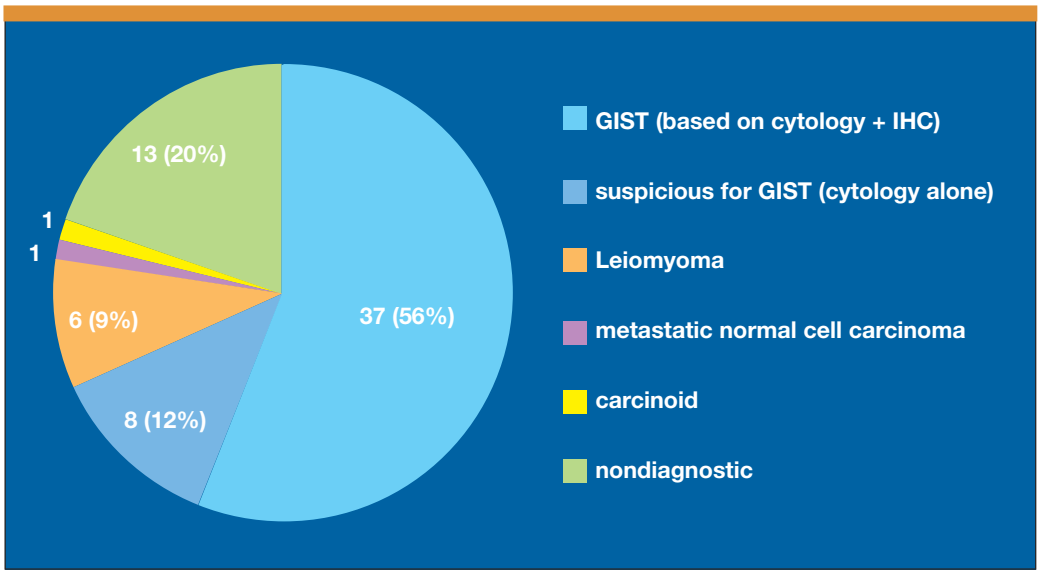

Fig. 1. Cytologic diagnoses from endoscopic ultrasound fine needle aspiration (EUS-FNA)

of the stomach. Although many malignant features of GIST in EUS have been introduced, the sensitivity and specificity have not been promising,[7-9] and definitive diagnosis has been usually made by immunohistochemical analysis after resection. EUS-guided fine needle aspiration (EUS-FNA) or core biopsy can offer histological diagnosis, but it is difficult for EUS-FNA to obtain enough tissue in small-sized GIST for evaluation of mitotic index.[10,11]

Our approach to diagnosis and management of GISTs in our institution is as follows:

1) 2 cm is used as a cutoff for surgery. This is not an absolute number, and the decision to pursue surgical resection is dependent upon the patient's age and comorbidities.
2) Older patients with significant comorbidities may not be candidates for surgery because of the expected slow growth of their GIST.
3) There are two methods of obtaining tissue via endoscopic ultrasound - FNA (fine needle aspiration) or trucut which obtains a core biopsy. The trucut can be difficult for smaller lesions (<1cm) and cannot always be obtained.
4) Special staining is performed on the specimen to confirm the presence of GIST (c-kit being the most common)

Endoscopic Ultrasonography—Assessment in the Pre-GIST Era

EUS is now a pivotal test to help diagnose GIST. Early reports on its use were done before GIST was differentiated from other gastric tumors and recognized as a distinct entity. Early data by Tio et al12 showed that EUS was superior to diagnosing subepithelial lesions versus other non-invasive techniques. The capability of endoscopic maneuvering of the transducer provides accurate assessment of lesions by employing cross-sectional, longitudinal, and oblique sections. Real-time endosonographic imaging allows for greater diagnostic technique versus static imaging studies such as CT or other contrast studies.

GIST Presents a Formidable Diagnostic Challenge

As EUS became the technique of choice for both the staging of GI and pancreatic malignancies,13-16 efforts focused on how the method could be improved as imaging alone did not provide definitive diagnosis. Because of this pitfall, tissue sampling is required.[17]

Despite the advent of EUS, the diagnosis of GIST can be challenging, and misdiagnosis can occur.[17] GIST is a firm lesion which can contain fibrosis, making tissue sampling somewhat difficult without substantial penetrative force of the needle for aspiration of cells.[18] Some have reported success in diagnosing GIST when combining cytology along with immunocytochemical staining methods.[19-21] The use of immunocytochemistry may also be helpful in differentiating low-grade from high-grade GISTs on the basis of spindle cell features. Tumor cells from GIST should be positive for c-KIT, whereas smooth-muscle cells from the bowel wall and from spindle cell carcinoma should be negative for this marker. Spindle cell carcinoma is positive for cytokeratin expression, where-as GIST is not.

