Abbreviated Title: PhII SGI110 in Peds & Adults

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Title: A Phase II Trial of the DNA Methyl Transferase Inhibitor, SGI-110 (Guadecitabine), in Children and Adults with Wild Type GIST, Pheochromocytoma and Paraganglioma Associated with Succinate Dehydrogenase Deficiency and HLRCC-associated Kidney Cancer

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Investigator Roles:

A. *Obtain information by intervening or interacting with living individuals for research purposes*
B. *Obtaining identifiable private information about living individuals*
C. *Obtaining the voluntary informed consent of individuals to be subjects*
D. *Makes decisions about subject eligibility*

E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes

F. Studying, interpreting, or analyzing coded, linked data or specimens for research purposes

G. Some/all research activities performed outside NIH

Investigational Agents:

Drug Name:	SGI-110 (guadecitabine)
IND Number:	133390
Sponsor:	CTEP
Manufacturer:	Astex Pharmaceuticals

Commercial Agents: None

PRÉCIS

Background:

- Loss of activity of the Krebs cycle components succinate dehydrogenase (SDH) complex or fumarate hydratase (FH), has been identified as a mechanism of tumorigenesis in subsets of gastrointestinal stromal tumor (GIST), pheochromocytoma and paraganglioma (PHEO/PGL), and renal cell carcinoma.
- DNA hypermethylation has been demonstrated in these cancers. Loss of activity of SDH or FH leads to accumulation of the metabolites succinate and fumarate, respectively. Succinate and fumarate act as inhibitors of a broad array of α-ketoglutarate-dependent dioxygenases. The Ten-eleven Translocation (TET) family of αKG-dependent dioxengenase enzymes convert 5-methylcytosine to 5-hydroxymethycytosine leading to DNA demethylation. Inhibition of these enzymes due to SDH and FH deficiency causes DNA hypermethylation and has been verified in preclinical models.
- Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract, resistant to cytotoxic chemotherapy and radiation therapy. KIT and PDGFRA mutations have been identified as tumor initiating events in 85% of adult patients with GIST and these tumors are responsive to the tyrosine kinase inhibitor, Imatinib. In pediatric patients, however, 85% of GISTs lack *KIT* and *PDGFRA* mutations (wild-type) and imatinib is not effective.
- Recent work in the Pediatric and Wild-Type (wt) GIST Clinic at the NCI led to the identification of succinate dehydrogenase (SDH) deficiency in approximately 90% of wild-type GIST[1].
- In addition to wild-type GIST, SDH deficiency is also present in 30% of pheochromocytoma and paraganglioma (PHEO/PGL) and a subset of renal carcinoma. Loss of SDHB protein expression is seen in PHEO/PGL and wtGIST either due to mutation in SDH subunit genes or hypermethylation of the SDHC promoter region[2-4].
- Mutations leading to loss of function of FH have been identified in PHEO/PGL as well as type II papillary renal cell carcinoma in patients with hereditary leiomyomatosis and renal cell cancer (HLRCC)[3,5]. An FH-deficient paraganglioma had DNA hypermethylation as demonstrated by array and immunohistochemistry showed increased 5hmC levels in paragangliomas and pheochromocytomas.
- SGI-110 is a small molecule derivative of decitabine that acts as a DNA methyltransferase (DNMT) inhibitor and is resistant to inactivation by cytidine deaminase, hence may thus have a more favorable pharmacokinetic profile compared to decitabine. Subcutaneously administered SGI-110 is gradually converted to decitabine resulting in prolonged exposure with a several fold increase in apparent $T_{1/2}$ compared to intravenous decitabine. SGI-110 has been demonstrated in preclinical models to induce a dose-dependent decrease in global DNA methylation and up-regulate expression of specific genes including MAGE-A1 and NY-ESO-1 through decreased methylation.
- We are proposing a phase II trial with SGI-110 in these SDH-deficient and FH-deficient tumors.

Objectives:

To assess the clinical activity of SGI-110 in patients with wt-GIST, SDH-deficient PHEO/PGL, and HLRCC-associated RCC using RECIST (v1.1).

Eligibility:

- Adults and children (≥12 years of age) with wt-type GIST, SDH deficient PHEO/PGL, or HLRCC-associated RCC and measurable disease will be eligible.
- Newly diagnosed patients with PHEO/PGL or HLRCC-associated RCC with localized, resectable disease will not be eligible. Patients with PHEO/PGL or HLRCC-associated RCC with unresectable localized disease and/or metastatic disease will be eligible.
- Newly diagnosed patients with wt-GIST with completely resectable disease will not be eligible. Patients with wt-GIST with metastatic disease and/or residual or recurrent tumor following surgical debulking will be eligible
- Patients with wt-GIST or HLRCC-associated RCC who have not previously received systemic therapy are eligible as there are no standard chemotherapy regimens known to be effective for these cancers.
- Must have adequate performance status, may not be pregnant or breastfeeding, and must have adequate major organ function.
- No history of severe or uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic cardiovascular or pulmonary disease will be excluded.

Design:

- This is a single site, open label, phase II study using a small optimal two-stage design to evaluate the clinical response in three groups of patients:
    1. wild-type GIST (GIST without *KIT* or *PDGFRA* mutation)
    2. PHEO/PGL in patients with germline SDH subunit mutation, or
    3. RCC associated with HLRCC
- SGI-110 will be administered subcutaneously at 45mg/m^2/day x 5 days on a 28-day cycle to the three groups of patients.
- SGI-110 activity will be assessed by imaging response of measurable disease using RECISTv1.1, using CT, MRI and/or PET.
- Patients will be closely monitored for development of toxicity with regular physical examinations and laboratory evaluations. Toxicity will be graded using version 5.0 of the NCI Common Toxicity Criteria.
- SGI-110 related toxicities ≥ grade 3 will be considered treatment limiting toxicities, unless they are reversible within 72 hours with supportive care. Following recovery from toxicity up to 2 dose reductions will be allowed.
- Initially 7 evaluable patients in each group (strata) will be enrolled and if 0 of the 7 have a response, then no further patients will be accrued in that strata. If 1 or more the first 7 (14.3% or more) have a response, then accrual would continue until a total of 21 patients have enrolled in that strata. If at least 3 responses (at least 14.3%) are observed among the 21 evaluable patients, the agent should be considered worthy of further testing in this disease.

- Enrolling 2 patients/month, it is estimated to require 3 years to complete accrual to a maximum of 70 patients, a maximum of 63 evaluable patients allowing for a small number (7) of inevaluable patients.

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16.3.2 Pediatric PROMIS Instruments Spanish (6)

PROMIS Pediatric v.1.1 - Depressive Symptoms - Short Form 8b

Síntomas de depresión en pediatría - Cuestionario abreviado 8b

Responde a cada enunciado marcando una casilla por línea.

En los últimos 7 días...

		Nunca	Casi nunca	A veces	A menudo	Casi siempre
488R1	No pude dejar de sentirme triste.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
461R1	Sentí que estaba solo/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5041R1	Sentí que todo me salía mal en la vida.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5035R1	Sentí que no podía hacer nada bien.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
711R1	Me sentí solo/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
226R1	Me sentí triste.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
712R1	Me sentí descontento/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3952aR2	Me resultó difícil divertirme.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Spanish (Universal)
27 January 2014

16.3.5 Adult Patient PROMIS Instruments Spanish (6)

PROMIS Item Bank v. 1.2 – Physical Function – Short Form 10a

Capacidad de funcionamiento físico – Cuestionario abreviado 10a

Responda a cada pregunta marcando una casilla por línea.

		Nada	Poco	Algo	Mucho	No puedo hacerlo
PFA1	¿Limita su salud en este momento su capacidad para realizar actividades vigorosas, como correr, levantar objetos pesados o participar en deportes enérgicos?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36r1	¿Limita su salud en este momento su capacidad para caminar más de una milla (1.6 km)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	¿Limita su salud en este momento su capacidad para subir un piso de escaleras?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	¿Limita su salud en este momento su capacidad para levantar o llevar las bolsas del supermercado?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3	¿Limita su salud en este momento su capacidad para inclinarse, arrodillarse o agacharse?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Sin dificultad	**Con poca dificultad**	**Con alguna dificultad**	**Con mucha dificultad**	**No puedo hacerlo**
PFA11	¿Puede realizar tareas, como pasar la aspiradora o trabajar en el jardín?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	¿Puede vestirse sin ayuda, incluso amarrarse los zapatos y abotonarse la ropa?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	¿Puede lavarse el cabello con champú?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	¿Puede lavarse y secarse el cuerpo?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45r1	¿Puede sentarse y levantarse del inodoro (excusado)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Spanish (Universal)
21 January 2014

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To assess the clinical activity (CR or PR) of SGI-110 in patients with wt-GIST, SDH-deficient PHEO/PGL, and HLRCC-associated renal cell carcinoma using RECIST (v1.1).

1.1.2 Secondary

1.1.2.1 Evaluate the toxicity, progression-free (PFS) and overall survival (OS), and pain and quality of life (QOL) of patients on treatment with SGI-110.

1.1.2.2 Better define the pharmacokinetics (PK) of SGI-110 in all patients.

1.1.3 Exploratory

1.1.3.1 Determine the serum and urine concentration of succinate, fumarate and 2-hydroxyglutarate in patients with wild-type GIST, pheochromocytoma and paraganglioma associated with SDH deficiency and HLRCC-associated kidney cancer prior to and on therapy with SGI-110.

1.1.3.2 Explore changes in DNA methylation and gene expression including SDH, FH, and tumor testis antigens in response to treatment with SGI-110.

1.1.3.3 Assess the global DNA methylation status in tumors by determining LINE-1 methylation in archival pre-treatment tumor samples and in on-treatment tumor samples when available.

2 BACKGROUND AND RATIONALE

2.1.1 Background

Loss of activity of the Krebs cycle components succinate dehydrogenase (SDH) complex or fumarate hydratase (FH), has been identified as a mechanism of tumorigenesis in subsets of gastrointestinal stromal tumor (GIST), pheochromocytoma and paraganglioma (PHEO/PGL), and renal cell carcinoma.

DNA hyper-methylation has been demonstrated in these cancers[2,6,7]. Loss of activity of SDH or FH leads to accumulation of the metabolites succinate and fumarate, respectively. Succinate and fumarate act as inhibitors of a broad array of α-ketoglutarate-dependent dioxygenases. The Ten-eleven Translocation (TET) family of αKG-dependent dioxengenase enzymes convert 5-methylcytosine to 5-hydroxymethycytosine leading to DNA demethylation. Inhibition of these enzymes due to SDH and FH deficiency causes DNA hypermethylation[8]. It is hypothesized that a methylation inhibitor would impact tumor growth by reversing the DNA hypermethylation that is seen in this group of tumors with Krebs cycle abnormalities.

2.1.2 Gastrointestinal stromal tumors

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract, resistant to cytotoxic chemotherapy and radiation therapy. *KIT* and *PDGFRA* mutations have been identified as tumor initiating events in 85% of adult patients with GIST and these tumors are responsive to the tyrosine kinase inhibitor, Imatinib[9]. In pediatric patients, however, 85% of GISTs lack *KIT* and *PDGFRA* mutations (wild-type

GIST)[10] and imatinib is not effective. Recent work in the Pediatric and Wild-Type (wt) GIST Clinic at the NCI led to the identification of succinate dehydrogenase (SDH) deficiency in 88% of pediatric wild-type GIST[1,10]. Loss of SDHB protein expression is seen in PHEO/PGL and wt-GIST either due to mutation in SDH subunit genes or hypermethylation of the SDHC promoter region, which was seen in 21 of 95 wild-type GIST tumors examined[1,10].

2.1.3 Pheochromocytoma and Paraganglioma

In addition to wild-type GIST, SDH deficiency is also present in pheochromocytoma and paraganglioma (PHEO/PGL)[3,11]. Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are neuroendocrine tumors arising from the adrenal chromaffin cells and ganglia along the sympathetic and parasympathetic chains, respectively. Seventeen underlying germline mutations associated with PHEO/PGL have been identified and account for approximately 35% of PHEO/PGL[12]. Approximately 10-30% of PHEO/PGL are SDH-deficient[13,14] and there is an increased risk of more aggressive metastatic disease in patients with SDHB mutation. SDHC promoter hypermethyation has also been described in PHEO/PGL as mechanisms for SDH deficiency in isolated paraganglioma[15] as well as in patients with Carney Triad[16]. However, the percentage of SDH deficient PHEO/PGL with SDHC promoter hypermethylation is unknown. Surgical resection is the only curative therapy for patients with PHEO/PGL, however both radiation therapy and cytotoxic chemotherapy using cyclophosphamide, vincristine, and dacarbazine (CVD) have been used to treat patients with metastatic or recurrent disease[12]. Averbuch and colleagues reported a 57% response rate in pateints with malignant pheochromocytoma[17]. A recent retrospective analysis of 17 patients with metastatic PHEO/PGL showed a 47.1% rate of response to CVD[18]. A meta-analysis of patients with metastatic PHEO/PGL treated with CVD chemotherapy showed a 4% CR and 37% PR rate[19]. Approximately 60% of metastatic PHEO/PGL are methyl-iodobenzylguanine (MIBG) avid and can be treated with ^{131}I-MIBG[20]. A meta-analysis of patients treated with 131I-MIBG showed a complete response rate of 3% and PR rate of 27%[21]. A small number of patients with metastatic PHEO/PGL have also been reported to have disease response when treated with temozolomide. While CVD chemotherapy has been described as standard therapy for PHEO/PGL[20] the data supporting this therapeutic approach is limited. ^{131}I-MIBG in patients with MIBG avid tumors or cytotoxic chemotherapy (CVD or temozolomide) is required prior to enrollment on this trial. However, patients who have refused cytotoxic chemotherapy or for whom treatment on this protocol prior to receiving cytotoxic chemotherapy is felt to be in the best interest for the patient by the local investigator will also be eligible.

