New Findings on Hereditary GIST, Mutational Subtypes, Familial Screening

Immunotherapy & Sarcomas: Will It Bring a New Era in Treatment?

Groups
A. (+) SDHB IHC (11)
B. (+) SDHB IHC, (+ SDHx mutations (63)
C. (+) SDHB IHC, (+ SDHx mutations (21)

Circles
1. SDHB IHC
2. Global Methylation
3. SDHClass Zygosity
4. Mutations
   - NF1
   - CRL
   - BRF1
   - None
   - Male
   - Female
5. Gender

See About the Cover, Page 31
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.

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.

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)
• 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 discontinue if 24-hour urine protein is ≥3 g; discontinue SUTENT for 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 necrosis (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-naive 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 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 ≥24% of patients with GIST receiving SUTENT vs placebo) were neutropenia (40% vs 31%), decreased neutrophils (10% vs 7%), neutrophils (10% vs 0%), amylase (8% vs 6%), platelets (9% vs 1%), and 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 pNET 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 ≥24% of patients with pNET receiving SUTENT vs placebo) were neutropenia (30% vs 23%), decreased neutrophils (10% vs 7%), decreased lymphocytes (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%).
SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These hemorrhagic adverse event reported. Less common bleeding events included rectal, gingival, upper.

RCC patients (9%) on SUTENT and 3/360 patients (1%) on IFN-α compared with 13/360 patients (4%) on IFN-α.

Patients should be monitored for hypertension and treated as needed with standard.

of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose reduce for 24-hour urine.

Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

evaluations of LVEF should also be considered while these patients are receiving SUTENT. In patients

symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were.

Hepatotoxicity. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death.

in patients with moderate to severe proteinuria has not been systematically evaluated.

Electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4

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**Clinical Trials**

**Gastrointestinal disorders:** treating physician.

**Immune system disorders:**

Venous Thromboembolic Events. Occurred in two patients with pulmonary embolism and one with DVT. In treatment-naive RCC patients, one patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption was performed; one patient was Grade 2 and six were Grade 4, and six (2%) patients had DVT, including three Grade 3. One patient was Grade 4.

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>212 (56)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>ALP</td>
<td>211 (56)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>AST</td>
<td>156 (42)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>CK</td>
<td>116 (31)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>65 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>75 (20)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>116 (31)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>156 (42)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Amylase</td>
<td>130 (35)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Lipase</td>
<td>211 (56)</td>
<td>69 (18)</td>
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<tr>
<td>Calcium</td>
<td>165 (44)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Potassium</td>
<td>178 (47)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>177 (46)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Platelets</td>
<td>205 (56)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>256 (68)</td>
<td>40 (11)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>253 (68)</td>
<td>29 (8)</td>
</tr>
</tbody>
</table>

**Cardiovascular Toxicity Criteria for Adverse Events (CTCAE), Version 3.0**

Grade 4 laboratory abnormalities in patients on IFN-α included anemia (8%), leukocytes (2%), thrombocytopenia (2%), neutrophils (2%), platelets (2%), alanine transaminase (ALT), AST (1%), creatine kinase (1%), creatine, (1%), creatinine (1%), glucose increased (1%), calcium decreased (1%), phosphorus (<1%), potassium increased (1%), and sodium decreased (1%).

**Reversible Postleukemia Phosphorylation Syndrome.** There have been reports (<1%), some fatal, of reversible postleukemia phosphorylation syndrome. This toxicity is monitored by serial TSH and FT4 measurements. The syndrome is typically associated with high FT3 and FT4 levels. It is usually reversible with antithyroid medications and hormone replacement therapy.

**Cerebrovascular Accident.** Occurred in two patients with cerebrovascular accident.

**Contraindications:**

- **Hypersensitivity reactions:** including anaphylaxis.
- **Gastrointestinal disorders:**
  - Enterocolitis, jejunitis, ileitis, ileus.
  - Pancreatitis.
  - Gallbladder atony.
- **Hypersensitivity disorders:**
  - Urticaria, angioedema.
  - Hypersensitivity reactions.
PATIENT COUNSELING INFORMATION

Gastrointestinal Disorders. Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients 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].
Navigating the Brave New World of Virtual Medical Meetings: Is It as Good as Being There?

The obvious answer to that question is, of course not. But look at the quantum leaps made since 1985, in Silicon Valley, when a ragtag band of programmers began exploring the concept of virtual reality from a tiny cottage in Palo Alto. If virtual reality becomes a part of people’s day-to-day lives, more and more people may prefer to spend a majority of their time in virtual spaces. As the futurist Ray Kurzweil predicted, somewhat hyperbolically, in 2003, “By the 2030s, virtual reality will be totally realistic and compelling and we will spend most of our time in virtual environments. We will all become virtual humans.”

Not so fast. Let’s look at current developments. Anyone attending the 2016 meeting of the American Society of Clinical Oncology (ASCO) surely is aware of the parallel universe that ASCO has constructed—a virtual meeting branded on its website as the next best thing to being there. If you missed this year’s meeting—or even if you attended—there are abundant resources available, enabling you to review or keep pace with nearly all the sarcoma presentations and selected sessions—a virtual world of the ASCO sessions. Although much of the technology that supports virtual meeting tools is not new, the underlying software and infrastructure are maturing quickly, in some cases allowing medical education to benefit from real-time interaction for remote programs as well as offering new opportunities for traditional, residential education.

