

**A Phase II Study of Sirolimus and Erlotinib in
Recurrent/Refractory Germ Cell Tumors**

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Abstract

While platinum-based current front-line therapy for malignant germ cell tumor results (MGCT) in greater than 80% overall survival, major challenges remain. 15-20% of patients still eventually die of their disease, either from primarily refractory disease or recurrent disease. Currently, therapy for patients with relapsed MGCT consists of further platinum-based chemotherapy regimens with or without stem cell rescue. While a second course of such therapy can cure some patients, there are no curative options for patients whose disease fails to respond to platinum based therapy. There have been few studies of relapsed and refractory MGCT, and nearly all utilize combinations of previously utilized chemotherapeutics. New approaches based on novel agents are needed for this population. Our recent work has shown high levels of mTORC1 activity and EGFR pathway activation in pediatric and adult MGCT tumors as well as response to mTOR and EGFR inhibition *in vitro*. Targeted mTOR inhibitors such as sirolimus and EGFR inhibitors such as erlotinib have been developed and shown to have little toxicity when given in combination. Thus, this is a Phase II study to determine the efficacy of the mTOR inhibitor sirolimus in combination with the EGFR inhibitor Erlotinib in recurrent or refractory malignant germ cell tumors.

Experimental Design and Schema

Sirolimus will initially be given orally at 1 mg/m² daily (maximum 2mg). The dose will be adjusted weekly based on trough sirolimus levels to a goal trough of 10-15 ng/mL. Erlotinib will initially be given orally at 85mg/m² daily (maximum 150mg/day). Inpatient dose escalation is planned at cycle 2 for patients without toxicity to maximize EGFR pathway inhibition.

Each cycle is 28 days (or every 4 weeks). Cycle 2 and subsequent cycles begin on day 29 if treatment parameters outlined in study are met. Therapy will be discontinued if there is drug-related dose-limiting toxicity or progressive disease. Patients with stable disease or better who do not meet any criteria for removal from protocol therapy or off study criteria may continue receiving protocol therapy for a total of up to 25 cycles. Evaluation for tumor response will occur after every 2nd cycle.

Correlative biology studies are planned. This will include an evaluation of the incidence of mTOR and EGFR pathway activation in primary tumors and correlation of pathway activation with response.

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1.0 Goals and Objectives

1.1 Primary Aims

1.1.1 To determine the PFR, defined as the proportion of patients with refractory germ cell tumors free of objective disease progression after 4 cycles (16 weeks) of therapy with erlotinib and sirolimus

1.1.2 To describe the toxicities (including dose-limiting toxicities) of the combination of sirolimus and erlotinib administered on this schedule.

1.2 Secondary Aims

1.2.1 To assess the incidence of EGFR and mTOR pathway activation in banked tumor specimens.

1.2.2 To compare the progression-free interval (PFI) for patients with germ cell tumors with and without evidence of EGFR/mTOR pathway activation with this drug combination.

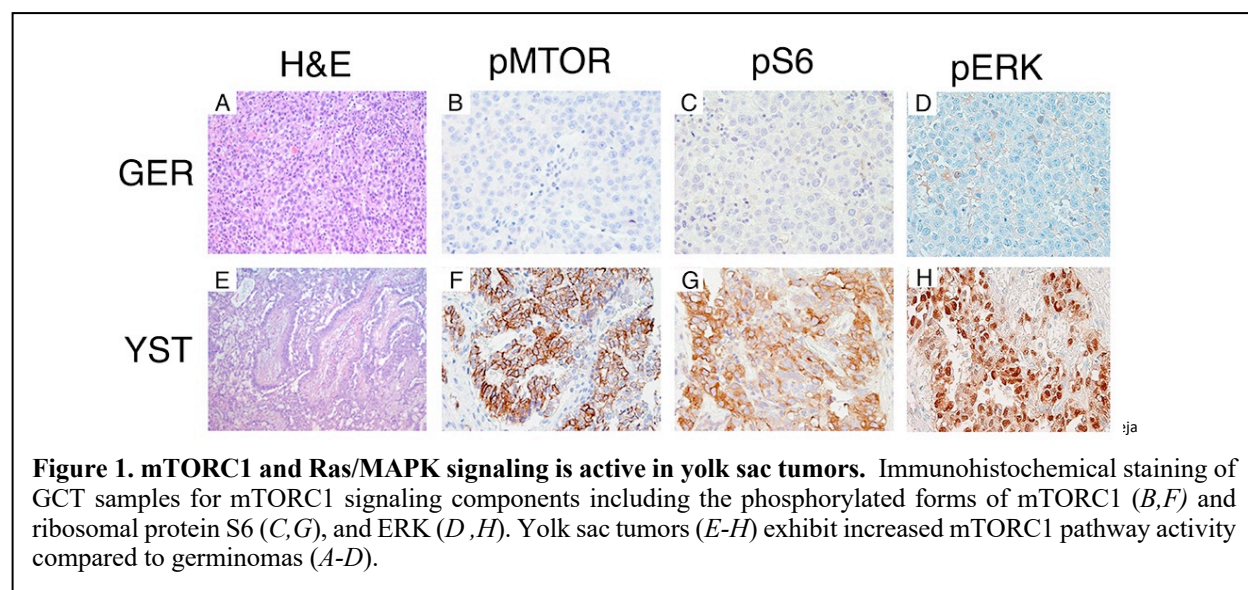
1.2.3 To determine the effect of concurrent administration of sirolimus on the pharmacokinetics of erlotinib