2.1.4 Renal Cell Carcinoma

Mutations leading to loss of function of FH have been identified in type II papillary renal cell carcinoma in addition to PHEO/PGL[6]. Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal-dominant hereditary syndrome due to mutations in FH[5]. Approximately 93% of patients with HLRCC have detectable mutations in FH[4]. While renal cell cancer occurs less often than leiomyomas in patients with HLRCC, HLRCC-associated kidney cancer is typically clinically aggressive with early development of metastatic disease. Nephron-sparing surgical therapy is standard for localized HLRCC-associated renal cancer[22]. While there is currently no standard systemic therapy for metastatic HLRCC-associated renal cell cancer, treatments targeting the VEGF and EGFR pathways are being investigated in ongoing clinical trials[22].

2.1.5 SGI-110

SGI-110 is a small molecule derivative of decitabine that acts as a DNA methyltransferase (DNMT) inhibitor and is resistant to inactivation by cytidine deaminase[23]. Subcutaneously administered SGI-110 is gradually converted to decitabine resulting in prolonged exposure with a several fold increase in apparent $T_{1/2}$ compared to intravenous decitabine. SGI-110 has been demonstrated in preclinical models to induce a dose-dependent decrease in global DNA methylation and up-regulate expression of specific genes including MAGE-A1 and NY-ESO-1 through decreased methylation.

2.1.5.1 Pharmacokinetics of SGI-110

Studies were conducted in mice, rats, monkeys and rabbits to examine the PK profile of SGI-110 available as a sodium salt. Intravenous, bolus, oral, and SC routes of administration were evaluated. Results of these studies are available in the Investigator's Brochure (Guadecitabine: Investigator's Brochure. Version 6.0, 10September 2015). In summary, *in vivo* oral bioavailability in rodents was greater than 30%, but *in vitro* permeability measured in human Caco-2-cells was poor. Additionally, SGI-110 degrades rapidly both chemically due to hydrolysis and enzymatically due to presence of phosphodiesterases and other enzymes (phosphatases, phosphorylases, etc.). These findings substantiate the selection of a parenteral route for dosing. Comparative studies indicate close to 100% bioavailability via subcutaneous (SC) administration. Once in the biological system, SGI-110 cleaves to decitabine, a known active moiety. The rate of this conversion to decitabine varies across species and appears to be much higher in rats and rabbits, compared to primates. When administered SC to non-human primates, SGI-110 releases decitabine slowly compared to other species, possibly prolonging the effect over more sustained periods. Therefore, SC route of administration is recommended.

The recommended safe starting dose of SGI-110 for human studies, [Regimen 1 (Daily x5): 3 mg/m^2/dose, and Regimen 2A (Weekly X3) 6 mg/m^2/dose], was based on (1) results from repeat-dose toxicology studies in rabbits (the most sensitive species) and rats; (2) results from a non-GLP non-human primate toxicology, PD and TK study; (3) the established PK and safety profile for decitabine.

2.1.5.2 Clinical Studies in Humans

As of 30 June 2015, 5 clinical trials of SGI-110 have been initiated: 3 as monotherapy in AML/MDS, 1 as monotherapy in HCC and 1 in combination with carboplatin in ovarian cancer. Three dosing regimens (Daily x 5, Once weekly, and twice weekly) were employed in the initial phase I study in adult patients with high-risk myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). In a subsequent Phase 2 study doses of 60mg/m^2/day Daily x5 and 90mg/m^2/day Daily x5 were used in subjects with MDS or AML. An additional cohort in this study was treated with 60mg/m^2/day for 10 days.

In a single agent study, the maximum tolerated dose of the drug for the first cycle when given Daily x 5 to patients with MDS was 90mg/m^2/dose. Dose limiting toxicities seen at 125mg/m^2/day in this patient population were thrombocytopenia, neutropenia, febrile neutropenia, and sepsis. The MTD was not reached for patients with AML with the highest dose administered 125mg/m^2/day Daily x5. In a phase II dose expansion for patients with AML and MDS dosing regimens of 60mg/m^2/day Daily x5 and 90 mg/m^2/day Daily x5 have been used. A total of 202 subjects have been treated using these regimens. There were no significant differences in complete response rates between 60mg/m^2/day Daily x5 and 90 mg/m^2/day Daily x5 in relapsed/refractory AML subjects (13% vs 19% respectively) or in treatment naïve elderly subjects with AML (54% vs 55%, respectively). The biologically effective dose was determined by assaying LINE-1 demethylation. In these patients there

was also no significant difference in LINE-1 demethylation between patients treated on the two different dosing regimens. A smaller number of patients with AML and MDS have been treated using a schedule of 10 days of treatment per cycle (days 1-5 and days 8-12).

Patients with platinum-resistant ovarian cancer were enrolled on a phase II combination trial of SGI-110 and carboplatin (NCT01696032). In combination with carboplatin a starting dose of SGI-110 of 45mg/m^2/day Daily x5 was not tolerated and the dose was de-escalated to 30mg/m^2/day. Dose of SGI-110 of 30mg/m^2/day + carboplatin AUC 4 was well-tolerated and is being used for stage II of the study. In patients with HCC, a Phase II study of mono-therapy with SGI-110 is ongoing (NCT01752933). Dosing started at 60mg/m^2/day on days 1-5 every 28 days. This dose was reduced to 45mg/m^2/day Daily x5 due to grade >/=3 hematological toxicity. Thirty-six subjects received this dose on stage 2 of this study. Overall, 22 of 50 subjects (44%) had SAEs in this study. Most subjects had SAEs considered not related to study treatment. No SAE with an outcome of death was considered related to study treatment.

2.1.6 Health-Related Quality of Life and Patient-Reported Symptoms

2.1.6.1 Study Measures

Distress and Symptom Checklist (Appendix **IV**): The Distress Thermometer [24] is a brief screening tool endorsed by the National Comprehensive Cancer Network (NCCN) to assess for distress in adult cancer patients. The Distress Thermometer (DT) is a visual-analog scale similar to those used to assess pain. The DT obtains an overall distress score based on the visual analog scale, and includes a "problem list", or checklist, where patients can identify specific physical and emotional symptoms and practical and family concerns that can cause their distress. The DT has been widely validated in adult (≥18 years old) cancer patients, and has been recognized as a good alternative to many of the longer measures commonly used to screen for distress in cancer patients [25-27].

Whereas the Distress Thermometer was originally written for adult cancer patients, early evaluation of the scale shows validity for children and adolescents with cancer [28]. In an ongoing study at the NIH with 163 pediatric patients ages 7-21 undergoing treatment for cancer, NF1, HIV or a primary immune deficiency and their caregivers, an adapted DT has shown convergent validity when compared with standardized measures and with specific items on the symptom checklist. It has also shown reasonable concordance with parent and provider ratings [29]. For this study, we will use the DT as a distress and symptom rating tool. It is quick to administer and a low burden to patients and their caregivers [29]. Whereas most patient reported outcome measures utilize a 7–day recall period (including the PROMIS measures), the adapted DT utilizes a 30 day recall period which allows problems or symptoms that might have been present in the past month, but not necessarily the past week to be documented. The distress and symptom rating scales will take approximately 5 minutes to complete.

Patient-Reported Outcomes Measurement Information System (PROMIS) is a health related quality of life measurement tool that was developed by NIH to standardize patient-reported outcomes for national use by research clinicians. Two versions of PROMIS are available to researchers: computer-adaptive tests (CATs) and short forms. The short forms are brief, static instruments that have demonstrated similar reliability to the longer, dynamic CATs, which provide precise measures for studying populations with widely varied responses and longitudinal self-report data [30]. Each short form includes 4 to 8 items, measures reported health outcomes in the past 7 days on a Likert type scale, and takes approximately 5 minutes

to complete. PROMIS instruments, measuring a broad range of health domains, have been validated for adults (≥18) with a variety of health conditions [31].

Early evaluation of PROMIS pediatric instruments indicates validity for children ages 8 to 17 [32], hence this is appropriate for the age group 12-17 years old in this trial. Six pediatric PROMIS instruments and six parallel Parent Proxy PROMIS instruments (See Appendix **III**) are available to assess five quality of life health domains (physical function, pain interference, fatigue, emotional health, and social health) and are intended for use with both healthy and chronically ill pediatric populations. This protocol will utilize pediatric PROMIS short forms and the Parent Proxy short forms to assess symptoms that can be associated with GIST. These include physical function, anxiety, depressive symptoms, fatigue, pain interference, and peer relationships.

Assessments of Health-Related Quality of Life will be administered at the start of therapy, at the end of cycle 4 and then every 4 cycles thereafter, and then at the end of therapy. The PROMIS Patient Outcome Measures (6) and patient-reported symptom severity (Distress and Symptom Checklist) will provide us with essential information regarding how symptoms may change over the course of treatment, and will also provide a more in-depth assessment of the known toxicities associated with SGI-110 in this patient population.

The PI of the study will be notified of participants who have scores 2 standard deviations above the mean normative t-score of 50 (so a t-score of 70) on the PROMIS depression short form (suggesting high depression), and these participants will be assessed for suicidal ideation by a member of the psychosocial team. Those found to have suicidal ideation will be referred to the NIH psychiatry service.

2.1.7 Rationale

Based on the dosing regimens that have been tolerated in these ongoing trials we propose a starting dose for single agent therapy of 45mg/m^2/day daily x5 on a 28 day cycle. The majority of patients enrolled on our trial will not have had extensive therapy with cytotoxic agents and hence would not be expected to experience the degree of bone marrow toxicity that was observed in patients on these earlier trials. Because GIST, RCC, and PHEO/PGL are more indolent tumors it may be expected that a more prolonged course of treatment will be given to our patients. In order to facilitate more long-term dosing of the drug two dose de-escalations of approximately 30% will be allowed.

3 PATIENT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 Inclusion Criteria:

Patients must:

3.1.1.1 Have recurrent or refractory/unresectable disease for which there is no known curative therapy.

- Wild type-GIST: Patients with recurrent or progressive disease will be eligible. Newly diagnosed patients with resectable localized disease will not be eligible. Newly diagnosed patients with metastatic disease and newly diagnosed patients with residual tumor following surgical debulking will be eligible.

- PHEO/PGL: Patients with recurrent or progressive disease will be eligible. Newly diagnosed patients with PHEO/PGL that is metastatic at diagnosis and/or unresectable will be eligible Patients with PHEO/PGL with localized (non-metastatic), resectable disease will not be eligible.
- Renal cell cancer associated with HLRCC: Patients with localized, resectable HLRCC-associated renal cell cancer will not be eligible. Patients with metastatic and/or unresectable HLRCC-associated renal cell cancer will be eligible.

3.1.1.2 Have one of the following confirmed histologically, cytologically, or through biochemical testing:

- wild-type GIST (GIST without KIT or PDGFRA mutation);
- PHEO/PGL with a germline mutation in SDHA, SDHB, SDHC, or SDHD;
- renal cell cancer associated with HLRCC.

Testing will be performed in CLIA certified labs using genetic tests for KIT/PDGFRA and testing panels developed for patients with PHEO/PGL. Results from outside labs will be accepted. Pathologic diagnosis will be reviewed and verified at the Clinical Center.

3.1.1.3 Age: be ≥ 12 years of age

Because there is no dosing or adverse event data currently available on the use of SGI-110 in children < 18 year of age, children < 12 years of age will be excluded from this study, but may be eligible for future pediatric trials should the results of the study be positive.

3.1.1.4 Measurable disease:

Have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See Section **8.2.2** for the evaluation of measurable disease (RECIST v1.1).

3.1.1.5 Prior Therapy

3.1.1.5.1 Prior therapy requirements:

- Wt-GIST: Because there are no standard chemotherapy regimens known to be effective for wt-GIST, previously untreated participants are eligible.
- PHEO/PGL with germline SDH subunit mutation: ^{131}I-MIBG in patients with MIBG avid tumors or cytotoxic chemotherapy (CVD or temozolomide) is required prior to enrollment on this trial. However, patients who have refused cytotoxic chemotherapy or for whom treatment on this protocol prior to receiving cytotoxic chemotherapy is felt to be in the best interest for the patient by the local investigator will also be eligible.
- HLRCC-associated renal cell cancer: Because there are no standard chemotherapy regimens known to be effective for HLRCC-associated renal cell cancer, previously untreated participants are eligible.