"The use of immunocytochemistry may also be helpful in differentiating low-grade from highgrade GISTs on the basis of spindle cell features. Tumor cells from GIST should be positive for c-KIT, whereas smooth-muscle cells from the bowel wall and from spindle cell carcinoma should be negative for this marker. Spindle cell carcinoma is positive for cytokeratin expression, whereas GIST is not."

Early work mentioned above using fine-needle aspiration helped lay the groundwork for later studies to further characterize the use of EUS-FNA. In a 4-year retrospective analysis, Watson et al showed the yield of EUS-FNA for subepithelial lesions of the upper GI tract, and determined the performance of characteristics of EUS-FNA for diagnosing GISTs.[22]

A total of 65 patients (**Figure 1**) underwent EUS-FNA of 66 submucosal lesions during the study period. EUS-FNA was either diagnostic (68%) or suspicious (12%) in a total of 80%. EUS-FNA yielded the following diagnoses: GIST based on cytology and immuno- histochemistry (56%), suspected GIST (12%), leiomyoma (9%), other neoplasm (3%), and non-diagnostic (20%). Larger lesion size, gastric location, and presence of on-site cytopathology were associated with higher yield in univariate analysis. Larger needle size and number of FNA passes were not associated with improved yield. Based on

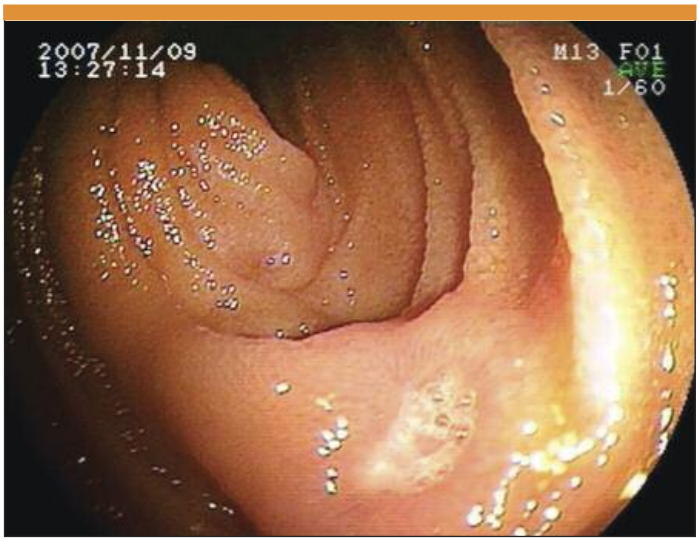

Fig. 2. Neuroendocrine tumor of the jejunum detected at DBE in an 80-year-old woman with obscure gastrointestinal bleeding and video capsule endoscopy demonstrating bleeding in the jejunum. (Source for Figures 2,3,4: Partridge BJ, et al. *Dig Dis Sci*. 2011;56:2701-2705)

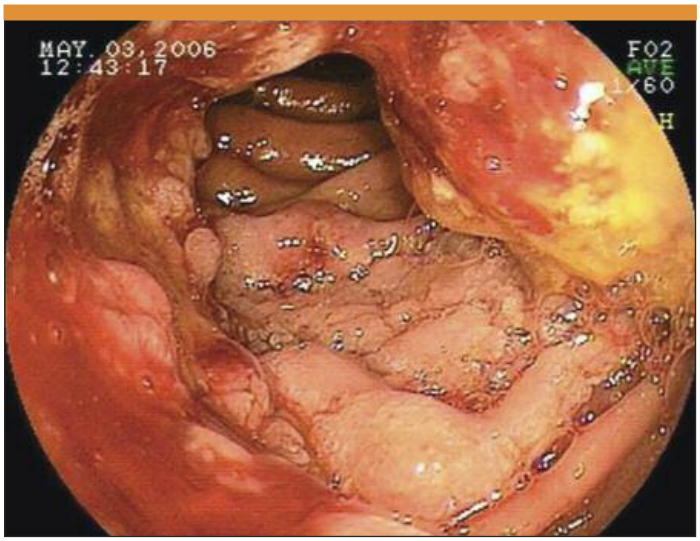

Fig. 3. Adenocarcinoma of the jejunum identified in a 61-year-old man with early satiety, weight loss, and a jejunal mass detected on CT scan.

resection pathology from 28 specimens, the EUS-FNA performance characteristics for diagnosing GISTs revealed a sensitivity of 82%, a specificity of 100%, and an overall accuracy of 86%.