On the ASCO website the Virtual Meeting grants you full access to every session—you can watch and listen to more than 150 captured sessions on your computer, tablet, or mobile device. As ASCO promotes its service: “Virtual Meeting is the next best thing to being at the 2016 Annual Meeting in person, and without travel expense or time away from work.”

But virtual analyses such as those at the ASCO meeting are widely available to oncologists and gastroenterologists elsewhere. The Life Raft Group partnered with the National Institutes of Health to launch the first Pediatric GIST Virtual Tumor Board. This initiative was so successful within a year that LRG expanded the applications to review adult GIST and reach the global patient community.

The purpose of the Virtual GIST Tumor Board is to bring together leading experts to discuss GIST cases, while serving as an educational resource for local physicians. If selected, doctors of GIST patients are able to log on and review their de-identified patient case with a panel of experts by using the internet, secure servers, and video conferencing software. Participants virtually

(continued on page 42)
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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Contact information
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:

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Checkpoint Inhibitors and Sarcomas: ASCO Offers Insights Into What to Expect and Why There Is Optimism

This interview was conducted with Breelyn A. Wilky, MD, Assistant Professor, Sarcoma Program, Sylvester Comprehensive Cancer Center, Division of Hematology/Oncology at the Leonard M. Miller School of Medicine at the University of Miami. The interview includes content that Dr Wilky reviewed at the 2016 scientific sessions of the American Society of Clinical Oncology.

Q. How does the history of immunotherapy and its potential application to sarcomas have an impact on our current views of this strategy?

Dr Wilky: The concept that a link may exist between sarcomas and the immune system is not new, but it is underexplored. In the 1890s, William Coley first reported a patient with complete resolution of a sarcoma, after suffering a severe erysipelas infection. Though his attempts to repeat these observations in other patients by injecting streptococcus were unsuccessful, through the years, investigators have tried to boost anti-tumor immunity by using cytokines and vaccines, with largely disappointing results. This began to change at the beginning of this decade, when Dr Steven Rosenberg and others began reporting exciting results with adoptive T-cell therapy in NY-ESO positive synovial sarcomas. Today, with the sudden explosion of novel immunotherapy approaches and dramatic responses in other cancer types, it’s clear that our explorations of the role of the immune system in sarcoma are just beginning.

Q. As we consider the role of immunotherapy in the treatment of sarcomas, what are some of the basic concepts that clinicians need to be aware of, particularly with respect to various pathways and mechanisms in the immune system?

Dr Wilky: The immune system is incredibly complex and eloquent, with a remarkable ability to balance between immune stimulation and inflammation, and timely suppression to protect healthy cells from long term dysregulation and damage. Immune cells exhibit different phenotypes, either pro or anti-inflammatory, and the ratio between these states fluctuates depending on the surrounding microenvironmental cues. These critical signals from the microenvironment include cytokines and expression of various regulatory receptors including immune checkpoint proteins.

Q. What can you tell us about mechanisms within some cancer cells that evolve to the point where the tumor can evade and suppress immune response?

Dr Wilky: Newly transformed cancer cells express various danger signals, including tumor-specific neoantigens or pro-apoptotic signals. Through the process of immunosurveillance, pro-inflammatory immune cells and cytokines generate an attack on the tumor cells, and may lead to elimination prior to detection of a tumor mass. However, if subpopulations of the tumor cells are inherently less immunogenic, those cells may persist through the immune response, leading to a residual tumor that is “immuneedited.” Essentially this process selects for inherently immunoresistant cells that differ from the initial tumor bulk. If the cancer cells evolve additional abilities to avoid immune destruction and suppress the ongoing immune response, the tumor will grow and proliferate, escaping the immune system and becoming clinically detectable.

Q. Please expand on this point and delineate concepts like checkpoint proteins and their role in manipulating the microenvironment and the immune response.

Dr Wilky: There are three main mechanisms by which cancer cells may evade the immune system. First, the tumor cells may lose expression of key immunogenic neoantigens as well as the MHC complex which is required for recognition by cytotoxic T cells. The tumor cells can also produce a variety of suppressive cytokines and express checkpoint proteins like PD-L1 that blunt the immune response. As the tumor grows and develops, cytokines like VEGF also affect the microenvironment and drive faulty tumor angiogenesis that can lead to poor tumor blood flow as well as suppression of immune cell trafficking. And finally, even if immune cells are physically able to infiltrate the tumor bed, cytotoxic T cells and macrophages may shift to more suppressive...
phenotypes through expression of checkpoint proteins, evolution to an anergic or exhausted state, or become T regulatory cells. Overall, the tumor cells produce an environment that causes the immune cells to become suppressed or tolerant, rather than inflammatory.

Q. Are we winning the battle to enhance T-cell response and to what extent are innovative strategies playing a role in improving immune cell infiltration in the tumor cell?