3.1.1.5.2 Prior therapy wash-out period requirements

- Participants must be at least 4 weeks from prior surgical procedures and surgical incisions must be healed.

- Participants must have had their last fraction of external beam radiation therapy at least 4 weeks prior to enrollment. Participants with prior radiation therapy must be at least 4 weeks post therapy *and* have had progression of disease outside the radiation port.
- Participants must have had their last dose of cytotoxic chemotherapy at least 28 days prior to enrollment, their last dose of biological therapy, such as biological response modifiers (e.g., cytokines), immunomodulatory agents, vaccines, differentiating agents, used to treat their cancer at least 28 days prior to enrollment, their last dose of a monoclonal antibody at least 28 days prior to enrollment, and their last dose of any investigational agent at least 28 days prior to enrollment.
- Participants must have recovered from the acute toxic effects of prior therapy to a grade 1 (CTCAE v.5.0) level prior to enrollment (does not apply to alopecia).

3.1.1.6 Performance Level: ECOG performance status $\leq$2 or Karnofsky $\geq$60% in patients > 16 years of age, Lansky $\geq$ 60 for patients $\leq$ 16 years of age (See Appendix **I**).

3.1.1.7 Have normal organ and marrow function as defined below:

– absolute neutrophil count	$\geq$1,500/mcL
– platelets	$\geq$100,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	$\leq$2.5 X institutional upper limit of normal
– creatinine	within normal institutional limits
	OR
– creatinine clearance	$\geq$60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.1.8 Birth Control:

The effects of SGI-110 on the developing human fetus are unknown. For this reason and because decitabine is known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, and for 6 months following participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.1.9 Ability of subject or legal guardians (if the patient is <18 years old) to understand and the willingness to sign a written informed consent document.

3.1.2 Exclusion Criteria

Patients with any one the following will be excluded:

3.1.2.1 Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, immunotherapy, or biologic therapy, including investigational agents for their disease.

3.1.2.2 History of allergic reactions to SGI-110 or decitabine.

3.1.2.3 Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, symptomatic

pulmonary disease or psychiatric illness/social situations that would limit compliance with study requirements.

3.1.2.4 Pregnant or breastfeeding

Pregnant women are excluded from this study because SGI-110 is a derivative of decitabine which has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with SGI-110, breastfeeding should be discontinued if the mother is treated with SGI-110. These potential risks may also apply to other agents used in this study.

3.1.2.5 Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses, or renal transplant, including any patient known to have hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) will be excluded. Patients with HIV who have adequate CD4 count, not requiring antiretroviral medication, may be enrolled.

3.1.2.6 Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

4 RECRUITMENT AND REGISTRATION

4.1 RECRUITMENT

In addition to posting this study on clinicaltrials.gov and the NCI website, patients who may be eligible will be invited to undergo screening during their participation in CCR Clinical studies, i.e. GIST Clinic held by POB, and RCC Clinic held by UOB, and PHEO/PGL Clinic held by NICHD.

4.2 SCREENING EVALUATION

Eligibility will be determined during a pre-study evaluation period after subjects have signed a consent (either a screening consent or this treatment consent). Subject information must be entered onto a screening log and for subjects not registered (enrolled) on the treatment portion of the study, a brief reason will be entered onto the screening log.

Screening blood tests should be performed within 72 hours and imaging studies within 4 weeks prior to enrollment on the trial unless otherwise stated. Any abnormal laboratory result that might preclude eligibility can be repeated within 24 hours.

4.2.1 History and physical examination

- Complete history, including prior and concurrent therapy; physical examination including documentation of measurable disease, performance status, blood pressure, height, weight, signs and symptoms.

4.2.2 Imaging evaluation

- Assessment of measurable disease sites by appropriate radiological evaluation. This may include a CT scan of chest, abdomen and pelvis and primary tumor, MRI scan of primary tumor and FDG-PET scan, as clinically indicated.

4.2.3 Hematology

- Complete blood count with differential and platelets.

4.2.4 Chemistries

- Electrolytes (including sodium, potassium, chloride, CO_2), calcium, phosphorus, magnesium, creatinine, BUN, glucose, ALT, bilirubin, urinalysis, total protein, albumin, CPK, and chromogranin A. Evaluation of catecholamine production by tumor (serum normetanephrine and metanephrine, urine if possible) will be performed in patients with PHEO/PGL only.

4.2.5 Urine or serum pregnancy test for all females of childbearing potential.

4.2.6 Pathologic/Tissue Evaluation

- Pathologic diagnosis will be reviewed and verified at the Clinical Center. Expression of SDH complex subunits and/or FH will be evaluated by immunohistochemistry in available pre-treatment tumor samples in the Clinical Center Laboratory of Pathology. GIST without Kit or PDGFRA mutation will be determined using standard approved tests.

4.2.7 For patients with PHEO/PGL

- Germline SDH subunit mutations will be determined using standard approved testing. Approved testing done outside of the Clinical Center will be accepted for these patients.

4.3 REGISTRATION PROCEDURES

4.3.1 IWRS

Patient Enrollment will be facilitated using the Interactive Web Response System (IWRS). IWRS is a web-based registration system available to users on a 24/7 basis. On a successful registration, IWRS will assign a patient number and assign the treatment. Patient enrollment data entered by Registrars in IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave. IWRS will provide a printable confirmation of registration and treatment information. Please retain a copy of this confirmation for your records.

- Users must have a valid CTEP-IAM account (*i.e.*, CTEP username and password) to access the IWRS system.
- Users defined with the Registrar role will have the ability to register patient in the study.
- Users defined with the Client Administrator role will have the ability to manage accrual limits, open and close treatment assignments as well as approve slot reservations, if applicable to the study.

4.3.2 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in

OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please retain a copy of this confirmation for your records.

4.3.3 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 LOCAL REGISTRATION FOR NCI CCR

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agent. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

5 STUDY IMPLEMENTATION

5.1 STUDY DESIGN

This is a single site, open label, phase II study design using a small optimal two-stage design to evaluate the clinical response in three groups of patients:

1. wild-type GIST (GIST without Kit or PDGFRA mutation)
2. PHEO/PGL in patients with germline SDH subunit mutation (SDH deficient PHEO/PGL), or
3. RCC associated with HLRCC

Adults and children (greater than or equal to 12 years of age) with measurable localized or metastatic or unresectable wild-type GIST, SDH deficient PHEO/PGL, or HLRCC-associated

RCC will be eligible for trial participation. SGI-110 will be administered subcutaneously at 45mg/m^2/day x 5days on a 28-day cycle. Cycles may be repeated until there is evidence of tumor progression clinically or by RECISTv1.1 or there is intolerable toxicity that is not alleviated by dose reduction.

SGI-110 activity will be assessed by radiographic response of measurable disease using RECISTv1.1. Patients will be carefully monitored for toxicity and response. Time to progression, overall survival and quality of life will be evaluated as secondary objectives.

5.2 DRUG ADMINISTRATION

SGI-110 will be administered subcutaneously, preferably in the abdominal area at 45mg/m^2/day x 5 days on a 28-day cycle. SGI-110 is available in a two-vial system, (1) SGI-110 for Injection 100 mg, and (2) SGI-110 Diluent for Reconstitution 3 mL.

SGI-110 drug product admixed with the custom diluent as described in section **15.1**. The reconstituted SGI-110 solution is stable for 1 week under refrigerated conditions.

SGI-110 should be injected slowly (up to one minute) as some injection site discomfort or pain may be experienced. Care must be taken to avoid intradermal injection as this may result in injection site pain. To prevent injection site pain, patient should be directed to apply ice packs to the injection site before and after the injection. If the injection pain continues despite these measures, pre-treatment with topical or systemic analgesics may be considered. Patients will be observed in clinic for at least one hour after the first dose of SGI-110.Vital signs including blood pressure, heart rate, and respiratory rate will be obtained and injection site will be monitored for signs of local reaction every 20-30 minutes in clinic for 1-hour post injection after the initial dose of SGI-110.

5.3 DOSE MODIFICATIONS

Although not a phase 1 study, toxicity will be evaluated and treatment limited by the toxicities defined below. This study will utilize the CTEP Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for toxicity and Adverse Event grading and reporting. An adverse event must be judged to be possibly, probably, or definitely related to SGI-110 to be a treatment limiting toxicity. Because it is possible that longer-term administration of the drug may be required in these patient populations, two dose reductions of approximately 30% will be allowed for patients who develop toxicity determined to be treatment related.

If a subject misses or skips a dose the dose will be given the next day. When a missed or skipped dose occurs, the research team should be notified to provide guidelines to the subject on whether to proceed with further doses.

SGI-110 will be held for treatment-limiting toxicities and re-started at the reduced dose after resolution of toxicity to a grade 1 or baseline.

Treatment-limiting toxicity is defined as:

- Toxicities that are possibly, probably or definitely related to SGI-110 and are ≥ grade 3, **unless** the toxicity resolves/reversible within 72 hours with supportive care.
- In addition, persistent grade 2 toxicities will be considered dose-limiting if they are intolerable to the patient.

If the patient experiences a treatment limiting toxicity after two dose reductions, SGI-110 will be discontinued permanently.

Dose Level	Dose reduction (mg/m^2/dose)	Dose reduction (%)
Dose -1	30mg/m^2/dose	~30%
Dose -2	20mg/m^2/dose	~30%

5.4 QUESTIONNAIRES (APPENDIX III AND APPENDIX IV)

The pediatric PROMIS instruments and the Distress Rating Tool will be administered to all consenting patients who speak English or Spanish with parallel Parent Proxy instruments administered to parents of patients ages 12-17. These instruments will be administered at baseline, at the end of cycle 4 and every 4 cycles thereafter, and at the time a patient is taken off treatment (see Section **5.7**). Since the measures have not been validated in other languages, participation in this portion of the study will be limited to subjects who speak either English or Spanish.

5.4.1 PROMIS

The Patient–Reported Outcome Measurement Information System (PROMIS®), funded by the National Institutes of Health to provides clinicians and researchers access to efficient, precise, valid, and responsive parent– and child–reported measures of health and well–being.

5.4.2 Distress Rating Tool

All patients ages 12 years or older will complete the Distress Thermometer. The Distress Thermometer takes less than 5 minutes to complete.

5.5 ON-STUDY EVALUATION

5.5.1 Baseline Assessment

Laboratory values must be no older than 72 hours from the time of eligibility evaluation and starting therapy. Imaging studies must be no older than 4 weeks of enrollment at enrollment. Testing outside of this window must be repeated prior to starting study drug.

If a post-enrollment/pre-treatment laboratory value is outside of the limits of eligibility, this laboratory value must return to the eligibility requirement prior to initiating therapy. If the laboratory value does not return to the limits of eligibility within 14 days, patient may not receive protocol therapy.

The evaluations required prior to starting treatment portion of the study are listed in Section **5.6**, Study Calendar. Screening labs will be repeated if they are older than 72 hours.

5.6 STUDY CALENDAR

Procedure	*Screening*	*Baseline*	*Cycle 1 (± 3 days)*					*Subsequent Cycles (± 3 days)*		*Post Therapy Follow-up (approximately 30 days after final dose of study drug)*
			Day 1	*Day 2-5*	*Day 7*	*Day 14*	*Day 28*	*Day 1-5*	*Day 28*	
History	X							X		
Physical Exam	X	X[a]						X		
Vital signs	X	X	X[i]					X		
Performance Score	X	X[a]								
SGI-110 Administration			X	X				X		
Labs • Complete blood count with diff, platelets • Electrolytes (including sodium, potassium, chloride, CO_2), calcium, phosphorus, magnesium, creatinine, BUN, glucose, ALT, bilirubin, urinalysis, total protein, albumin, and CPK	X	X[a]						X		
Serum normetanephrine and metanephrine (if possible, urine), and chromogranin A (in patients with PHEO/PGL only)	X							X[j]		

Procedure	*Screening*	*Baseline*	*Cycle 1 (± 3 days)*					*Subsequent Cycles (± 3 days)*		*Post Therapy Follow-up (approximately 30 days after final dose of study drug)*
			Day 1	*Day 2-5*	*Day 7*	*Day 14*	*Day 28*	*Day 1-5*	*Day 28*	
Urine/serum pregnancy test for all females of childbearing potential	X							X[k]		
Biopsies	X[c]							X[g]		
1) Tumor expression of SDH complex subunits and FH by IHC	X							X[g]		
2) Tumor expression of NY-ESO-1 by IHC		X[f]						X[g]		
LINE-1 demethylation analysis (Dr. Meltzer research)		X				X				
Pharmacokinetic testing		X	X[d]	X[d]						
Pharmacodynamic testing[e]		X			X	X	X			
Response evaluation of disease [b]	X	X[b]							X[b]	
Quality of Life (Distress thermometer and PROMIS)		X							X[h]	X[h]
Adverse Events			X	→	→	→	→	→		X
Concomitant Medications			X	→	→	→	→	→		X

[a] Laboratory tests older than 2 weeks (14 days) at the start of therapy must be repeated. For abnormal test results, refer to Section 4.2.