Although it was a retrospective study, the Watson report[24] supports the routine role of EUS-FNA as a safe and accurate modality for characterizing these lesions. The authors noted a higher diagnostic yield with larger sized lesions, tumors in the stomach, and the presence of an on-site cytopathologist.

EUS-FNA vs Trucut Biopsy

There are limitations to EUS-FNA that should be addressed. Immunohistochemical analysis is not always feasible from EUS-FNA samples because of the small number of cells obtained by aspiration. It has been suggested that these limitations might be overcome by using a needle with a larger bore or a trucut. EUS-guided trucut biopsy (EUS-TCB) has emerged as a method to resolve such limitations when a core tissue specimen is needed. However, trucut biopsy can be difficult to obtain when dealing with smaller lesions.

Fernandez-Esparrach et al[23] prospectively compared endoscopic ultrasound (EUS)-guided fine-needle aspiration (EUS-FNA) and EUS-guided trucut biopsy (EUS-TCB) in 40 patients with suspected gastric subepithelial tumors. All patients underwent both EUS-FNA and EUS-TCB in a randomized sequence; 27 of the 40 patients were found to have GIST and device failure occurred in 6 of 40 patients. Accurate diagnosis was obtained in 70% of patients who underwent EUS-FNA and in 60% of patients who underwent EUS-TCB. Among the samples that were adequate, immunohistochemistry could be performed in 74% of EUS-FNA samples and in 91% of EUS-TCB samples ($P = 0.025$). When inadequate samples were included, the overall diagnostic accuracy of EUS-FNA was 52% and that of EUS-TCB was 55% (P = NS). No patients developed complications.

The authors concluded that EUS-TCB is not superior to EUS-FNA in GISTs because of the high rate of technical failure of trucut. The caveat to this is that if a trucut biopsy is able to be performed, then it should be done as it has a higher diagnostic yield.

"Patients who present with GI bleeding can undergo wireless capsule endoscopy when an upper endoscopy and colonoscopy do not find a source. This is designed to diagnose a small bowel source for either obscure overt or obscure occult GI bleeding."

Combined Endoscopic/Laparoscopic Intragastric Enucleation: When Should It Be Used?

Definitive surgical treatment of GIST typically involves full-thickness resection of the lesion with normal gastric wall as the margin.[26] This can be accomplished safely with a laparoscopic approach in most cases.[25-27] In the case of lesions that are located in the proximal area of the stomach, open resection is a safer technique.

There are instances where a gastroenterologist can work with a laparoscopic surgeon in more proximal gastric cases. Although this report [26] consists of a relatively rare subset of GIST patients, it is the first study to report on the long-term outcome for combined endoscopic/laparoscopic enucleation. Since no recurrences were observed over 5 years, the technique is appropriate in selected patients. The combined approach seems to be gaining additional support from clinicians based on considerations of tumor size and location. For example, the updated NCCN task force on GISTs recommends laparoscopic tumor excision for lesions up to 5 cm.[28] Others suggest that combined hybrid methods with tumor enucleation may provide a safer modality to treat pathology found on the posterior wall or near the esophagogastric junction. For tumors as large as 7 cm located in

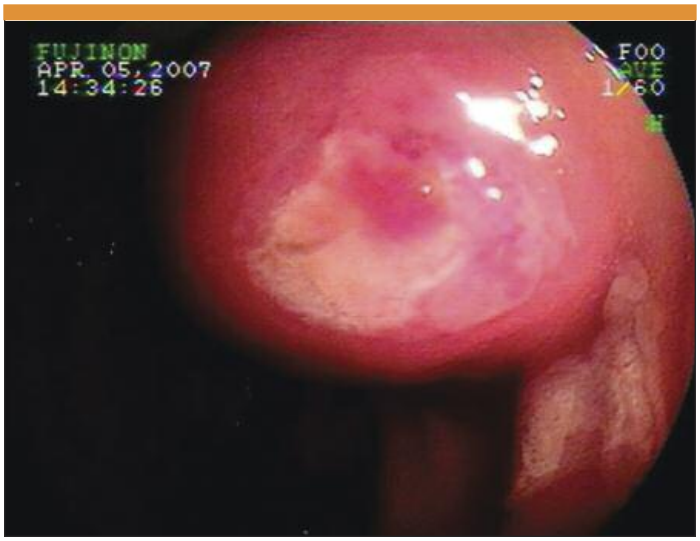

Fig. 4. GIST of the jejunum diagnosed at DBE in a 53-year-old woman with obscure gastrointestinal bleedingon CT scan.