Dr Wilky: The goal of modern immunotherapy is to combat these escape routes used by the cancer cells and reset the balance to a pro-inflammatory immune environment rather than a suppressive one. Vaccines, utilizing potent, immunogenic tumor antigens or externally derived dendritic cells, aim to boost the initial antigen-presenting phase to the patient’s immune system. Adoptive T cell therapy genetically alters the patient’s own T cells to be specific for cancer cell targets like NY-ESO-1 for synovial sarcoma. This bypasses natural antigen presentation, and ensures at least an initial supply of specific T cells are available. Therapies that affect the tumor microenvironment aim to improve immune cell infiltration into the tumor, and may include chemotherapy, radiation, or potentially anti-VEGF tyrosine kinase inhibitors.

Finally, there are over 50 immune cell receptors that regulate activation or suppression of immune responses, and it is these receptors that are really getting the most attention in modern drug development, including checkpoint inhibitors, or stimulatory agonists.

Q. There is so much interest today in checkpoint inhibition. Can it be effectively applied in sarcomas?

Dr Wilky: So we are just beginning to see the first results from checkpoint inhibitors for sarcomas. Dr Robert Maki had previously done a small study using ipilimumab for synovial sarcomas which was not effective. However, at ASCO this year Dr. Tawbi presented the initial data for pembrolizumab, a PD-1 inhibitor for bone and soft tissue sarcomas. Out of 40 patients with four different kinds of soft tissue sarcoma, we saw tumor responses in about 19% of patients. The highest rates of benefit were seen in patients with dedifferentiated liposarcoma and undifferentiated pleomorphic sarcomas. This rate is comparable to response rates to single agent PD-1 inhibition in other types of solid tumors. Importantly, Dr Tawbi’s study met the progression-free rate endpoint over historical controls often used in single arm phase 2 studies, suggesting that pembrolizumab would meet definitions for an active second line regimen for metastatic sarcoma.

Unfortunately, the results did not look so promising in bone sarcomas, and Dr. Suzanne George and Dr. Rosen presented data for uterine leiomyosarcoma which showed that overall these subtypes are much less sensitive than the soft tissue subtypes. The problem is that even in these resistant subtypes, there are still the occasional patients who have a great response and benefit.

Q. Is there still reason for optimism regarding checkpoint inhibitors and sarcomas?

Dr Wilky: Absolutely. In Dr. Rosen’s study with nivolumab either with or without pazopanib, partial responses were observed in osteosarcoma, dedifferentiated chondrosarcoma, and a Ewing sarcoma, with a durable partial response in the chondrosarcoma patient lasting over 9 months and ongoing. Stable disease was also seen with monotherapy in one patient with LMS, intimal sarcoma, and osteosarcoma. So clearly, there are patients who can greatly benefit from immunotherapy and checkpoint inhibitors – the challenge is figuring out how to identify them ahead of time.

Q. What are the pitfalls in relying on histology to determine response to checkpoint inhibitors in sarcomas? What direction do we need to pursue to truly evaluate response to these agents?

Dr Wilky: While histology-specific expansion cohorts are certainly appealing for UPS and dedifferentiated liposarcoma based on the results of the Tawbi study, this would miss the rare responders in other histologies. We know that in sarcoma, patients with the same histology often demonstrate dramatically different responses to chemotherapy or targeted therapy. This appears to also be the case for immunotherapy. Thus a critical need exists for analysis of potential biomarkers in responders, in hopes that later enrollment on these therapies can be stratified by something other than histology alone.

Q. So what do we know about biomarkers for response to PD-1 therapy from other cancers and what is the “take-home” message for using this treatment in sarcomas?

Dr Wilky: The best characterized biomarker in other tumor types for PD-1 checkpoint inhibition so far appears to be PD-L1 tumor expression. Most tumors that express PD-L1 appear to respond better to PD-1 directed therapy; however there are still some responders even in PD-L1 negative tumors. For example, in melanoma, PD-L1 expression was not required for response to therapy. There are many issues with using PD-L1 as a biomarker, including differences in staining thresholds and fluctuating expression and heterogeneity within the tumor. Regardless, the results reported by Dr George and Dr Talmone confirm previous published data that about 20% of sarcomas seem to express PD-L1 ligand on tumor cells. The analysis from Dr Tawbi’s study will be helpful to understand more about whether PD-L1 expression is linked to response in sarcomas.

Q. Did you find evidence at ASCO suggesting progress in identifying a valid biomarker for evaluating treatment success in sarcomas?

Dr Wilky: Yes, there was an abstract that was exciting, which identifies a new potential prognostic biomarker for (continued on page 42)
KIT and PDGFRA mutations represent the molecular hallmark of gastrointestinal stromal tumor (GIST). However, the recent identification of other molecular characteristics beyond KIT and PDGFRA are driving a new view of the disease. Identification of germline mutations underscores the need for patients with these familial risk factors to undergo genetic counseling to determine appropriate follow up and management, both for the patients and their affected family members. As new reports elucidate distinctions between subtypes of hereditary GIST, we are discovering how these mutations of GIST differ clinically, pathologically, and behaviorally from sporadic gastric tumors.

Deeper insights into the biology of GISTs are reshaping perceptions about this tumor, its genetic risk factors and a diverse set of mutations and genotype features with clinical implications. Although GIST typically affects patients over the age of 40 years, recognition of its epidemiology in children and young adults has been increasingly recognized even though these younger groups account for only 1.4% of patients with the tumor.