[b] Imaging studies will be repeated if older than 4 weeks at the start of therapy. Imaging evaluation selection may include CT and/or MRI, and/or FDG-PET as clinically indicated. Staging should be performed prior to the second cycle and then prior to every other cycle. The same imaging strategy will be used throughout study participation for tumor evaluation.

[c] when archival tissue is not available.

[d] active metabolite (decitabine) will be assayed in plasma prior to first dose in cycle 1 and at 0.5 hour (+/- 15 minutes), 1 hour (+/- 15 minutes), 2 hour (+/- 30 minutes), 4 hour (+/- 30 minutes), 6 hour (+/- 1 hour) and 24 hours (+/- 2 hours) after the first dose of drug in Cycle 1.

[e] LINE-1 demethylation in PBMC using pyrosequencing and urine and plasma glycolytic metabolytes at baseline and day 7, 14, and 28 of cycle 1.

[f] pre-treatment tumor samples on archival tissue may be used for initial NY-ESO-1 evaluation.

[g] On-treatment biopsy will be performed when a core biopsy may be safely performed in consenting patients ≥ 18 years of age. On treatment biopsy will be optional.

[h]at the end of cycle 4 and then every 4 cycles thereafter (e.g. at the end of cycle 8, 12, 16, etc.), and at the end of therapy.

[i]Vital signs will be obtained on day 1 per section **5.2**.

[j]At each restaging timepoint

[k]Prior to each cycle

5.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

5.7.1 Criteria for removal from protocol therapy

Patients participating in this study may be removed for therapy with SGI-110 due to any one of the following events:

- Completed 30-day safety follow-up period
- Progressive disease
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in Section **5.3**
- Investigator discretion
- Positive pregnancy test

5.7.2 Off-Study Criteria

Patients who are removed from treatment permanently for any reason should be monitored until resolution or stabilization of toxicity, or until 30 days after the last dose of SGI-110, whichever is later. In addition, the following criteria will result in removal from study:

- Participant requests to be withdrawn from study
- Lost to follow up
- Death

5.7.3 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

Note: all minors will be kept on study and followed until the age of 18 to allow for consent.

6 CONCOMITANT MEDICATIONS/MEASURES

There will be no concomitant disease directed therapy allowed while patients are participating in this study.

Supportive standard therapies and preventive measures should be instituted to address known toxicities, including the following:

6.1 INJECTION SITE REACTIONS

Care must be taken to avoid intradermal injection, and administer by slow subcutaneous injection. If injection site pain occurs, apply ice packs to the site both before and after injection.

If injection site reactions occur despite these measures, pre-treatment with topical or systemic analgesic can be considered.

6.2 MUCOSITIS

To prevent mucositis, participants should be directed to increase brushing teeth with the softest tooth brush, every 4 hours and at bedtime, and rinse frequently with mouth rinses, to keep the mouth moisturized. Patients with a healthy mouth may use non-alcoholic mouthwash 4 to 6 times daily (e.g. after each meal), or according to the instructions, during the study.

Saline mouthwashes (Sodium chloride 0.9%) are preferred in cases of stomatitis, and should be used at a different time than toothbrushing (e.g. after tea).

Consider treating stomatitis at an early stage (CTCAE grade 1) or as soon as the patient complains of a sore mouth. Consider using an oral topical analgesic, with or without topical steroids, depending on the patient's clinical condition and the local standard medical practice.

6.3 DIARRHEA

Patients should be made aware that they may experience diarrhea, and should record the number of stools and associated symptoms. Patients should inform the physician if they develop diarrhea. The following dietary advice should be considered: BRAT diet (bananas, rice, apple sauce, toast, plain pasta), readily digestible food, avoidance of lactose-containing products and fried, fatty or spicy foods, increased fluid intake (8-10 glasses of clear fluids/day (including water, clear broth, fluids containing salt and sugar). Patients should be given loperamide to take home and should start taking loperamide after the first episode of unformed, loose stool. If diarrhea persists and after consulting with the investigator, loperamide can be continued at a dose of 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Monitor and replace fluid and electrolytes. Patients should contact their physician or study nurse if they have persistent diarrhea, diarrhea complicated by vomiting or fever, or inability to take oral liquids

7 BIOSPECIMEN COLLECTION

7.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

7.1.1 Pharmacokinetics

Pharmacokinetic analysis will be performed in patients during cycle 1 according to Section **5.6**, Study Calendar. The observed decitabine $T_{1/2}$ following SC administration of SGI-110 in adults is 2.4 hours[23]. The active metabolite of SGI-110 (decitabine) will be assayed in plasma prior to the first dose of drug in cycle 1 and at 0.5 (+/- 15 min), 1 (+/- 15 min), 2 (+/- 30 min), 4 (+/- 30 min), 6 (+/- 1 hour), and 24 hours (+/- 2 hours). Blood samples (3mL) will be collected into 6 mL sodium heparin green top tubes. PK analysis will be performed in the laboratories of Dr. Figg. Plasma levels of decitabine will be determined using a validated liquid chromatography-mass spectrometry method.

This PK data will be used to develop a population PK model (using Phoenix NLME®, Certara, Cary, NC and RStudio) that will assess the impact of covariates including (but not limited to) age, body size (weight, height, surface area), sex, race, PD endpoints, hepatic and renal function.

The degree of change in decitabine PK based on the covariates available will be assessed to determine if dose adjustments are required.

7.1.2 Expression of SDH complex subunits and FH

Expression of SDH complex subunits and FH will be evaluated by immunohistochemistry in available pre-treatment and on treatment tumor samples in the Clinical Center Laboratory of pathology under the direction of Dr. Marino and Dr. Miettenen. This analysis will be performed in archival tumor tissue and in on-treatment biopsies when available. Paraffin-embedded tissue sections will be utilized for this analysis and staining will be performed using published methodology that was developed in the laboratory of pathology for FH, SDHA and SDHB[2,33].

7.1.3 DNA hyper-methylation

The DNA-methylome will be evaluated for pre-treatment and on-treatment tumor biopsies (when available) in the laboratory of Dr. Paul Meltzer. Methylation assay and methylation data analysis will be done using paraffin-embedded samples. The EZ DNA Methylation kit (Zymo Research) will be used for bisulfite conversion of gDNA extracted from paraffin-embedded tumor samples. The GoldenGate Cancer Panel Methylation Array 1 (Illumina) will be utilized and data analyzed as previously described[2].

7.1.4 NY-ESO-1 expression

Available pre-treatment tumor samples will be used for initial NY-ESO-1 evaluation and on-treatment biopsies will be optional for patients >18 years old when core biopsy can be safely performed. NY-ESO-1 expression before and on treatment in paired tumor biopsy samples when available, using immunohistochemistry in the Laboratory of Pathology at the Clinical Center under the direction of Dr. Miettenen and Dr. Marino. Paraffin-embedded tissue sections will be utilized for this analysis and staining will be performed using published methodology that was developed in the laboratory of pathology[34]. NY-ESO-1 staining intensity will be assessed by two pathologists using the following scoring system: 1+ = weak, 2+ = moderate, 3+ = strong.

7.1.5 Serum and Urine Concentrations of glycolytic metabolites

Impaired activity of the Krebs cycle enzymes SDH complex or FH leads to aberrant cellular concentrations of glycolytic metabolites including fumarate and succinate[35,36]. Systemic levels of 2-hydroxyglutarate have been investigated as a method of identifying patients with glioblastoma with isocitrate dehydrogenase mutation[37]. In these patients, the plasma/urine ratio of 2-hydroxyglutarate was significantly different between patients with mutant isocitrate dehydrogenase enzymes. Systemic levels of glycolytic metabolites are not well-defined in patients with wt-GIST, HLRCC, or PHEO/PGL. We will begin to explore the metabolomic profile of patients with tumors related to Krebs cycle defects. Serum and urine 2-hydroxyglutarate, succinate, and fumarate will be determined at baseline and on treatment. Plasma and urine samples will be collected at baseline and on day 7, 14, and 28 of cycle 1. Urine samples will be cooled to 4 C, centrifuged, aliquoted and stored at -80 C until analysis. Blood samples (3mL) will be collected in EDTA tubes and cooled to 4 C, centrifuged, and plasma will be aliquoted and stored at -80 C until analysis. Concentrations of 2-hydroxyglutarate succinate and fumarate will be analyzed using liquid chromatography/mass spectrometry (LC/MS) as previously described[37,38].

5.1.6 LINE-1 demethylation analysis of PBMCs

LINE-1 methylation status in peripheral blood mononuclear cells will be assessed as an estimate of global DNA methylation. This analysis will be performed on samples at baseline and on days 7, 14, and 28 of cycle 1. Analysis will be performed in the laboratory of Dr. Meltzer using a previously described quantitative bisulfate pyrosequencing method[39].

Study	Test/Lab Location	Sample Time Points	Volume/type of blood sample	Tube	Notes
PK- analysis of decitabine	Liquid Chromatography-mass spectrometry method, Dr. Figg's lab	Pre-dose 1, and 0.5, 1, 2, 4, 6, and 24 hrs post dose 1	3mL blood	6 mL sodium heparin green top	Tubes will be cooled to 4 degrees C and centrifuged. Plasma will be aliquoted and stored at -80 C until analysis.
Expression of SDH complex subunits and FH y	IHC, CC Laboratory of Pathology (Dr. Marino and Dr. Miettenen	If available: prior to dose 1 and during treatment	Archival samples may be used for pretreatment, on treatment biopsies performed in patients ≥ 18 years, if safely obtainable.	NA	Block (can be same block that is used for DNA hypermethylation) or 10 unstained slides Samples will be fixed and processed by the laboratory of pathology.
NY-ESO-1 expression	IHC, CC Laboratory of Pathology (Dr. Marino and Dr. Miettenen	If available, prior to dose 1 and during treatment	Archival samples may be used for pretreatment, on treatment biopsies performed in patients ≥ 18 years, if safely obtainable.	NA	
DNA hypermethylation	EZ DNA Methylation kit (Zymo Research) will be used for bisulfite conversion of gDNA, and The GoldenGate Cancer Panel Methylation Array 1 (Illumina) will be utilized in the laboratory of Dr. Paul Meltzer	Prior to dose 1 and during treatment	Archival samples may be used for pretreatment, on treatment biopsies performed in patients ≥ 18 years, if safely obtainable.	NA	Block (can be same block that is used for NY-ESO-1 expression) or10 unstained slides of FFPE samples will be supplied to Dr. Meltzer's laboratory for processing.
LINE-1 demethylation analysis	EZ DNA Methylation kit (Zymo Research) will be used for bisulfite conversion of gDNA, and The GoldenGate Cancer Panel Methylation Array 1 (Illumina) will be utilized in the laboratory of Dr. Paul Meltzer	Prior to dose 1 and Cycle 1, Day 14 (±3 days)	10 mL blood	lavender top	Samples will be collected and spun by Dr. Figg's Lab and then sent to Paul Meltzer's lab. PBMC will be collected and aliquoted and stored until analysis.

Study	Test/Lab Location	Sample Time Points	Volume/type of blood sample	Tube	Notes
Urine glycolytic metabolites (PD)	LC/MS Laboratory of Dr. Widemann	At baseline at days 7, 14, and 28 of cycle 1.	Urine samples 10-15 ml	15ml Conical tube	Samples will be collected. and cooled to 4 C. Dr. Figg's lab to process: spin briefly to remove debris. Sample will then be aliquoted and stored at -80 C until analysis.
Serum glycolytic metabolites (PD)	LC/MS Laboratory of Dr. Widemann	At baseline at days 7, 14, and 28 of cycle 1.	Blood sample 3mL	3 ml SST	Samples will be collected and cooled to 4 C. Dr. Figg's lab to process: Spin, and . Plasma will then be aliquoted and stored at -80 C until analysis.

7.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (a.k.a LabSamples) utilized by the CPP. This is a secure program, with access to LabSamples limited to defined CPP personnel, who are issued individual user accounts. Installation of LabSamples is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LabSamples creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LabSamples access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location, and date samples are sent to the investigator or shipped to outside institutions. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

7.2.1 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at -80°C in accordance to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LabSamples. All

researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **10.2.1**.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LabSamples. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

The study will remain open and status reported to the NIH Intramural IRB until all samples have been analyzed, reported or destroyed. Unintentional loss or destruction of any samples will be reported to the NIH Intramural IRB per the requirements of section **10.2.1**. Any use of these samples for purposes not described in this protocol will require prospective NIH Intramural IRB review and approval.

Data from patient reported outcomes and functional endpoints will be sent to POB NCI for data analysis. All data will be identified using the study number; no personal identifying information should be sent to NCI.