Table. Primary gastrointestinal stromal tumors (GIST) risk assessment guidelines

Tumor parameters		Risk of progression* (%)	
Mitotic index	**Size**	**Stomach*** **	**Small bowel*** **
≤5 per 50 highpower field (HPF)	≤2 cm	No (0 %)	No (0 %)
	>2–≤5 cm	Very low (1.9 %)	Low (4.3 %)
	>5–≤10 cm	Low (3.6 %)	Moderate (24 %)
	>10 cm	Moderate (10 %)	High (52 %)
>5 per 50 HPF	≤2 cm	No**	High**
	>2–≤ 5 cm	Moderate (16 %)	High (73 %)
	>5–≤10 cm	High (55 %)	High (85 %)
	>10 cm	High (86 %)	High (90 %)

* Defined as metastasis or cancer-related death
** Small number of cases
*** See stomach for omentum and other locations (esophagus, colon, peritoneum and mesentery) see small bowel

the upper third of the stomach Mino et al found that the technique provided negative margins.

Capsule endoscopy: Potential Role in the Diagnostic Work-up

Patients who present with GI bleeding can undergo wireless capsule endoscopy when an upper endoscopy and colonoscopy do not find a source. This is designed to diagnose a small bowel source for either obscure overt or obscure occult GI bleeding.

A prospective study by Urgesi et al[29] was conducted in 500 patients referred to an endoscopy unit for small bowel evaluation with capsule endoscopy. Obscure-occult or obscure-overt bleeding were the main indications for CE in 289 of the patients. The technique identified a small bowel tumor 20 patients (4.0%) and 9 tumors turned out to be GISTs (45.0%). Traditional endoscopic and radiological imaging failed to detect the GIST in all these cases. In one case a small bowel GIST was diagnosed by angiography and CE proved false negative. Overall, CE was able to diagnose a small bowel GIST in 9 out of 10 cases. All patients underwent surgical treatment and showed normalized hemoglobin levels at follow-up. The main limitation of this study is the small number of cases; however, it is an accepted diagnostic modality for those cases where a bleeding source is not found on upper endoscopy or colonoscopy. Additionally, if further workup is needed beyond capsule endoscopy, a deep enteroscopy with balloon-assisted upper or lower endoscopy can be utilized by the gastroenterologist.

In a case report, [30] an 89-year-old man was admitted with melana. He had extensive PMH of CAD post-CABG/AICD, AAA repair, chronic anemia, myelodysplastic syndrome, lung cancer after resection, and recurrent GIB. Prior EGDs, colonoscopies, and upper device-assisted enteroscopy showed duodenal ulcer, A-V malformation s/p cauterization, and angioectasia. On admission, Hb was 6.0 g/dL. An endoscopic capsule study showed an ulcerated tumor in the ileum. CT showed no distant metastasis. The lesion was resected successfully and confirmed as a high-grade GIST. The patient was discharged with no further bleeding. Although early diagnosis for patients with ileal GIST is often challenging, the implications from this case report is that video capsule endoscopy and double balloon enteroscopy could be useful diagnostic tools. Various case reports illustrate how capsule endoscopy and CT are used to diagnose obscure GIST. (**Figures 2,3,4**)

Current Guidelines Suggest Diagnostic Algorithm

Various groups have proposed guidelines for the diagnosis of GIST. One such group is called GEIS (Grupo Espanol de Investigacion en Sarcomas/Spanish Group for Research in Sarcoma.2 In their report last year, they presented their third version of the GIST guidelines. Among the recommendations:

- Pathologic diagnosis is based on both unique microscopic features and ancillary techniques (CD-117, CD34, actin, desmin, S-100 and ki-67), which are very important to confirm diagnosis.
- The pathology report must include tumor size; number of mitoses per 50 HPF (10 mm2) counted in the most active regions; and margins status.
- It is advisable to refer the complex or unusual cases to experienced centers.
- Regarding tumors with typical morphology GIST, an extended phenotype of DOG1 as well as KIT and PDGFRA gene mutation analysis is required.
- Albeit optional, it is convenient to include the risk group separated by site. (**Table**) and histologic grading defined exclusively by the number of mitosis (low grade ≤5/50HPF, high grade >5/50HPF).