Though the majority of GISTs appear to arise sporadically, a number of families with high frequencies of GISTs and other associated tumors have been reported and germline mutations have been identified. The true frequency of all GIST diagnoses has been difficult to determine because the definition of GIST was derived in 1990 before it was molecularly characterized. One United States report from the Surveillance, Epidemiology, and End Results (SEER) database indicated that, from 1992 to 2000, the yearly incidence rate in the United States was 6.8 cases per million, making it relatively rare compared to other cancers.

Most GISTs occurring in adults are driven by activating mutations in either the KIT or PDGFRA genes. New findings on molecular classification, however, have dramatically changed the nomenclature for various GISTs and contributed to an improved understanding of hereditary and familial factors. For example, 85% of GISTs in children and 10% to 15% of GISTs in adults are negative for KIT and PDGFRA mutations and were commonly referred to as wild-type (WT) GIST until recently. Because these malignant neoplasms are rare, efforts to delineate their natural history and determine their response to treatment have been difficult. This is particularly true with regard to the use of kinase inhibitor therapies: WT GIST generally does not respond as well to tyrosine kinase therapy known to be effective in non-WT GIST. From institutional series and case reports WT GIST has been characterized as primarily affecting young females, presenting as multifocal disease, and primarily having a gastric location.

Characterizing WT GIST and Germline Mutations

Within the last 3 years, the biology of WT GIST has been further elucidated; in fact, WT GIST (i.e., non-KIT, non-PDGFRA mutated tumors) is now also referred to as SDH-deficient GIST based on recent understanding of the molecular biology of this subtype of GISTs. The latest report to evaluate the clinical and tumor genomic features of WT GIST comes from the National Institutes of Health (NIH) Gastrointestinal Stromal Tumor Clinic. One of the goals of these type of reports is to develop an expanded molecular characterization of WT GIST. This characterization could become a useful tool to determine the risk of germline mutation—and the need for—genetic counseling and of non-GIST tumors. Previous reports had established that WT GIST, along with paraganglioma, is a component of the Carney-Stratakis syn-
drome, an inherited predisposition syndrome caused by germ-line mutations leading to protein damage of the succinyl dehydrogenase (SDH) B, C, or D subunit. 

Earlier papers had further identified SDHA, SDHB, SDHC, and SDHD mutations in some but not all WT GIST. As a whole, these comprise the SDHx mutations. There is additional evidence for the existence of yet another entity of WT GIST—a nonfamilial multitumor syndrome called the Carney triad. This triad consists of WT GIST, paraganglioma and pulmonary chondroma and so far has not been linked to SDH germline mutations.

The NIH report is especially timely in view of how hereditary GIST has been further characterized within the last 5 years. The NIH GIST Clinic report was based on patient clinical assessment along with molecular testing of archived tumor samples. This enabled investigators to propose a molecular classification of these tumors with potential impact on prognosis and treatment. A key finding in this study concerned the 95 patients whose GIST lacked C-KIT/PDGFRA mutations; 84 had SDH-deficient GIST (75% due to SDHx mutations and 25% to SDHC promoter hypermethylation). In the cohort, 18 had syndromic GIST with chondroma and/or paragangliomas; SDHx mutations were often germline.

Confirming their observation of the hereditary nature of SDH-deficient GIST, Boikos et al. suggest that there are compelling clinical reasons to determine the molecular subtype of GIST in all patients with WT GIST, including SDH status. The implications and recommendations:

- A diagnosis of SDH-deficient GIST should be considered in patients with gastric GIST when routine diagnostic evaluation does not identify KIT or PDGFRA mutations. This is especially true if the patient is under 30 years of age at diagnosis.
- The SDH status of the tumor should first be determined to separate SDH-competent from SDH-deficient GIST. SDHB IHC can easily distinguish between these subtypes.
- If IHC determines the status is SDH deficient, sequencing of SDHx genes in tumor and germline should be done.
- If no SDHx mutation is identified, then the presence or absence of SDHC promoter methylation should be determined.

This subtyping is essential because it can identify patients with SDHx-mutant GIST for referral to a cancer genetics clinic with genetic counseling in order to evaluate the risk for an SDHx-related germline cancer predisposition syndrome. Patients, and family members, with germline SDHx mutations may be at risk for other tumors and early tumor surveillance can be initiated, including annual screening with MRI as needed. Screening in the SDHx-mutated germline subgroup is also needed for SDHx-related paragangliomas and pheochromocytomas. Of note, genetic counseling is not called for if SDHC promoter hypermethylation is found since these cases do not involve germline alterations.

### Treatment Considerations, Implications

One of the key clinical questions, particularly for individuals with SDH-competent GIST is whether targeted therapy is appropriate. In this subtype, identification of kinase mutations suggests that a trial of targeted therapy should be considered. However, the potential benefit of such treatment in patients with SDH-deficient GIST is marginal at best. A common multifocal presentation means that surgery is not an option because the disease frequently is unresectable. Patients in this category are unlikely to benefit from sunitinib or imatinib, making clinical management challenging.