8 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated for response after the first 4 weeks and then every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.1 DEFINITIONS

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with *SGI-110.*

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified

according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

8.2 DISEASE PARAMETERS

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters

will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.2.1 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT

introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

8.2.2 Response Criteria

8.2.2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.2.2.2 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest

measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.2.3 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

9 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

9.1 COMPREHENSIVE ADVERSE EVENT AND POTENTIAL RISK LIST (CAEPRS)

9.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR for SGI-110 (NSC 780463)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 757 patients*. Below is the CAEPR for SGI-110 (Guadecitabine).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, May 8, 2019[1]

Adverse Events with Possible Relationship to SGI-110 (Guadecitabine) (CTCAE 5.0 Term) [n= 757]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
EYE DISORDERS			

Adverse Events with Possible Relationship to SGI-110 (Guadecitabine) (CTCAE 5.0 Term) [n= 757]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Periorbital edema	
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
		Edema face	
Fatigue			***Fatigue (Gr 2)***
	Fever		
Injection site reaction			***Injection site reaction (Gr 2)***
	Pain		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		***Bruising (Gr 1)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Tumor lysis syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
PSYCHIATRIC DISORDERS			
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			

Adverse Events with Possible Relationship to SGI-110 (Guadecitabine) (CTCAE 5.0 Term) [n= 757]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspnea		
	Epistaxis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Purpura		
	Rash maculo-papular		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on SGI-110 (Guadecitabine) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that SGI-110 (Guadecitabine) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (agranulocytosis); Blood and lymphatic system disorders - Other (coagulopathy); Blood and lymphatic system disorders - Other (febrile bone marrow aplasia); Blood and lymphatic system disorders - Other (histiocytosis hematophagic); Blood and lymphatic system disorders - Other (lymphadenopathy); Blood and lymphatic system disorders - Other (pancytopenia); Bone marrow hypocellular; Leukocytosis; Thrombotic thrombocytopenic purpura

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (atrial tachycardia); Cardiac disorders - Other (bradycardia); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Palpitations; Sinus tachycardia

CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (phimosis)

EAR AND LABYRINTH DISORDERS - Ear pain; Vertigo

ENDOCRINE DISORDERS - Adrenal insufficiency

EYE DISORDERS - Blurred vision; Eye disorders - Other (eye/retinal/conjunctival hemorrhage)

GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Belching; Cheilitis; Colitis; Dry mouth; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (small intestinal hemorrhage); Gastrointestinal disorders - Other (tongue discoloration); Gastrointestinal pain;

Gingival pain; Hemorrhoids; Ileus; Lip pain; Lower gastrointestinal hemorrhage; Oral hemorrhage; Oral pain; Periodontal disease; Rectal hemorrhage; Rectal pain; Small intestinal mucositis; Small intestinal obstruction; Toothache; Typhlitis; Upper gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Gait disturbance; General disorders and administration site conditions - Other (exercise tolerance decreased); General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS]); Infusion site extravasation; Localized edema; Malaise; Multi-organ failure; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Cholecystitis

IMMUNE SYSTEM DISORDERS - Allergic reaction

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Investigations - Other (elevated c-reactive proteins [c-reactive protein increased]); Investigations - Other (klebsiella test positive); Investigations - Other (reticulocyte count decreased); Investigations - Other (thrombocytosis); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Acidosis; Alkalosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (gout)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Flank pain; Generalized muscle weakness; Joint range of motion decreased; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (joint contracture); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Myalgia; Neck pain; Pain in extremity

NERVOUS SYSTEM DISORDERS - Ataxia; Dysgeusia; Lethargy; Paresthesia; Presyncope; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Delirium; Depression

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Urinary frequency; Urinary tract pain; Urinary urgency

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Penile pain; Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Bronchopulmonary hemorrhage; Cough; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal blistering); Rhinorrhea; Sneezing; Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Hyperhidrosis; Lipohypertrophy; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders -

Other (dermal cyst); Skin and subcutaneous tissue disorders - Other (granuloma annulare); Skin and subcutaneous tissue disorders - Other (onychoclasis); Skin induration; Skin ulceration

VASCULAR DISORDERS - Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: SGI-110 (Guadecitabine) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2 ADVERSE EVENT CHARACTERISTICS

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section **9.1.1**) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section **9.3.3**.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

9.3 EXPEDITED ADVERSE EVENT REPORTING TO CTEP

9.3.1 Expedited AE reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section **9.3.3**).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour

notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

9.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

9.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **<u>ANY</u>** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

<u>ALL</u> <u>SERIOUS</u> adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes

Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

9.4 ROUTINE ADVERSE EVENT REPORTING TO CTEP

All Adverse Events must be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

9.5 SECONDARY MALIGNANCY

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

9.6 SECOND MALIGNANCY

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting unless otherwise specified.

10 NIH INTRAMURAL RESEARCH PROGRAM REPORTING

10.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

10.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/ IRB REPORTING

10.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

10.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

10.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP/IRB in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

11 STUDY OVERSIGHT AND DATA REPORTING/REGULATORY REQUIREMENTS

11.1 STUDY OVERSIGHT

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **10.2.1**.

11.2 DATA REPORTING

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

11.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

11.3 DATA SHARING PLANS

11.3.1 Human Data Sharing Plan

I will share coded, linked human data generated in this research for future research in a NIH-funded or approved public repository at the time of publication or shortly thereafter.

11.3.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy

12 STATISTICAL CONSIDERATIONS

SGI-110 activity will be assessed by radiographic response of measurable disease using RECISTv1.1. The study will be conducted as a small, optimal two-stage phase II trial[40], in order to rule out an unacceptably low 5% overall response rate (ORR; p0=0.05), in favor of a slightly higher response rate of 30% (p1=0.30). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), the study will initially enroll 7 evaluable patients in each group (strata) and if 0 of the 7 have a response, then no further patients will be accrued in that stratum. If 1 or more the first 7 (14.3.1% or more) have a response, then accrual would continue until a total of 21 patients have enrolled in that stratum. Only complete responses (CR) and partial responses (PR) will be counted towards the overall response rate. As it may take several weeks to months to determine if a patient has experienced a response, a temporary pause in the accrual to that stratum in the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 1 to 2 responses in 21 patients, this would be an uninterestingly low response rate, while if there were 3 or more responses in 21 (14.3% or more) patients, then this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 70%. With three cohorts of up to 21 patients apiece, the maximum number of evaluable patients required would be 63. In order to allow for a small number of inevaluable patients, the accrual ceiling will be set to 70.

Descriptive summaries of the secondary outcome variables (toxicity, progression-free survival, overall survival, quality of life, pharmacokinetics, pharmacodynamics) will be presented at the time of the primary analysis, and will be repeated in subsequent analyses to characterize the extent to which changes are maintained over a longer follow-up period. Each of these secondary endpoints will be assessed in a hypothesis generating manner, without formal adjustment for multiple comparisons but reported in the context of the number and type of evaluation being performed.

In addition, progression-free survival and overall survival will be reported separately for each stratum. Changes in QOL will be evaluated relative to any degree of response and summary statistics will be described over time. As these evaluations may be performed in a post hoc manner based on the response results obtained, the findings will need to be carefully presented in the context of the exploratory nature of the analyses undertaken.

13 COLLABORATIVE AGREEMENTS

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator"

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

14 HUMAN SUBJECTS PROTECTIONS

14.1 RATIONALE FOR SUBJECT SELECTION

Patients of both genders, from all racial and ethnic groups are eligible for this trial if they meet the eligibility criteria outlined in Section **3.1**. There is no clinical information that suggests differences in SGI-110 metabolism or response among racial or ethnic groups or between the genders, indicating that results of the trial will be applicable to all groups. This phase II trial of SGI-110 will be conducted in children greater than or equal to 12 years of age and adults measurable, localized or metastatic or unresectable wild-type GIST, SDH deficient PHEO/PGL, or HLRCC-associated RCC will be eligible for trial participation. Patients with PHEO/PGL or RCC must have recurrent or refractory disease. Efforts will be made to extend the accrual to a representative group from this population, but with these uncommon diseases and with a planned accrual of 24 patients, a balance must be struck between completing the trial in a timely fashion on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

14.1.1 Gender and Minority Accrual Estimates

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	

DOMESTIC PLANNED ENROLLMENT REPORT					
American Indian/ Alaska Native	1	1			2
Asian	1	3			4
Native Hawaiian or Other Pacific Islander	0	0			0
Black or African American	4	5			9
White	22	25	3	4	54
More Than One Race	1				1
Total	29	34	3	4	70

14.2 Participation of Children

Children greater than or equal to 12 years of age will be eligible and the drugs pharmacokinetics will be explored in this age group. The safety of SGI-110 has not been established in children and therefore younger age groups will be excluded until more safety data is available in this age group. Children greater than or equal to 12 years of age will be enrolled and the study will be conducted by pediatric oncologists who have extensive experience in performing investigational drug trials in children. Patients enrolled at the POB, NCI will be cared for in the POB outpatient clinic or day hospital. When patients require hospital admission, they will be cared for on the 1NW Pediatric Unit by the POB staff.

14.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **14.5**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP14E for

appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

14.4 Evaluation of Benefits and Risks/Discomforts

14.4.1 Risks of SGI-110

The primary risk to patients participating in this research study is from toxicity of SGI-110. In adults, SGI-110 has been relatively well tolerated. The dose limiting toxicities observed with SGI-110 include grade 4 neutropenia and thrombocytopenia and grade 5 sepsis. The most common toxicities reported with SGI-110 monotherapy include neutropenia, thrombocytopenia, fatigue, diarrhea, injection site pain (including pain, burning, irritation, erythema, inflammation, bleeding, pain, or subcutaneous nodules), anemia, febrile neutropenia (See Section **9.1**).

14.5 Risks/Benefits Analysis

Gastrointestinal stromal tumors (GISTs) are resistant to cytotoxic chemotherapy and radiation therapy. KIT and PDGFRA mutations have been identified as tumor initiating events in 85% of adult patients with GIST and these tumors are responsive to the tyrosine kinase inhibitor, Imatinib. In pediatric patients, however, 85% of GISTs lack KIT and PDGFRA mutations (wild-type) and imatinib is not effective. SDH deficiency is present in the majority of patients with wt-GIST and guadecitabine may have activity in this population of patients.

Approximately 10-30% of PHEO/PGL are SDH-deficient[13,14] and there is an increased risk of more aggressive metastatic disease in patients with SDHB mutation. Surgical resection is the only curative therapy for patients with PHEO/PGL, however both radiation therapy and cytotoxic chemotherapy using cyclophosphamide, vincristine, and dacarbazine (CVD) have been used to treat patients with metastatic or recurrent disease[12]. While responses can be seen with this therapy, complete durable responses are rare and additional therapeutic options are lacking. Guadecitabine may have activity in this population of patients with SDH-deficient PHEO/PGL.

HLRCC-associated kidney cancer is typically clinically aggressive with early development of metastatic disease. Nephron-sparing surgical therapy is standard for localized HLRCC-associated renal cancer[22]. While there is currently no standard systemic therapy for metastatic HLRCC-associated renal cell cancer, treatments targeting the VEGF and EGFR pathways are being investigated in ongoing clinical trials[22]. HLRCC is an autosomal-dominant hereditary syndrome due to mutations in FH5.

All three of these tumors (SDH deficient PHEO/PGL, HLRCC-associated RCC, and wt-GIST) have limited treatment options for metastatic and locally recurrent disease and are associated with deficiency in the Krebs cycle components SDH and FH. These tumors exhibit global DNA hypermethylation and may be responsive to guadecitabine. Therefore, this phase II protocol involves greater than minimal risk to children, but presents the prospect for direct benefit to individual child-subjects (Category 2).

14.6 Consent and Assent Process and Documentation

The procedures and tests involved in this study and the associated risks, discomforts and benefits of these processes, will be carefully explained to the patient or the patient's parents or guardian if

he/she is a child, and a signed informed consent document will be obtained prior to entry onto the study.

The investigators are requesting a waiver from the IRB to allow only one parent to sign the treatment informed consent form to enter a child on the protocol. Because many patients must travel to the NIH from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. The parent who signs the consent for a minor must be a legally recognized parent or guardian. When guardianship status of the child is uncertain, documentation of custody status must be obtained.

In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained by telephone via the procedure described in section **14.6.1**.

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Verbal assent will be obtained as appropriate for children ages 7-11 and the parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent. Children under the age of 18, but who are age 12 or older will be asked to sign an age appropriate assent form. Children under the age of 12 will not be required to provide assent as they typically do not have the cognitive ability to fully understand the nature of research. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable.

14.6.1 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. Given the length of time that has transpired for some of the subjects since their last visit for this study, we request waiver of informed consent for those individuals who become lost to follow up or who have been taken off study prior to reaching the age of majority.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(3) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
    a. We only plan to request a waiver of reconsent for those subjects who have been lost to follow-up

14.6.2 Telephone consent

The following procedure may be used in cases where reconsent is required. This process may also be used to obtain initial consent of an absent parent when both parental signatures are required. The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented in the medical record.

15 PHARMACEUTICAL INFORMATION

15.1 SGI-110 (GUADECITABINE) (NSC 780463)

Chemical Name or Amino Acid Sequence:

Sodium (2*R*,3*S*,5*R*)-5-(4-amino-2-oxo-1,3,5-triazin-1(2*H*)-yl)-2-(hydroxymethyl) tetrahydrofuran-3-yl ((2*R*,3*S*,5*R*)-5-(2-amino-6-oxo-1*H*-purin-9(6*H*)-yl)-3-hydroxytetrahydrofuran-2-yl)methyl phosphate

Other Names: Guadecitabine

Classification: DNA methylation inhibitor

Molecular Formula: $C_{18}H_{23}N_9NaO_{10}P$ **M.W.:** 579.39 Da

Approximate Solubility*:* It is water soluble at about 30 mg/mL over a pH range of 6.0 to 7.0. It is unstable in aqueous solutions and is relatively more stable at neutral pH. SGI-110 is soluble in common organic solvent systems such as methanol, dimethylamine (DMA), and dimethyl sulfoxide (DMSO).