With regard to small GIST <2 cm, the Spanish group has recommended that a small GIST found accidentally in a surgical resection specimen does not require any additional therapy. In those uncommon cases of small GIST diagnosed before surgery, the excision is not clear enough and a shared decision-making process with the patient should be offered.

The mitotic index of those tumors should be taken into account, although the incidence of small size and high mitotic index is very low according to the literature.

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Case Report: R0 Resection of Large GIST After Neoadjuvant Therapy With Imatinib

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Introduction

Gastrointestinal stromal tumors (GISTs) represent only 1% of all primary gastrointestinal tumors but are the most common GI mesenchymal tumor.[1,2] Though the first usage of the term GIST was in 1983, the diagnosis was seldom made until the early 2000s when they became a focus for more research.[3,4] Researchers found in the late 1990s that GISTs appear to arise from the interstitial cells of Cajal in the GI tract.[5] The vast majority of GISTs (~95%) stain positive for the KIT protein which is a CD117 antigen, part of the c-kit tyrosine kinase receptor.[2] The overall incidence of GISTs is predicted to be 10-20 cases per million per year.[2] The location of GISTs vary throughout the GI tract. About 50-60% are found in the stomach, roughly 35% in the small intestine, 2-4% in the colon, 4-7% in the rectum and <1% in the esophagus.[6,7] Their size can range from as small as several millimeters to over 30 cm with a median size of 5 to 8 cm .[8,9] We present the case of a large (>20 cm) GIST and its treatment.

Case

A 39 year-old old male presented to our office for surgical management of a large gastric GIST. The patient had presented to another physician about a year and a half before with an upper GI bleed. At that time an upper endoscopy was performed which demonstrated an exophytic tumor bulging into the lumen without active ulceration. The gastric lumen was still patent and without stricture. Biopsies taken at this time provided the diagnosis of a GIST tumor that was KIT positive but without reporting a mitotic rate. A CT scan done at this point showed a 22 cm x 14.4 cm x 19.1 cm mass with compression of surrounding organs, including the liver, enlarged lymph nodes, but no distant metastases. The patient was treated with imatinib over the next year before being sent to our office for surgical management.

At presentation the patient complained of only mild abdominal pain. He had no other medical history and had no further episodes of bleeding after his initial presentation. He was tolerating diet without any issues and was maintaining weight with a BMI of 32.87. Bowel function was normal and he was able to perform all activities normally. He was not experiencing any side effects of the imatinib.

On examination the patient appeared well-nourished and not in any distress. Abdominal exam revealed a large mass in the epigastric region. The mass was firm, non-mobile and non-tender. Hgb/Hct was 14.6/43.7. Other labs, including liver enzymes, were likewise within normal limits. A repeat CT scan done just prior to presentation showed a 21.3 cm x 14.8 cm x 18.7 cm gastric mass with compression of liver and adjacent organs (**Figure 1**). Scattered lymph nodes were once again seen inferior to the mass. Once again, no metastases were seen.

The patient was forced to delay surgery for about three months due to personal reasons. During this time he continued treatment with imatinib. When he finally presented for surgery we performed an upper endoscopy at the outset of the case in conjunction with an exploratory laparotomy. Similar to the initial scope, this one showed an intact lumen with the mass bulging into the distal lesser curvature without macroscopic mucosal involvement. The tumor was, however, externally adherent to the left lateral lobe of the liver so we performed an en bloc resection including hepatic segments II and III. We were able to perform a partial gastrectomy and the tumor was removed without violation of its pseudocapsule (**Figures 2, 3**). One enlarged lymph node in the gastrocolic ligament was seen during the procedure and

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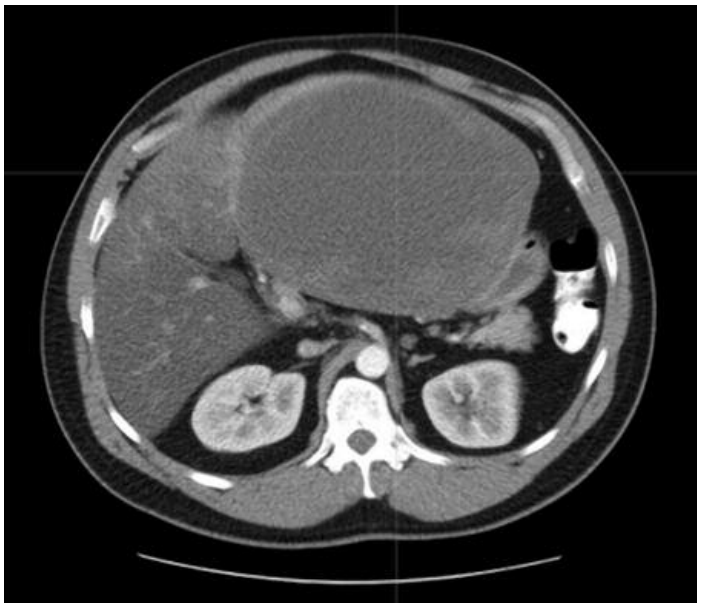