Further information on mechanisms surrounding SDH regulation may yield insights into how patients with different subtypes could be managed or offer new possibilities for developmental therapeutic research. Postow and Robson, for example, suggest that the increasing knowledge of various germline mutations associated with hereditary GIST indicates that different clinical approaches may ultimately show increased benefit. For example, when GIST presents in patients with paragangliomas (Carney-Stratakis Syn-

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### Table. Comparison Between 36 SDHA-negative and 91 SDHA-positive, SDHB-negative (SDH-deficient) GISTs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SDHA-negative GISTs (n=36)</th>
<th>SDHA-positive GISTs (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) (y)</td>
<td>34 (8-83)</td>
<td>21 (8-77)</td>
</tr>
<tr>
<td>No. patients r16 y</td>
<td>3/36 (8%)</td>
<td>29/91 (32%)</td>
</tr>
<tr>
<td>No. patients &gt;40y</td>
<td>13/36 (36%)</td>
<td>11/91 (12%)</td>
</tr>
<tr>
<td>Female:male ratio</td>
<td>1.8 (23:13)</td>
<td>3.1 (69:22)</td>
</tr>
<tr>
<td>Median tumor size (range) (cm)</td>
<td>5.0 (1.2-21.5)</td>
<td>5.0 (1-21)</td>
</tr>
<tr>
<td>Cases with tumor Z10 cm</td>
<td>4 (0-26)</td>
<td>12/73 (16%)</td>
</tr>
<tr>
<td>Median mitotic count/50 HPF, 5mm2 (range)</td>
<td>4 (5-10)</td>
<td>5 (0-102)</td>
</tr>
<tr>
<td>Cases with Z10 mitoses/50 HPF</td>
<td>8/35 (23%)</td>
<td>28/84 (33%)</td>
</tr>
<tr>
<td>Patients alive without disease</td>
<td>5/20 (25%)</td>
<td>33/59 (56%)</td>
</tr>
<tr>
<td>Patients alive with metastases</td>
<td>8/20 (40%)</td>
<td>16/59 (27%)</td>
</tr>
<tr>
<td>Patients dead of disease</td>
<td>4/20 (20%)</td>
<td>9/59 (15%)</td>
</tr>
<tr>
<td>Patients dead of unrelated causes</td>
<td>3/20 (15%)</td>
<td>1/59 (2%)</td>
</tr>
</tbody>
</table>

The median follow-up 14 y: Median follow-up 16 y

The total in each line refers to patients with data available.
A generic form of GLEEVEC® (imatinib mesylate) is now available. Patients could have questions about how this may affect their current treatment plan. Please help support your patients by explaining their options.

If you decide that branded GLEEVEC is the right option for your patient, you may choose to include “Dispense as Written” (“DAW”), or your state or territory’s required language, on his or her prescription.

Please note that out-of-pocket costs may differ for branded GLEEVEC and generic imatinib mesylate. A patient’s insurance plan is an important factor in determining his or her out-of-pocket expenses for branded or generic medications. In addition, costs can be affected by statutes related to a state or territory’s specific DAW requirements.
drome, CSS), these tumors lack mutations in KIT and PDGFRA (WT GIST) and therefore may be less sensitive to imatinib. This may also be true for inherited GIST associated with NF1 mutations as KIT mutations are only found in small proportions of NF1 GIST. Inherited GIST associated with CSS has been shown to be related to deficits in SDH, and improved understanding of the mechanisms surrounding SDH regulation may lead to future therapeutic approaches. Unfortunately, patients with advanced WT GIST when treated with imatinib show decreased objective response, decreased time to tumor progression, and decreased overall survival compared to patients with KIT exon 11 mutations. Mutations in SDHx and NF1 may explain the non-KIT mediated pathogenesis in patients with WT GIST, and patients with inherited SDHx mutations, and possibly NF1 mutations, may ultimately benefit from alternative targeted treatment. The relationship between SDHx and NF1 signaling to GIST pathogenesis will first need to be further clarified.

Patients whose GISTS are characterized by a deficiency in SDHB by immunohistochemistry (SDH-deficient GISTS) have been described to have a somewhat different clinical course from the majority of GIST patients. Specifically, one study found that deficiency of SDHB was associated with a female predominance, gastric primary location, lymph node involvement, and similar morphology to GIST arising in pediatric patients. Since these patients’ GISTS followed a more indolent course, SDHB deficient tumors may ultimately need to be managed differently. Larger studies like those from the NIH GIST Clinic will be helpful in understanding the clinical course of WT GIST and developing clinical recommendations.

**SDH-deficient GISTS: Salient Biological Features**

SDH-deficient GISTS typically are restricted to the stomach, and commonly occur in children and young adults representing a spectrum of clinical behavior from indolent to progressive. They tend to progress slowly even after metastatic spread has taken place, and many patients live years with metastases. SDH-deficient GISTS have characteristic morphologic features including multinodular gastric wall involvement, often multiple separate tumors, common lymphovascular invasion, and occasional lymph node metastases.