Mode of Action: Guadecitabine (SGI-110) is a potent inhibitor of DNA methylation. Guadecitabine is a dinucleotide of decitabine and deoxyguanosine linked with a phosphodiester bond. Decitabine is the active metabolite. Guadecitabine is a new chemical entity that was designed to enhance pharmacokinetic (PK) properties compared with decitabine, with potential to improve pharmacodynamics (PD), clinical efficacy, and safety.

How Supplied: SGI-110 for Injection is supplied by Astex Pharmaceutical and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as follow:

- **SGI-110 for Injection**: 100 mg dry powder lyophile containing free acid equivalent in a single-use vial;

- **Diluents for Reconstitution**: Two fill volumes: 3 mL or 1.2 mL
  - 3 mL single-use vial containing non-aqueous diluent of propylene glycol, glycerin, and ethanol. (Will be phased out around July 2019)
  - 1.2 mL single-use vial containing non-aqueous diluent of propylene glycol, glycerin, and ethanol. (Will be available for use around July 2019)

All vials are packaged in clear glass vials with stoppers made of **latex-free rubber stopper** and capped with an aluminum flip-off seal.

Preparation:

1. Allow SGI-110 vial(s) and diluent vial(s) to reach room temperature approximately 60 minutes.
2. Next, loosen the lyophilized powder of SGI-110 by gently tapping and rotating the vial on a hard surface.
3. Use a 1 mL syringe and withdraw 0.9 mL of diluent and add it to the SGI-110 vial resulting in a final concentration of 100 mg/mL. Manually shake or mechanically vortex the diluted vial(s).
   - Manually shake: Intermittently shake the reconstituted vial vigorously (approximately 5 minutes). In general, the shaking process will take 5 to 10 minutes. Rotate the vial and inspect the vial contents to ensure that all lyophilized SGI-110 powder has dissolved. After dissolution, allow the vial to rest until all bubbles have dissipated (approximately 10 minutes).
   - Mechanically shake (vortex): Before vortexing, rotate or shake the vial to ensure that the drug powder is thoroughly wetted with diluent. Then, vortex for 5-10 minutes at a speed setting of 5. Remove the vial from the holder and invert it 2-3 times. Place the vial on the vortex and mix for another 10 minutes. Ensure that all SGI-110 powder is completely dissolved. Repeat the process if partially dissolved. Once all drug is dissolved, allow the solution rest until all bubbles dissipate (approximately 10 minutes).
4. The final solution of the diluted vial should be colorless to pale yellow.
5. Withdraw the diluted solution into a syringe. If two or more syringes are needed to deliver the total prescribed dose, all dispensed syringes should have equivalent volumes for consistency and ease of administration.

Note: If SGI-110 powder has not dissolved 60 minutes after completion of manually shaking or vortex, do not use the vial(s).

Vortex: Sites that do not have access to a vortex may request it directly from Astex Pharmaceuticals, Inc.

Contact: Richard Morishige

Phone: (925) 560-2882

Email: Richard.Morishige@astx.com

Storage:

- Store SGI-110 lyophilized powder refrigerated between 2^0 and 8^0 C (36^0 and 46^0 F)

- Store 3 mL diluent between 2^0 and 30^0 C (36^0 F and 86^0 F)
- Store 1.2 mL diluent between 2^0 and 8^0 C (36^0 and 46^0 F)

If a storage temperature excursion is identified, promptly return SGI-110 vials and the diluents to the recommended storage temperatures above and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies of SGI-110 intact vials are ongoing.

- Upon reconstitution, the diluted drug solution is good for 8 days refrigerated at 2 to 8 C

Route*(s)* of Administration: subcutaneous injection

Method of Administration: Administer by slow subcutaneous injection. Care must be taken to avoid intradermal injection. If injection site pain is reported upon injection, apply ice packs to the injection site both before and after injection for 5 – 10 minutes each; however, using icepack for the first dosing is not recommended. Pretreatment of topical or systemic analgesics can be considered.

Potential Drug Interactions*:* Drug-drug interaction studies have not been conducted with guadecitabine or decitabine. In vitro studies suggested that guadecitabine is unlikely to inhibit or induce major P450 enzymes and is not a CYPs substrate. Furthermore, guadecitabine nor the active metabolite decitabine inhibit major human drug transporters.

Special Handling: SGI-110 is a cytotoxic agent. Use PPE when preparing the drug. Direct contact of SGI-110 to skin must be washed immediately with soap and copious amount of water. The drug degrades rapidly in soap water. If SGI-110 contacts the mucous membranes, flush the affected area thoroughly with water.

Drug spilling can be inactivated by either using a 2 N sodium hydroxide solution or water and kericide CR Biocide B which consists of a blend of stabilized chlorine dioxide and a quaternary ammonium compound

15.1.1 Agent Ordering and Agent Accountability:

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability – The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order

Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts:

CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/

NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov

PMB policies and guidelines:

http://ctep.cancer.gov/branches/pmb/agent_management.htm

PMB Online Agent Order Processing (OAOP) application:

https://ctepcore.nci.nih.gov/OAOP

CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/

CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

IB Coordinator: IBCoordinator@mail.nih.gov

PMB email: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

15.1.2 Incompatibilities

Drug-drug interaction studies have not been conducted with SGI-110 or decitabine. *In vitro* studies in human hepatocytes suggest that SGI-110 is unlikely to inhibit or induct cytochrome p450 enzymes. Thus p450-mediated drug-drug interactions are not anticipated for SGI-110.

16 APPENDICES

16.1 APPENDIX I-PERFORMANCE STATUS CRITERIA

Patient C3D Study ID:_____ Patient's Age:_____

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

PERFORMANCE STATUS:

ECOG Score: _____ OR Karnofsky Score: _____

16.2 APPENDIX II: PERFORMANCE STATUS SCALES/SCORES IN PATIENTS ≤16 YEARS OF AGE

Patient C3D Study ID: _____ Patient's Age:_____

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky (> 16 years of age)		**Lansky (≤16 years of age)**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

PERFORMANCE STATUS:

Karnofsky Score: _____ OR Lansky Score: _____

16.3 APPENDIX III: QUALITY OF LIFE TOOLS

16.3.1 Pediatric PROMIS Instruments English (6)

PROMIS™ Pediatric Item Bank v.1.0 - Physical Function - Mobility - Short Form 8a

Pediatric Physical Function - Mobility - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…..	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
I could do sports and exercise that other kids my age could do.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could get up from the floor.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could keep up when I played with other kids.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could move my legs.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could stand up by myself.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could stand up on my tiptoes.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I could walk up stairs without holding on to anything.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
I have been physically able to do the activities I enjoy most.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

PROMIS Pediatric Item Bank v2.0 – Anxiety – Short Form 8a

Pediatric Anxiety – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
2220R2r	I felt like something awful might happen..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
713R1r	I felt nervous.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
227bR1r	I felt scared.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5044R1r	I felt worried.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3459bR1r	I worried when I was at home	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2230R1r	I got scared really easy.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
231R1r	I worried about what could happen to me..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3150bR2r	I worried when I went to bed at night	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS Pediatric Item Bank v2.0 – Depressive Symptoms – Short Form 8a

Pediatric Depressive Symptoms – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
488R1r	I could not stop feeling sad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
461R1r	I felt alone.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5041R1r	I felt everything in my life went wrong.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5035R1r	I felt like I couldn't do anything right.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
711R1r	I felt lonely	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
228R1r	I felt sad.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
712R1r	I felt unhappy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3952aR2r	It was hard for me to have fun.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS™ Pediatric Item Bank v.1.0 - Fatigue - Short Form 10a

Pediatric Fatigue - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…….

	Never	Almost Never	Sometimes	Often	Almost Always
Being tired made it hard for me to play or go out with my friends as much as I'd like.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt weak.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I got tired easily.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Being tired made it hard for me to keep up with my schoolwork.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I had trouble finishing things because I was too tired.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I had trouble starting things because I was too tired.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was so tired it was hard for me to pay attention.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to do sports or exercise.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to do things outside.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was too tired to enjoy the things I like to do.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS™ Pediatric Item Bank v.1.0 - Pain Interference - Short Form 8a

Pediatric Pain Interference - Short Form

Please respond to each item by marking one box per row.

In the past 7 days…..	Never	Almost Never	Sometimes	Often	Almost Always
I had trouble sleeping when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I felt angry when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I had trouble doing schoolwork when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard for me to pay attention when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard for me to run when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard for me to walk one block when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard to have fun when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
It was hard to stay standing when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS™ Pediatric Item Bank v.1.0 - Peer Relationships - Short Form 8a

Pediatric Peer Relationships - Short Form

Please respond to each item by marking one box per row.

In the past 7 days....

	Never	Almost Never	Sometimes	Often	Almost Always
I felt accepted by other kids my age.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was able to count on my friends.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was able to talk about everything with my friends.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
I was good at making friends.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
My friends and I helped each other out.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Other kids wanted to be my friend.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Other kids wanted to be with me.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Other kids wanted to talk to me.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

16.3.2 Pediatric PROMIS Instruments Spanish (6)

PROMIS Pediatric v.1.1 - Depressive Symptoms - Short Form 8b

Síntomas de depresión en pediatría - Cuestionario abreviado 8b

Responde a cada enunciado marcando una casilla por línea.

En los últimos 7 días...

		Nunca	Casi nunca	A veces	A menudo	Casi siempre
488R1	No pude dejar de sentirme triste.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
461R1	Sentí que estaba solo/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5041R1	Sentí que todo me salía mal en la vida.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5039R1	Sentí que no podía hacer nada bien.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
711R1	Me sentí solo/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
228R1	Me sentí triste.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
712R1	Me sentí descontento/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3952a/R2	Me resultó difícil divertirme.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Spanish (Universal)
27 January 2014

PROMIS™ Pediatric Item Bank v.1.0 - Fatigue - Short Form 10a

Agotamiento en niños - Cuestionario abreviado 10a

Responde a cada enunciado marcando una casilla por línea.

En los últimos 7 días...

		Nunca	Casi nunca	A veces	A menudo	Casi siempre
4236aR2	El cansancio hizo que fuera difícil para mí estar al día con las tareas escolares.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4212R1	Como estaba cansado/a, me resultó difícil jugar o salir con mis amigos/as tanto como me habría gustado.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4213R1	Sentí debilidad.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3876R1	Me cansé fácilmente.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4221R1	Tuve dificultad para terminar las cosas porque estaba demasiado cansado/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4220R1	Tuve dificultad para comenzar las cosas porque estaba demasiado cansado/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4210R2	Estuve tan cansado/a que me fue difícil prestar atención.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4241R2	Estuve demasiado cansado/a para practicar deportes o hacer ejercicio.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4208aR2	Estuve demasiado cansado/a para hacer actividades (a)fuera.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4196R1	Estuve demasiado cansado/a para disfrutar de las cosas que me gusta hacer.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Spanish (Universal)
26 February 2013

PROMIS™ Pediatric Item Bank v.1.0 - Physical Function - Mobility - Short Form 8a

Capacidad de funcionamiento físico en niños - Movilidad - Cuestionario abreviado 8a

Responde a cada enunciado marcando una casilla por línea.

En los últimos 7 días…

		Sin dificultad	Con poca dificultad	Con alguna dificultad	Con mucha dificultad	No pude hacerlo
2951R1	Pude practicar los mismos deportes y ejercicios que hacían otros niños/as de mi edad.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4124R1	Pude levantarme del piso (suelo).	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2951R1	Pude mantener el mismo ritmo cuando jugaba con otros niños/as.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3892R1	Pude mover las piernas.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2648R1	Pude ponerme de pie sin ayuda.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4189R1	Pude ponerme de puntillas (sobre las puntas de los pies).	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2707R2	Pude subir escaleras sin agarrarme a nada.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5023R1	He podido hacer físicamente las actividades que más me gustan.	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Spanish (Universal)
26 February 2013

PROMIS™ Pediatric Item Bank v.1.0 - Pain Interference - Short Form 8a

Efectos del dolor en niños - Cuestionario abreviado 8a

Responde a cada enunciado marcando una casilla por línea.

En los últimos 7 días...

		Nunca	Casi nunca	A veces	A menudo	Casi siempre
1606bR1	Me sentí enojado/a cuando tuve dolor.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2035R1	Cuando tuve dolor, tuve problemas para hacer las tareas escolares.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3793R1	Tuve problemas para dormir cuando sentí dolor.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9004	Cuando tuve dolor, me fue difícil prestar atención.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2045R1	Cuando tuve dolor, me fue difícil correr.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2049R1	Cuando tuve dolor, me fue difícil caminar una manzana (cuadra).	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
1703R1	Cuando tuve dolor, fue difícil para mí divertirme.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2180R1	Cuando tuve dolor, fue difícil para mí quedarme de pie.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Spanish (Universal)
26 February 2013

PROMIS Pediatric Item Bank v.1.0 - Peer Relationships - Short Form 8a

Relaciones entre iguales en niños - Cuestionario abreviado 8a

Responde a cada enunciado marcando una casilla por línea.