Figure 1. CT Scan s/p Imatinib Therapy

sent for frozen section. The results returned benign. A roux-en-y reconstruction was done.

The patient had no complications during his post-operative course and was discharge on post-op day four. He will continue treatment with imatinib for two years. The pathology report showed a 22.5 cm x 20 cm x 12 cm GIST with marked cystic, necrotic changes. About 90% of the tumor was grossly necrotic. The mitotic rate was found to be 0 mitoses per 50 HPF and was KIT positive. The tumor invaded into the gastric submucosa and perigastric soft tissue and though tightly adherent to the liver, did not invade it. Margins were negative. Three resected lymph nodes were likewise negative.

Discussion

The treatment of GISTs has evolved throughout the years. Before the development of tyrosine kinase inhibitors, the only available therapy was surgical. Radiation therapy and chemotherapy were found to be of no real benefit. Even with complete gross resection of a tumor, the outcomes were mostly poor with a five year survival rate around 42-54%. If resection was incomplete, survival fell to around 9%. [6,10,11] The development of imatinib and sunitinib helped to change this. Both are potent inhibitors of KIT. Imatinib was the first of the drugs developed and sunitinib was subsequently developed and found to be useful in treatment of imatinib-resistant tumors.[12-14]

Imatinib has been found to both shrink and stabilize unresectable or metastatic +KIT tumors. This has helped to make unresectable tumors resectable. It is typically used in tumors that are 5 cm or greater in size for at least 8-12 weeks prior to surgery. Studies have found varying rates of response with reduction of tumor size in 7-50% of patients but tumor stabilization in around 80% of patients.[12,13] Imatinib is also used for adjuvant therapy in +KIT tumors of at least 3 cm in size.[11,13] In addition the side effect profiles for

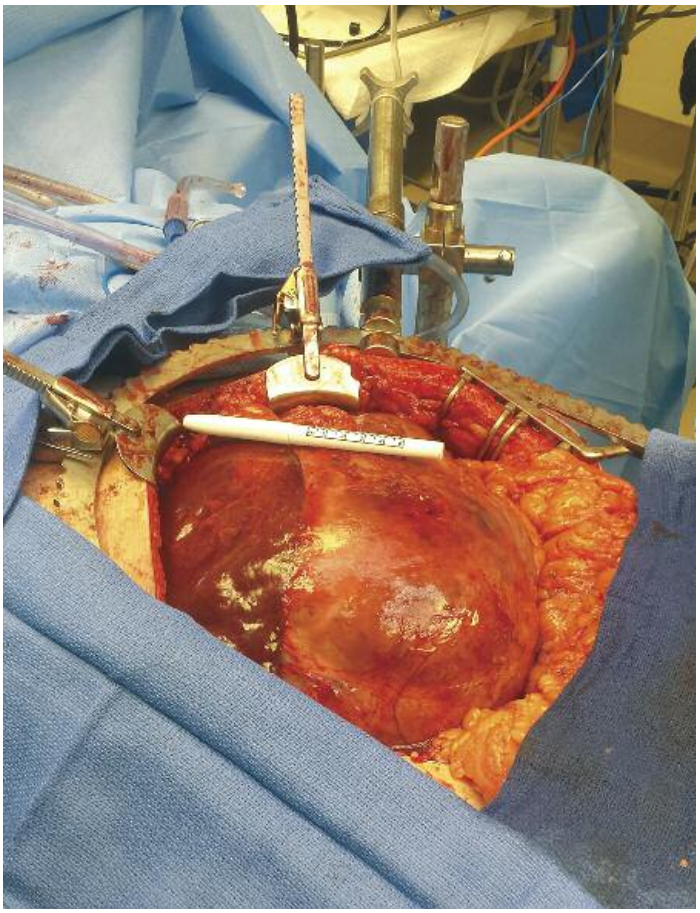

Figure 2. GIST in abdomen

both imatinib and sunitinib have been very minor.[13,14] Studies combining this multi-modal approach have shown much better results than surgery alone. One study showed mortality of only 9.5% within 3 years of treatment with progression-free survival of 88% at 2 years and 59% at 3 years.[15] Positive results have also been seen in large tumors with high mitotic rates. In a British study that had R0 resection and adjuvant imatinib treatment of gastric tumors of size greater than 9.4 cm and a mitotic rate averaging 6.2 mitoses/50 hpf only 4% of patients developed recurrence compared to 67% of the control patients.[11]