The diagnosis is confirmed by the loss of succinate dehydrogenase subunit B (SDHB) from the tumor cells and this can be assessed by immunohistochemistry. Likewise, SDHA protein is lost in cases associated with SDHA mutations. If SDHx mutations are present, regardless of SDH subtype, the entire SDH complex often will be inappropriately assembled and SDHB IHC loss previously was used as a proxy for any type of SDHx dysfunction. Approximately half of the patients have SDH subunit gene mutations, often germline and most commonly A (30%), and B, C or D (combined total 20%), with both alleles inactivated in the tumor cells according to the classic tumor suppressor gene model. Half of the cases are not associated with SDH-mutations and epigenetic silencing of the SDH complex is the possible pathogenesis. Extensive genomic methylation has been observed in these tumors, in contrast to other non-SDH deficient GISTS. SDH-loss causes succinate accumulation and activation of pseudohypoxia signaling via overexpression of HIF-proteins. Activation of insulin-like growth factor 1-signalizing is also typical of these tumors. SDH-deficient (wild type) GISTS are a unique group of GISTS with an energy metabolism defect as the key oncogenic mechanism.
Clinicopathology and Morphology of SDH-Deficient GIST

There is a relatively high frequency of tumors at more than one site with many patients showing coalescent or separate tumor nodules involving the gastric wall, according to Miettinen et al. Although SDH-deficient GISTs can involve any part of the stomach, there is some predilection to distal stomach and antrum. Of all GISTs, lymph node metastases are an almost exclusive feature of SDH-deficient GISTs; yet this occurrence is still seen in a minority of 10% or less patients. A similar clinicopathological profile has emerged from the studies of Carney triad-associated GISTs. SDH-deficient GISTs are also differentiated by multinodular gastric wall involvement with interspersed tracts of gastric wall smooth muscle; this feature is often referred to a “plexiform” pattern.

The tumor cells typically have an epithelioid morphology with variably eosinophilic cytoplasm, whereas KIT-mutant GISTs more often are composed of spindle-shaped cells with a paler cytoplasm. Lympho-vascular invasion is relatively common, seen in up to 50% of cases, and its presence may explain not only some propensity to lymph node metastases but also the multinodular gastric involvement and high local recurrence rate following apparently curative surgery.

Clinical Aspects of SDH-deficient GISTs

Clinically, SDH-deficient GISTs are a heterogeneous group ranging from indolent tumors that never recur or metastasize to those that are metastatic at presentation, with some of these being fatal in a few years. These SDH-deficient tumors do not follow well the predictions of behavior made for GISTs based on mitotic activity and tumor size and therefore a separate set of criteria should be developed for them in the future. While SDH-deficient GISTs that are relatively small and contain low mitotic activity (<5 mitoses/5 mm2) are usually indolent, a small proportion of them metastasize to liver, often after a long delay of 10 years of more following presentation. In one series, the longest reported was 42 years from primary tumor to liver metastasis. Based on this finding, lifelong follow-up is necessary for metastatic relapse of SDH-deficient GIST.

Nevertheless, many patients can survive with metastases, including liver metastases; in fact, the 10-year survival in this context is not unusual and is similar to patients treated for a KIT mutant GIST. Higher mitotic rates often relate to earlier development of metastases. Perhaps the apparent slow growth of the SDH-deficient GISTs is related to the metabolic handicap provided by the succinate dehydrogenase deficiency in the tumor. Overall tumor mortality seems to be at least 15% but probably will be higher after longer observation than has been so far available. Long-term follow-up comparison between all SDH-deficient GISTs and SDHA-mutant GISTs have not shown any clear clinicopathological differences, except that the latter tend to occur at an older age. Similar clinicopathologic features and overall mortality has also been reported on pediatric GISTs associated with paragangliomas, pulmonary chondromas, or both in Carney triad. Occurrence of other SDH-deficient tumors can be highly asynchronous. In some cases, paragangliomas have been detected 25 years before or after the detection of GIST.

SDH-Deficient Subunit Mutations—SDHA, SDHB, SDHC, SDHD

Mutational inactivation or loss of any SDH component (A, B, C, or D) results in loss of the entire succinate dehydrogenase complex, including the SDH subunit B (SDHB), so that SDHB immunohistochemistry may be used as a surrogate to identify the SDH-deficient GISTs, according to a review of literature by Beadling et al. The SDH complex converts succinate to fumarate. The succinate that accumulates instead of turning into fumarate when SDH complex activity is impaired leads to reduced turnover of hypoxia-induced factor 1 alpha (HIF1α) and heightened expression of HIF1A target genes including vascular endothelial growth factor. The most commonly mutated SDH subunit in SDH-deficient GISTs is SDHA, with an estimated reported frequency of 28% of all SDH-deficient GISTs. In most cases, these are germ line mutations. SDHA mutations have been associated with very few paragangliomas.

SDHA germ line mutations have an excellent correlation with immunohistochemical loss of SDHA protein expression, so SDHA IHC loss is a superb screening tool and surrogate marker for SDHA mutation analysis. Because the information on germ line SDHA mutations is very recent and the data is based mostly on the study of patients with detected tumors, precise guidelines for clinical surveillance are still forthcoming. However, it would be reasonable to consider the recommendations for other SDHx-related disorders including MRI whole body imaging and plasma catecholamines.

Although mutations in the other SDH subunit genes (SDHB, SDHC, and SDHD) are regularly associated with SDH-deficient para-gangliomas, these mutations seem to occur only in a minority of SDH-deficient GISTs, estimated at 20–30%. Most of these SDH-mutations in GISTs have also been germ line. Moreover, 20% of patients with GISTs due to SDHx germ line mutations, also have paragangliomas. Up to half of SDH-deficient GIST appears to lack known SDH-subunit germ line mutations.