	En los últimos 7 días...	Nunca	Casi nunca	A veces	A menudo	Casi siempre
5018R1	Me sentí aceptado/a por los otros niños/as de mi edad.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5058R1	Pude contar con mis amigos/as.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5056R1	Pude hablar de todo con mis amigos/as.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
1147R1	Me fue fácil hacer amigos/as.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5055R1	Mis amigos/as y yo nos ayudamos.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
233R2	Otros niños/as quisieron ser mis amigos/as.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
210R1	Otros niños/as quisieron estar conmigo.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
902DR1	Otros niños/as quisieron hablar conmigo.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Spanish (Universal)
26 February 2013

PROMIS Pediatric v.1.1 - Anxiety - Short Form 8b

Ansiedad en pediatría - Cuestionario abreviado 8b

Responde a cada enunciado marcando una casilla por línea.

En los últimos 7 días...

		Nunca	Casi nunca	A veces	A menudo	Casi siempre
2220R2	Sentí que podría pasar algo terrible.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
713R1	Me sentí nervioso/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2276R1	Sentí miedo.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5044R1	Me sentí preocupado/a.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
34586R1	Me preocupé cuando estaba en casa.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2230R1	Me asusté con mucha facilidad.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
231R1	Me preocupó lo que pudiera pasarme.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31506R2	Me preocupé al acostarme por las noches.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Spanish (Universal)
27 January 2014

16.3.3 Parallel Parent Proxy PROMIS Instruments English (6)

PROMIS Parent Proxy Item Bank v1.0 – Physical Function Mobility 8

Physical Function Mobility – Short Form 8

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
Pf1mobil3	My child could do sports and exercise that other kids his/her age could do.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil9	My child could get up from the floor	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf4mobil4	My child could keep up when he/she played with other kids	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil8	My child could move his/her legs	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf3mobil3	My child could stand up without help.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf2mobil7	My child could stand up on his/her tiptoes	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf2mobil4	My child could walk up stairs without holding on to anything.....	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
Pf1mobil1	My child has been physically able to do the activities he/she enjoys most	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

PROMIS Parent Proxy Item Bank v1.0 – Anxiety 8

Anxiety – Short Form 8

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf1anxiety8	My child felt nervous	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety2	My child felt scared.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety9	My child felt worried.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety1	My child felt like something awful might happen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety6	My child thought about scary things.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1anxiety7	My child was afraid that he/she would make mistakes	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1anxiety3	My child worried about what could happen to him/her.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2anxiety4	My child worried when he/she went to bed at night.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS Parent Proxy Item Bank v1.0 – Depressive Symptoms 6

Depressive Symptoms – Short Form 6

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf2depr7	My child could not stop feeling sad	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1depr7	My child felt everything in his/her life went wrong.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1depr5	My child felt like he/she couldn't do anything right	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2depr10	My child felt lonely.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2depr3	My child felt sad.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2depr5	My child thought that his/her life was bad	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS Parent Proxy Item Bank v1.0 – Fatigue 10

Fatigue – Short Form 10

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf4fatigue12	Being tired made it hard for my child to play or go out with friends as much as he/she would like.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4fatigue8	My child felt weak.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4fatigue3	My child got tired easily.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2fatigue8	Being tired made it hard for my child to keep up with schoolwork.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2fatigue4	My child had trouble finishing things because he/she was too tired	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3fatigue7	My child had trouble starting things because he/she was too tired	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3fatigue12	My child was so tired it was hard for him/her to pay attention.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3fatigue8	My child was too tired to do sports or exercise.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3fatigue4	My child was too tired to do things outside	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4fatigue4	My child was too tired to enjoy the things he/she likes to do.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS Parent Proxy Item Bank v1.0 – Pain Interference 8

Pain Interference – Short Form 8

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf2pain5	My child had trouble sleeping when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3pain7	My child felt angry when he/she had pain .	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2pain2	My child had trouble doing schoolwork when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3pain2	It was hard for my child to pay attention when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2pain4	It was hard for my child to run when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1pain4	It was hard for my child to walk one block when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3pain4	It was hard for my child to have fun when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4pain6	It was hard for my child to stay standing when he/she had pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

PROMIS Parent Proxy Item Bank v1.0 – Peer Relationships 7

Peer Relationships – Short Form 7

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf3socabil9	My child felt accepted by other kids his/her age	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf4socabil12	My child was able to count on his/her friends	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3socabil4	My child was good at making friends	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2socrole4	My child and his/her friends helped each other out.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf1socabil2	Other kids wanted to be my child's friend.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf3socrole4	Other kids wanted to be with my child	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2socabil9	Other kids wanted to talk to my child	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

16.3.4 Adult Patient PROMIS Instruments English (6)

PROMIS Item Bank v1.0 –Physical Function - Short Form 10a

Physical Function – Short Form 10a

Please respond to each item by marking one box per row.

		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFA01	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36	Does your health now limit you in walking more than a mile?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA05	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA03	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16	Are you able to dress yourself, including tying shoelaces and doing buttons?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45	Are you able to get on and off the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Item Bank v.1.0 – Emotional Distress – Anxiety- Short Form 7a

Emotional Distress - Anxiety – Short Form 7a

Please respond to each item by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX05	I felt anxious	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX30	I felt worried	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS Item Bank v. 1.0 – Emotional Distress – Depression - Short Form 8b

Emotional Distress - Depression – Short Form 8b

Please respond to each item by marking one box per row.

In the past 7 days....

		Never	Rarely	Sometimes	Often	Always
EDDEP04	I felt worthless……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP05	I felt that I had nothing to look forward to……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP17	I felt sad……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP22	I felt like a failure……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	I felt unhappy……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS Item Bank v. 1.0 - Fatigue -Short Form 7a

Fatigue - Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Item Bank v1.0 – Pain Interference - Short Form 6b

Pain Interference – Short Form 6b

Please respond to each item by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ3	How much did pain interfere with your enjoyment of life?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ8	How much did pain interfere with your ability to concentrate?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ10	How much did pain interfere with your enjoyment of recreational activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ14	How much did pain interfere with doing your tasks away from home (e.g., getting groceries, running errands)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
PAININ26	How often did pain keep you from socializing with others?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS v.1.0/1.1 - Global

Global Health Scale

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS v.1.0/1.1 - Global

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		None	Mild	Moderate	Severe	Very severe
Global08	How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Global07	How would you rate your pain on average?	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst imaginable pain

16.3.5 Adult Patient PROMIS Instruments Spanish (6)

PROMIS Item Bank v. 1.2 – Physical Function – Short Form 10a

Capacidad de funcionamiento físico – Cuestionario abreviado 10a

Responda a cada pregunta marcando una casilla por línea.

		Nada	Poco	Algo	Mucho	No puedo hacerlo
PFA1	¿Limita su salud en este momento su capacidad para realizar actividades vigorosas, como correr, levantar objetos pesados o participar en deportes enérgicos?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36r1	¿Limita su salud en este momento su capacidad para caminar más de una milla (1.6 km)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	¿Limita su salud en este momento su capacidad para subir un piso de escaleras?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	¿Limita su salud en este momento su capacidad para levantar o llevar las bolsas del supermercado?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3	¿Limita su salud en este momento su capacidad para inclinarse, arrodillarse o agacharse?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Sin dificultad	**Con poca dificultad**	**Con alguna dificultad**	**Con mucha dificultad**	**No puedo hacerlo**
PFA11	¿Puede realizar tareas, como pasar la aspiradora o trabajar en el jardín?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	¿Puede vestirse sin ayuda, incluso amarrarse los zapatos y abotonarse la ropa?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	¿Puede lavarse el cabello con champú?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	¿Puede lavarse y secarse el cuerpo?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45r1	¿Puede sentarse y levantarse del inodoro (excusado)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Spanish (Universal)
21 January 2014

PROMIS Item Bank v.1.0 – Emotional Distress - Anxiety – Short Form 7a

Trastorno emocional - Ansiedad – Cuestionario abreviado 7a

Responda a cada enunciado marcando una casilla por línea.

	En los últimos 7 días...	Nunca	Rara vez	Algunas veces	A menudo	Siempre
EDANX01	Sentí miedo	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX05	Sentí ansiedad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX30	Me sentí preocupado/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	Tuve dificultad para concentrarme en otra cosa que no fuera mi ansiedad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	Me sentí nervioso/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	Me sentí intranquilo/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	Me sentí tenso/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Spanish (Universal)
24 April 2012

PROMIS Item Bank v. 1.0 – Emotional Distress - Depression – Short Form 8b

Trastorno emocional - Depresión – Cuestionario abreviado 8b

Responda a cada enunciado marcando una casilla por línea.

	En los últimos 7 días...	Nunca	Rara vez	Algunas veces	A menudo	Siempre
EDDEP04	Sentí que no valía nada	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP05	Sentí que nada me ilusionaba	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	Me sentí indefenso/a (que no podía hacer nada para ayudarme)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP17	Me sentí triste	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP22	Me sentí fracasado/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	Me sentí deprimido/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	Me sentí descontento/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	Me sentí desesperanzado/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Spanish (Universal)
27 April 2012

PROMIS Item Bank v. 1.0 – Fatigue – Short Form 7a

Agotamiento – Cuestionario abreviado 7a

Responda a cada pregunta marcando una casilla por línea.

En los últimos 7 días…

		Nunca	Rara vez	Algunas veces	A menudo	Siempre
FATEXP20	¿Con qué frecuencia se sintió cansado/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	¿Con qué frecuencia sintió extenuación extrema?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	¿Con qué frecuencia se quedó sin energía?..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	¿Con qué frecuencia se vio limitado/a en el trabajo debido al agotamiento (incluya el trabajo en el hogar)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	¿Con qué frecuencia sintió demasiado cansancio como para pensar con claridad? ..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	¿Con qué frecuencia sintió demasiado cansancio como para darse un baño o una ducha?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	¿Con qué frecuencia tuvo suficiente energía como para hacer ejercicio vigoroso?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Spanish (Universal)
16 August 2012

PROMIS Item Bank v.10 – Pain Interference – Short Form 6b

Efectos del dolor – Cuestionario abreviado 6b

Responda a cada pregunta marcando una casilla por línea.

En los últimos 7 días…

		Nada	Un poco	Algo	Mucho	Muchísimo
PAININ3	¿En qué medida el dolor interfirió en su capacidad para disfrutar de la vida?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ8	¿En qué medida el dolor interfirió en su capacidad para concentrarse?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ9	¿En qué medida el dolor interfirió en sus actividades diarias?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ10	¿En qué medida el dolor interfirió en su capacidad para disfrutar de actividades recreativas o de ocio?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ14	¿En qué medida el dolor interfirió en su capacidad para realizar tareas fuera del hogar (p. ej., hacer la compra o los mandados)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

En los últimos 7 días…

		Nunca	Rara vez	Algunas veces	A menudo	Siempre
PAININ26	¿Con qué frecuencia el dolor le impidió socializar con otras personas?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Spanish (Universal)
12 September 2012

PROMIS Item Bank v.1.0/1.1 – Global

Salud general

Responda a cada enunciado marcando una casilla por línea.

		Excelente	Muy buena	Buena	Pasable	Mala
Global01	En general, diría que su salud es	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	En general, diría que su calidad de vida es	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	En general, ¿cómo calificaría su salud física?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	En general, ¿cómo calificaría su salud mental, incluidos su estado de ánimo y su capacidad para pensar?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	En general, ¿cómo calificaría su satisfacción con sus actividades sociales y sus relaciones con otras personas?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	En general, califique en qué medida puede realizar sus actividades sociales y funciones habituales. (Esto comprende las actividades en casa, en el trabajo y en el área donde reside, así como sus responsabilidades como padre o madre, hijo/a, cónyuge, empleado/a, amigo/a, etc.)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completa-mente	**En su mayoría**	**Moderada-mente**	**Un poco**	**Para nada**
Global06	¿En qué medida puede realizar sus actividades físicas diarias, como caminar, subir escaleras, cargar las compras o mover una silla?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Spanish (Universal)
15 Feb 2012

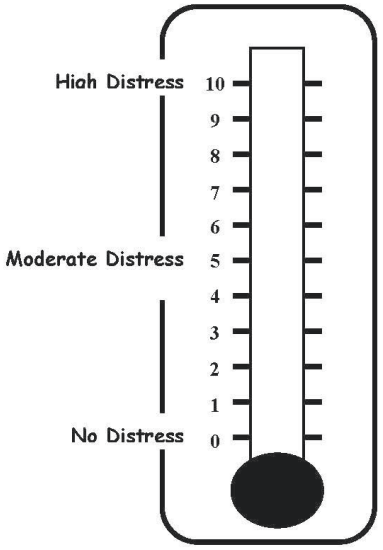
16.4 APPENDIX IV: THE DISTRESS AND SYMPTOM CHECKLIST: THE DISTRESS THERMOMETER

DISTRESS RATING TOOL
Patient

NAME: _____ DOB:_____ DATE: _____

INSTRUCTIONS: We know that all people can get sad and stressed out from time to time. Sometimes people can get overwhelmed and distressed by managing all the aspects of their own life along with their illness. When we say distress, we are referring to a range of feelings that can include sadness, being anxious, fearful, worried, or upset. These feelings may affect how you feel physically and emotionally.