Overall, the most important tenets of surgical management are the resection margin and lack of tumor rupture. [6,15,]Some debate remains as to whether an R0 resection is required or if an R1 resection is adequate, with many articles showing R1 resection being equivalent to R0 with or without adjuvant therapy.[6,15,17] Tumor rupture during removal has been linked with poor outcome.[16] Lymph node resection has been shown to be unnecessary as GISTs primarily metastasize hematologically.[6,16,17]

Prognosis has long been linked to three factors.[7,18] These are size, mitotic rate and location. Smaller tumors with lower mitotic rates have the best prognosis. Tumors <2 cm in size have the lowest rate of progression with 2-5 cm being a more moderate rate and >5 cm having the highest rate.[7,18] Mitotic rate is an even more important factor with a rate of

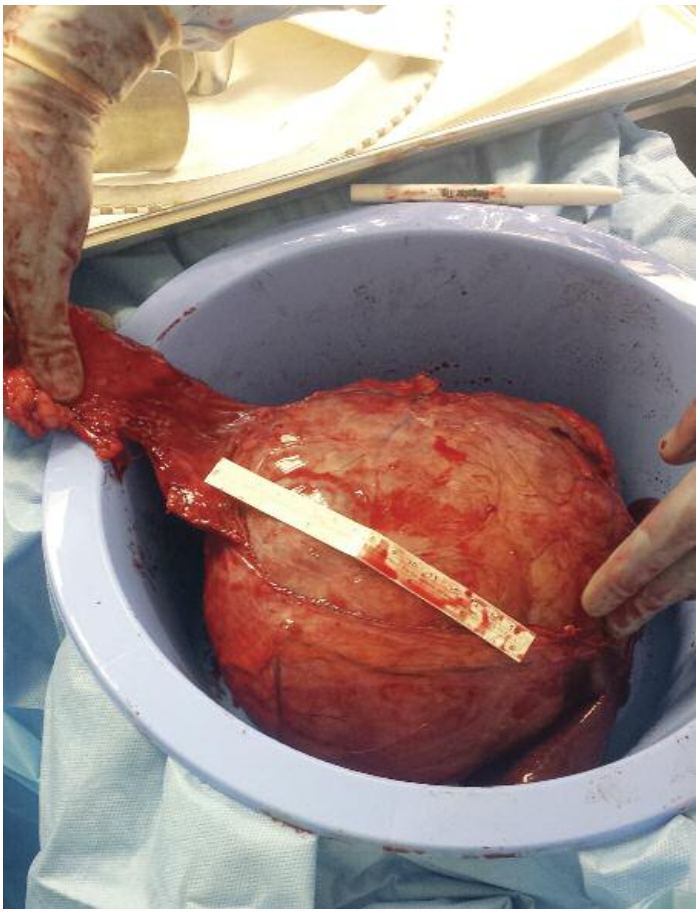

Figure 3. GIST after removal. Resected stomach held out to side.

<5 mitoses/50 hpf being associated with a better prognosis than a rate >5 mitoses/50 hpf.[7,18] The location of the tumor is also an important prognostic indicator. Gastric GISTs are most often benign and carry the lowest risk of metases.[6,18] All intestinal GISts have at least a moderate risk of metases.[7]

Our patient had a large tumor (>5 cm) presenting in the stomach with an unknown mitotic rate. At presentation this would place him at a moderate to high risk for progression.[7,18] He was treated for over a year with imatinib to make an R1 resection a more viable option. Though the tumor did not shrink, it did remain stable in size without signs of metases. We were able to complete an en bloc resection with microscopically negative margins (R0). The tumor was found to be 90% necrotic with a mitotic rate of 0 mitoses/50 hpf. He will receive adjuvant therapy with imatinib for two years. Overall this patient is at a moderate risk for recurrence due to tumor size, but has the positive prognostic factors of a low mitotic rate, non-progression with imatinib, an R0 resection and location in the stomach. In addition, though not discussed in the literature, the response to imatinib in terms of 90% of the tumor being necrotic would seem to be a positive survival indicator.