Methylation in SDH-deficient GISTs

Independent of SDHx gene status, all SDH-deficient GISTs have a high frequency of gene methylation, especially compared to KIT or PDGFRα-mutant GIST. Markedly higher number of hyper- vs. hypomethylated genes were detected in a screening for a large number of genes via Golden Gate® Assay for Methylation (Illumina, Inc.). Similar methylation patterns were also detected in IDH1-mutant gliomas, tumors with another Krebs cycle deficiency. Therefore, Krebs cycle enzyme deficiency may well be the unifying factor related to abnormal genome methylation. Hyper-methylation in GISTs may be related to disruption of DNA demethylation machinery by the downregulated TET enzyme.

(continued on next page)
Insulin-Like Growth Factor 1 Receptor: A New Molecular Target?

Although still in the early stages, tantalizing evidence exists that still another pathway could be a useful target in optimizing molecularly-targeted strategies. Recent data suggests high levels of expression of insulin-like growth factor 1 receptor (IGF1R) in SDH-deficient GIST (wild type). T It is not clear if all SDH-deficient GISTs express IGF1R, but new reports are elucidating how the expression of this receptor could further define the complexity and heterogeneity of SDH-deficient GIST.

A report by Beadling et al\(^{16}\) suggests the extent to which the receptor could play a potential role in tailoring therapeutic strategies. Ligands IGF1 and IGF2 can trigger enhanced cell proliferation and survival through downstream activation of mitogen-activated protein kinase and PI3K-signaling pathways. IGF1R is highly expressed at both the RNA and protein level in wild-type GISTs, and the receptor is activated, although not mutated in these tumors.\(^{16}\) SDHB-deficient, IGF1R-high expressing GISTs may therefore be considered candidates for therapies targeting VEGFR and/or IGF1R. Approximately 20% of the wild-type GISTs in the current series did not exhibit elevated IGF1R expression (ref). In the absence of augmented IGF1R expression, Beadling et al (16) point out that IGF-signaling pathways could potentially still be activated by elevated expression of other components of the IGF1 signaling pathway.

In a related report, Belinsky et al\(^{20}\) also studied the potential role of expressed IGF1R as they characterized 12 wild-type and 12 mutant GIST cases. The 12 mutant cases included 10 with KIT mutations and 2 with PDGFRA mutations. Strong IHC staining for IGF1R was seen exclusively in the 11 SDHB-absent GISTs, in agreement with another recent report.\(^{21}\) The one SDHB IHC present wild-type (non-KIT / non-PDGFRA mutated) sample in this analysis (case 12) showed both weaker IGF1R protein staining and lower IGF1R RNA expression than the other wild-type samples.\(^{20}\) The small bowel presentation, spindle-cell morphology, and multiple chromosomal aberrations of this GIST also distinguish this case from the other wild-type cases. Overexpression of IGF1R RNA may be part of a global RNA expression profile for wild-type GIST, according to these authors.\(^{20}\)

Conclusion

Identification of a subgroup of relatively rare GISTs involving the loss of the SDH complex has contributed to a new understanding of hereditary factors, and clinically and biologically unique features. These SDH-deficient (wild-type) GISTs are clinically heterogeneous and their increased genomic methylation differentiates them from the conventional KIT/PDGFR\(\alpha\) mutant GISTs commonly found in adults. Treatment with conventional tyrosine kinase inhibitors typically is not successful in SDH-deficient GISTs, and recent reports have focused on identifying other pathways to target such as IGF1R.

References

Do they need:
- News and updates about GIST and the latest research?
- Access to a support community?
- Information on clinical trials?
- Help navigating the treatment landscape?

The Life Raft Group is a non-profit organization with a simple focus: to cure a form of cancer – GIST (Gastrointestinal Stromal Tumor) – and to help those living with it until we do. To achieve this, we focus on three key areas: Patient Support & Education, Advocacy and Research.

Research
- A collaborative approach that expedites the research process
- World’s largest GIST Patient Registry
- GIST Collaborative Tissue Bank
- International team comprised of leading GIST experts

Patient Support and Education
- Newsletters
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- Clinical Trials Database
- Patient Gatherings
- In-person seminars
- Webcasts
- LRG Email Community
- Local and Global Support Groups

Advocacy
- Social Media Campaigns
- Lobby Day in D.C
- Aid patients in accessing effective treatments
- Advocate for mutational and plasma level testing
- Volunteer opportunities
- Network with other advocacy groups to affect change

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Editor's Memo (continued from page 31)

access radiology films such as CT scans and other necessary medical reports to help review the particular case and provide advice.

The Board also provides valuable access for patients and doctors who would ordinarily not be able to attend an in-person NIH clinic due to resources or distance. The NIH clinic is for Pediatric and Wild Type patients only. The Virtual GIST Tumor Board not only informs local doctors of the most up-to-date treatment options, trials, and studies, applicable to their patient, but also encourages a collaborative effort of GIST experts from around the world. The collaboration and educated, individualized discussions ensure the best care is offered to patients under evaluation.

What’s on the horizon for virtual meetings and interactive initiatives beyond webinars? Consider the idea recently announced in June by the Association of Community Cancer Centers (ACCC). The ACCC unveiled a virtual community for Oncology Care Model (OCM) practices to share tips, tools, and resources as they navigate new transformational cancer care delivery and payment models. Through this one-of-a-kind online platform, invited practices will gain access to need-to-know information and leading experts on trending OCM issues.