On the thermometer below, circle the number that best describes how much distress **YOU** have been feeling **IN THE PAST MONTH** with a "0" indicating no distress at all and a "10" indicating the most distress you could possibly feel. Then, after indicating the level of distress on the thermometer, please check the causes of YOUR distress.



Emotional
Have you been:

- ❑ Worried/Anxious
- ❑ Sad/Depressed
- ❑ Lonely/Feeling Alone
- ❑ Guilt/self-doubt
- ❑ Bored
- ❑ Irritable
- ❑ Afraid to be alone
- ❑ Hopeless
- ❑ Difficulty making decisions
- ❑ Worthless
- ❑ Unhappy with how your body looks (If so, what part_____)
- ❑ Having trouble concentrating
- ❑ Having racing thoughts
- ❑ Scared (of _____)
- ❑ Angry
- ❑ Other Problems: _____

Physical
Have you been having problems with:

- ❑ Pain
- ❑ Getting around
- ❑ Fatigue/lack of energy
- ❑ Too much energy
- ❑ Sleeping through the night
- ❑ My weight(too high/too low)
- ❑ Eating too much, too little
- ❑ Headaches
- ❑ Hair loss
- ❑ Heart palpitations
- ❑ Trouble with my vision, eyes
- ❑ Stomach aches/pain
- ❑ Diarrhea/constipation (bowels)
- ❑ Not able to exercise
- ❑ Other Problems:

Practical
Have you been stressed about:

- ❑ Not understanding what is happening to my body
- ❑ School work, work
- ❑ Taking a lot of medications
- ❑ All my medical needs
- ❑ Doctor/hospital visits
- ❑ Future plans- job/career
- ❑ Not having good friends
- ❑ Other Problems:

Spiritual
Have you been stressed about:

- ❑ Spiritual Questions
- ❑ Difficulties Praying
- ❑ Feeling Distanced from God
- ❑ Loss of Faith
- ❑ Other Problems:

Family/Social
Have you been stressed about:

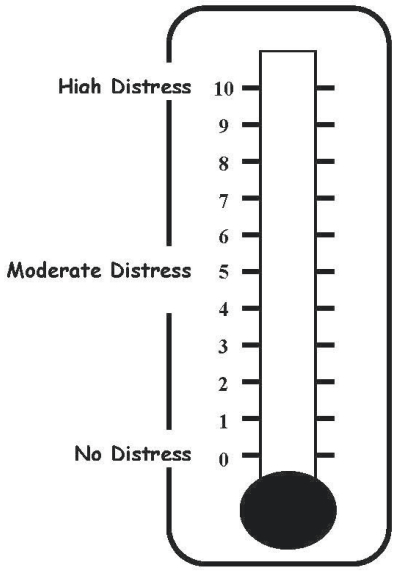
- ❑ Getting along with family
- ❑ Not having support
- ❑ Getting along with friends
- ❑ Lack of communication w/friends and family
- ❑ My parent(s) stress
- ❑ My sibling(s) stress
- ❑ Parent(s) being overprotective
- ❑ Other problems:

DISTRESS RATING TOOL
Caregiver

NAME: _____ RELATIONSHIP TO CHILD:_____
DATE: _____

INSTRUCTIONS: We know that people with a medical illness can get sad and stressed out from time to time. Sometimes people can get overwhelmed and distressed by managing all the aspects of their own life along with their illness. When we say distress, we are referring to a range of feelings that can include sadness, being anxious, fearful, worried, or upset. These feelings may affect how you feel physically and emotionally.

On the thermometer below, circle the number that best describes how much distress **YOUR child** has been feeling **IN THE PAST MONTH** with a "0" indicating no distress at all and a "10" indicating the most distress he/she could possibly feel. Then, after indicating the level of distress on the thermometer, please check the causes of YOUR CHILD'S distress.



Emotional
Has your child been feeling:

- ❑ Worried/Anxious
- ❑ Sad/Depressed
- ❑ Lonely/Feeling Alone
- ❑ Guilt/self-doubt
- ❑ Bored
- ❑ Irritable
- ❑ Afraid to be alone
- ❑ Hopeless
- ❑ Difficulty making decisions
- ❑ Worthless
- ❑ Unhappy with how his/her body looks (What part____)
- ❑ Having trouble concentrating
- ❑ Having racing thoughts
- ❑ Scared (of _____)
- ❑ Angry
- ❑ Other Problems: _____

Physical
Has your child had problems with:

- ❑ Pain
- ❑ Getting around
- ❑ Fatigue/lack of energy
- ❑ Too much energy
- ❑ Sleeping through the night
- ❑ Weight(too high/too low)
- ❑ Eating too much, too little
- ❑ Headaches
- ❑ Trouble with his/her vision
- ❑ Stomach aches/pain
- ❑ Diarrhea/constipation (bowels)
- ❑ Not able/willing to exercise
- ❑ Other Problems:

Practical
Has your child been stressed about:

- ❑ Not understanding what is happening to his/her body
- ❑ School work, work
- ❑ Taking a lot of medications
- ❑ Medical needs
- ❑ Doctor/hospital visits
- ❑ Future plans - job/career
- ❑ Not having good friends
- ❑ Other Problems:

Spiritual
Has your child been stressed about:

- ❑ Spiritual Questions
- ❑ Difficulties Praying
- ❑ Feeling Distanced from God
- ❑ Loss of Faith
- ❑ Other Problems:

Family/Social
Has your child been stressed about:

- ❑ Getting along with family
- ❑ Not having support
- ❑ Getting along with friends
- ❑ Lack of communication w/friends/family
- ❑ Parent's stress
- ❑ Sibling(s) stress
- ❑ Parent(s) being overprotective
- ❑ Other Problems:

17 REFERENCES

1. Boikos SA, Pappo AS, Killian JK, et al. Molecular Subtypes of KIT/PDGFRA Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. JAMA Oncol 2016.

2. Kelly L, Bryan K, Kim SY, et al. Post-transcriptional dysregulation by miRNAs is implicated in the pathogenesis of gastrointestinal stromal tumor [GIST]. PLoS One 2013;8:e64102.

3. Favier J, Briere JJ, Strompf L, et al. Hereditary paraganglioma/pheochromocytoma and inherited succinate dehydrogenase deficiency. Horm Res 2005;63:171-9.

4. Wei MH, Toure O, Glenn GM, et al. Novel mutations in FH and expansion of the spectrum of phenotypes expressed in families with hereditary leiomyomatosis and renal cell cancer. J Med Genet 2006;43:18-27.

5. Schmidt LS, Linehan WM. Hereditary leiomyomatosis and renal cell carcinoma. Int J Nephrol Renovasc Dis 2014;7:253-60.

6. Waterfall JJ, Killian JK, Meltzer PS. The role of mutation of metabolism-related genes in genomic hypermethylation. Biochem Biophys Res Commun 2014;455:16-23.

7. Letouze E, Martinelli C, Loriot C, et al. SDH mutations establish a hypermethylator phenotype in paraganglioma. Cancer Cell 2013;23:739-52.

8. Xiao M, Yang H, Xu W, et al. Inhibition of alpha-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors. Genes Dev 2012;26:1326-38.

9. Reichardt P, Joensuu H, Blay JY. New fronts in the adjuvant treatment of GIST. Cancer Chemother Pharmacol 2013;72:715-23.

10. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S A 2011;108:314-8.

11. Astuti D, Latif F, Dallol A, et al. Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. Am J Hum Genet 2001;69:49-54.

12. Martucci VL, Pacak K. Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment. Curr Probl Cancer 2014;38:7-41.

13. Kantorovich V, King KS, Pacak K. SDH-related pheochromocytoma and paraganglioma. Best Pract Res Clin Endocrinol Metab 2010;24:415-24.

14. Schiavi F, Boedeker CC, Bausch B, et al. Predictors and prevalence of paraganglioma syndrome associated with mutations of the SDHC gene. JAMA 2005;294:2057-63.

15. Richter S, Klink B, Nacke B, et al. Epigenetic Mutation of the Succinate Dehydrogenase C Promoter in a Patient With Two Paragangliomas. J Clin Endocrinol Metab 2016;101:359-63.

16. Haller F, Moskalev EA, Faucz FR, et al. Aberrant DNA hypermethylation of SDHC: a novel mechanism of tumor development in Carney triad. Endocr Relat Cancer 2014;21:567-77.

17. Averbuch SD, Steakley CS, Young RC, et al. Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. Ann Intern Med 1988;109:267-73.

18. Tanabe A, Naruse M, Nomura K, Tsuiki M, Tsumagari A, Ichihara A. Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine in patients with malignant pheochromocytoma and paraganglioma. Horm Cancer 2013;4:103-10.

19. Niemeijer ND, Alblas G, van Hulsteijn LT, Dekkers OM, Corssmit EP. Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. Clin Endocrinol (Oxf) 2014;81:642-51.

20. Fishbein L. Pheochromocytoma and Paraganglioma: Genetics, Diagnosis, and Treatment. Hematol Oncol Clin North Am 2016;30:135-50.

21. Yoshinaga K, Oriuchi N, Wakabayashi H, et al. Effects and safety of (1)(3)(1)I-metaiodobenzylguanidine (MIBG) radiotherapy in malignant neuroendocrine tumors: results from a multicenter observational registry. Endocr J 2014;61:1171-80.

22. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer 2014;13:637-44.

23. pharmaceuticals A. SGI-110 Investigator Brochure version number 5.0. 2014.

24. Network DTNCC. http://www.nccn.org/about/news/newsinfo.asp?NewsID=47.

25. Jacobsen PB, Donovan KA, Trask PC, et al. Screening for psychologic distress in ambulatory cancer patients. Cancer 2005;103:1494-502.

26. Ransom S, Jacobsen PB, Booth-Jones M. Validation of the Distress Thermometer with bone marrow transplant patients. Psycho-oncology 2006;15:604-12.

27. Zwahlen D, Hagenbuch N, Carley MI, Recklitis CJ, Buchi S. Screening cancer patients' families with the distress thermometer (DT): a validation study. Psycho-oncology 2008;17:959-66.

28. Patel SK, Mullins W, Turk A, Dekel N, Kinjo C, Sato JK. Distress screening, rater agreement, and services in pediatric oncology. Psycho-oncology 2011;20:1324-33.

29. Wiener L ZS, Battles H, Pao M. . Can an Adapted Distress Thermometer in the Pediatric Population be Valid and Clinically Meaningful? Psycho-oncology 2012;21.

30. Cella D, Gershon R, Lai JS, Choi S. The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2007;16 Suppl 1:133-41.

31. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. Journal of clinical epidemiology 2010;63:1179-94.

32. Varni JW, Stucky BD, Thissen D, et al. PROMIS Pediatric Pain Interference Scale: an item response theory analysis of the pediatric pain item bank. The journal of pain : official journal of the American Pain Society 2010;11:1109-19.

33. Miettinen M, Killian JK, Wang ZF, et al. Immunohistochemical loss of succinate dehydrogenase subunit A (SDHA) in gastrointestinal stromal tumors (GISTs) signals SDHA germline mutation. Am J Surg Pathol 2013;37:234-40.

34. Lai JP, Robbins PF, Raffeld M, et al. NY-ESO-1 expression in synovial sarcoma and other mesenchymal tumors: significance for NY-ESO-1-based targeted therapy and differential diagnosis. Mod Pathol 2012;25:854-8.

35. Saxena N, Maio N, Crooks DR, et al. SDHB-Deficient Cancers: The Role of Mutations That Impair Iron Sulfur Cluster Delivery. J Natl Cancer Inst 2015;108.

36. Aspuria PJ, Lunt SY, Varemo L, et al. Succinate dehydrogenase inhibition leads to epithelial-mesenchymal transition and reprogrammed carbon metabolism. Cancer Metab 2014;2:21.

37. Lombardi G, Corona G, Bellu L, et al. Diagnostic value of plasma and urinary 2-hydroxyglutarate to identify patients with isocitrate dehydrogenase-mutated glioma. Oncologist 2015;20:562-7.

38. Liesenfeld DB, Botma A, Habermann N, et al. Aspirin Reduces Plasma Concentrations of the Oncometabolite 2-Hydroxyglutarate: Results of a Randomized, Double-Blind, Crossover Trial. Cancer Epidemiol Biomarkers Prev 2016;25:180-7.

39. Yang AS, Estecio MR, Doshi K, Kondo Y, Tajara EH, Issa JP. A simple method for estimating global DNA methylation using bisulfite PCR of repetitive DNA elements. Nucleic Acids Res 2004;32:e38.

40. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1-10.