In conclusion, large gastric GISTs (>20 cm) that do not shrink with imatinib can still be resected with good results. Neoadjuvant imatinib can help stabilize the size of the tumor, prevent metases and cause tumor necrosis. With careful dissection an en bloc resection can be achieved, giving an R0 or R1 resection. With adjuvant therapy with imatinib the patient will have a good prognosis, especially with factors such as a low mitotic rate and gastric location.

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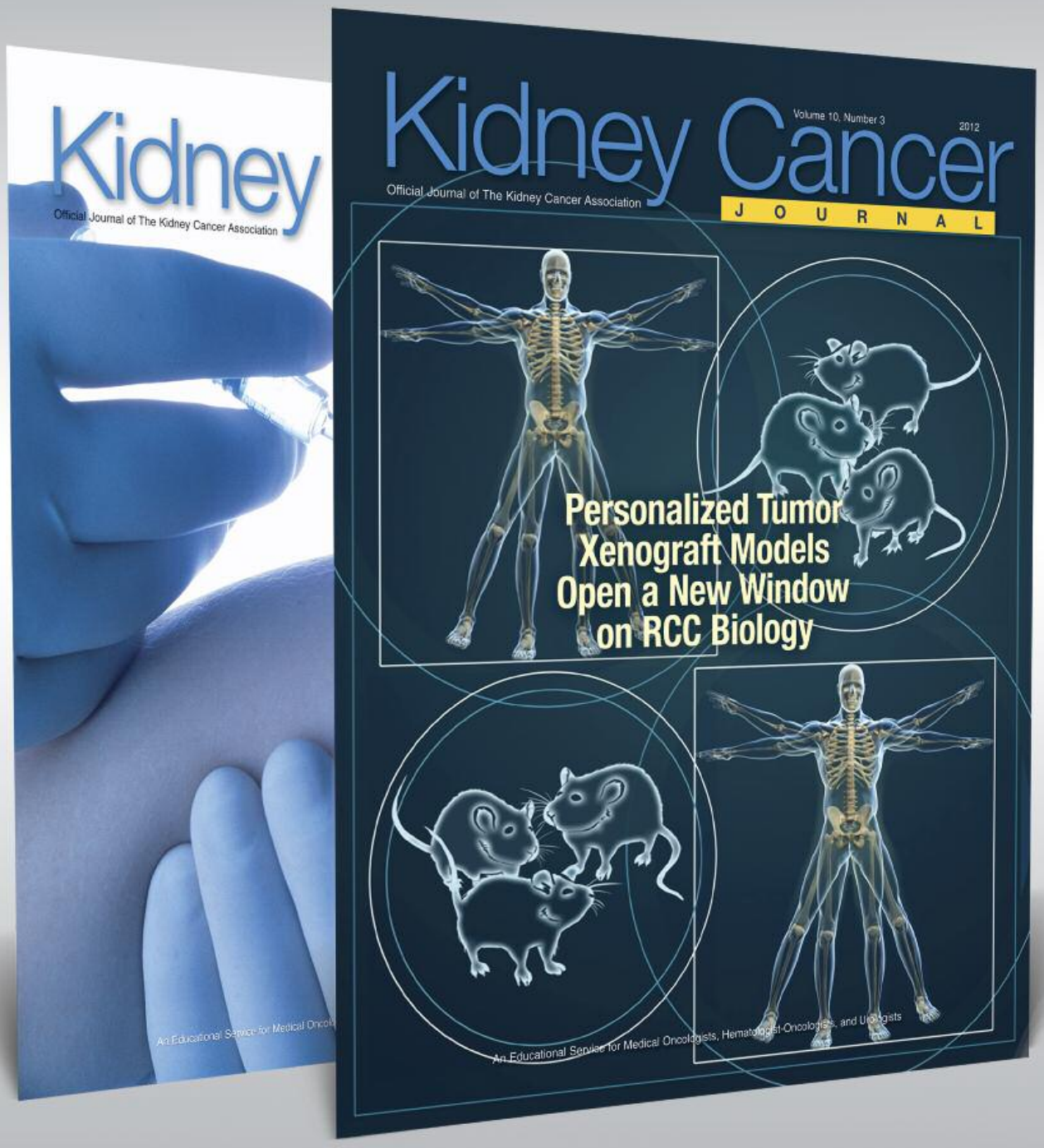

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