The community will foster robust dialogue and provide extensive peer-to-peer learning opportunities.

The online community is part of the ACCC OCM Collaborative, a broader effort to support OCM practices throughout implementation of the first oncology-specific payment reform model. The Collaborative provides a forum to share practical, how-to resources and best practices to assist in implementing and ultimately succeeding in the OCM. The Collaborative’s new “virtual community platform” will enable OCM participants to share their experiences, challenges, and strategies in real time, learning from one another as they implement the model. As practices sign their participation agreements, look to the ACCC OCM Collaborative in the coming months for live meetings, conference calls, and more.

As exciting and provocative as all of these online initiatives and resources are, let’s remember that we still need to attend scientific meetings in person, if possible. The exchange of ideas at the ASCO meeting and other gatherings remains the “real deal” and an invaluable experience and opportunity to exchange ideas. But virtual meetings are indeed, the next best thing to being there.

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

(continued from page 34)

sarcoma. Dr. Talamone and her colleagues showed that IDO1 and KYN are highly expressed in sarcomas. These are modulators that lead to a suppressive state within tumors. KYN positive sarcomas demonstrated a favorable overall survival historically in the setting of chemotherapy treatment, seeming to suggest that altered immunologic milieu within the sarcoma may be beneficial in terms of response to therapy. These markers should be included in correlative immunoprofiling for sarcoma patients treated with checkpoint inhibitors, as they could also be a potential predictive biomarker for immunotherapy.

Q. Wow can we prioritize, and really organize our optimization of immunotherapy moving forward?

Dr Wilky: I think there are several key unanswered questions that need to be priorities for future research in immunotherapy for sarcomas. First, is there a way that we can increase immunogenicity of the tumors, particularly our genetically “quiet” sarcomas. We know in other tumor types that the more genetically complex the cancer cell, the more likely they are to produce abnormal proteins that can be recognized by the immune system. Data exists in numerous cancers that the use of chemotherapy, radiation, TKIs, and epigenetics may diversify the antigen profile expressed and released in the tumor microenvironment. Perhaps we are using checkpoint inhibitors too far down the treatment pathway, and better results might be obtained by intensifying the immune response at a time with the highest antigen release from these other strategies, especially in genetically simple sarcomas.

Next, as I mentioned before, I think it is critical that we try to identify an immunoprofile of responding sarcomas, not necessarily in relation to histology, but more based on biological basis. In addition to expression of PD-L1 and PD-1, looking at other potential biomarkers like KYN and IDO1 may help us pick out potential responders so that we can focus on patients likely to benefit from these treatments.

I think that combinations are clearly key, to combat multiple steps in the tumor’s immune evasion mechanism. Let’s combine checkpoint inhibitors with adoptive T cells or vaccines, or other drugs that work on different mechanisms in the tumor cell’s ability to avoid destruction – like anti-VEGF therapies, or drugs to inhibit the suppressive T regulatory cells. Combination therapies have limited resistance, and the use of upstream with downstream agents has led to improved responses in many other treatment paradigms, like tyrosine kinase inhibitors in melanoma. And finally, we need to take advantage of the intense interest in immunotherapy from pharma, government funding strategies, and patients, to ensure that the new targets, agents, and techniques that are emerging for other cancers are explored in sarcoma as well.

Q. Despite some setbacks, over all there is good reason to be optimistic?

Background: This investigator-initiated trial provided the justification for the phase III GRID study resulting in worldwide regulatory approval of regorafenib as a third-line therapy for patients with metastatic gastrointestinal stromal tumors (GIST). This report presents the genotype analyses, long-term safety, and activity results from this initial trial of regorafenib in GIST.

Patients and methods: The trial was conducted between February 2010 and January 2014, among adult patients with metastatic GIST, after failure of at least imatinib and sunitinib. Patients received regorafenib orally, 160 mg once daily, days 1–21 of a 28-day cycle. Clinical benefit rate (CBR), defined as complete or partial response (PR), or stable disease lasting ≥16 weeks per RECIST 1.1, progression-free survival (PFS), overall survival (OS), long-term safety data, and metabolic response by functional imaging were assessed.

Results: Thirty-three patients received at least one dose of regorafenib. The median follow-up was 41 months. CBR was documented in 25 of 33 patients [76%; 95% confidence interval (CI) 58% to 89%], including six PRs. The median PFS was 13.2 months (95% CI 9.2–18.3 months) including four patients who remained progression-free at study closure, each achieving clinical benefit for more than 3 years (range 36.8–43.5 months). The median OS was 25 months (95% CI 13.2–39.1 months). Patients whose tumors harbored a KIT exon 11 mutation demonstrated the longest median PFS (13.4 months), whereas patients with KIT/PDGFRA wild-type, non-SDH-deficient tumors experienced a median 1.6 months PFS (P < 0.0001). Long-term safety profile is consistent with previous reports; hand–foot skin reaction and hypertension were the most common reasons for dose reduction. Notably, regorafenib induced objective responses and durable benefit in SDH-deficient GIST.

Conclusions: Long-term follow-up of patients with metastatic GIST treated with regorafenib suggests particular benefit among patients with primary KIT exon 11 mutations and those with SDH-deficient GIST. Dose modifications are frequently required to manage treatment-related toxicities.

Clinical trial number NCT01068769.

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