2.0 Background

Malignant germ cell tumors. Malignant germ cell tumors (MGCTs) are cancers of the gonads and extragonadal sites such as retroperitoneum, mediastinum, and brain and affect infants, children, and adults. MGCTs account for 15% of malignancies diagnosed during childhood and adolescence, and testicular GCT is the most common cancer in men aged 15 to 40[1, 2]. MGCTs arise from pluripotent embryonic germ cells[2]. Reflecting this pluripotency, MGCTs can present in a wide range of histologic forms. MGCTs that retain features of pluripotent, primitive germ cells are called seminomas in the testis and dysgerminomas in the ovary (collectively referred to as germinomas (GERs)). In contrast, non-germinomatous MGCTs exhibit differentiation into forms resembling somatic tissues (i.e., teratomas) or extraembryonic structures such as yolk sac. Yolk sac tumors (YSTs) are the most common malignant MGCTs in children. MGCTs are highly responsive to upfront cisplatin-based therapy such as bleomycin, etoposide, and cisplatin (BEP). However, standard regimens fail to cure about 15-20% of patients (and up to 50-60% of patients

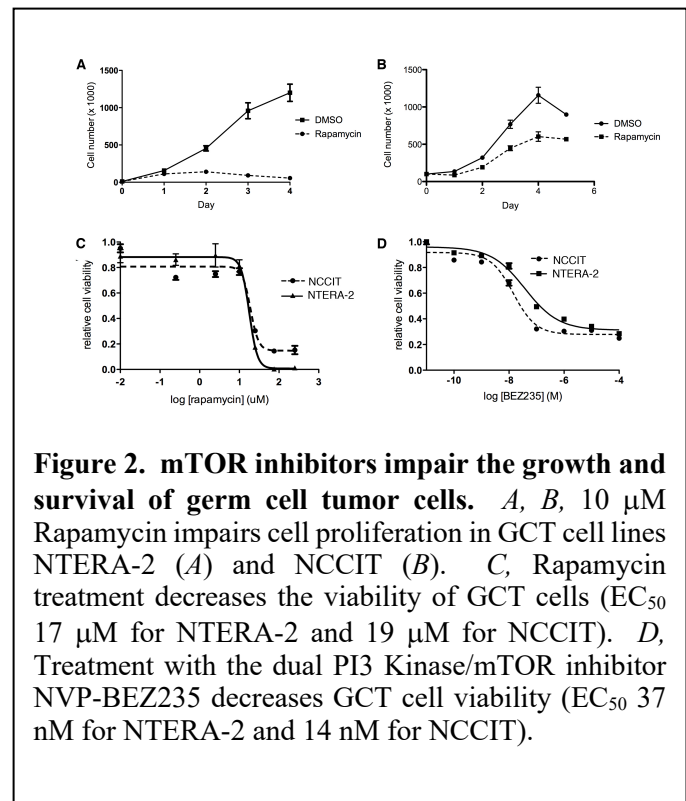
with primary mediastinal GCT) and are associated with significant long-term toxicity in survivors, including ototoxicity, nephrotoxicity, and risk of secondary malignancy[3, 4].

Current therapy for relapsed / refractory malignant germ cell tumors. The need exists for novel approaches to therapy for patients who germ cell tumor relapse after upfront therapy. There are few reports on salvage regimens in pediatric MGCTs, with most containing further platinum containing compounds[3]. Most pediatric patients are treated on salvage regimens based on adult data. Three primary salvage regimens have been developed and comparative efficacy data among them is lacking. In the early 1990s when BEP became the standard upfront therapy for malignant germ cell tumors, VeIP (vinblastine, ifosfamide, and cisplatin) was the most common salvage regimen. This regimen was shown to have a 50% CR rate and 25% long-term PFS rate for first salvage in the largest case series published [5]. During the 1990s, paclitaxel was demonstrated to have activity against germ cell tumors, and TIP (paclitaxel, ifosfamide, and cisplatin) was studied in relapsed patients and was shown to have a 70% CR rate with 63% long-term survival in a carefully selected population predicted to have a good outcome after salvage therapy[6]. The only randomized trial to compare these regimens closed early due to poor accrual (CALBG 90106). Most recently, there has been much interest in high dose chemotherapy with carboplatin and etoposide with stem cell rescue. The two largest series of patients published to date demonstrated an overall 29% 3 year EFS in 1996 [7], and more recently 63% EFS at a median of 3 years with two tandem cycles of this therapy [8]. While retrospective studies have shown a survival advantage to high dose chemotherapy over conventional salvage regimens, there has been no published randomized trial comparing these regimens. Such as study is currently under development through a collaboration of Alliance and EBMT [9]. Regardless, the outcome for patients who relapse after, or don't respond to, both an upfront and a salvage platinum-containing regimen is poor, justifying the need for trials of novel agents in this group of patients.



The mTORC1 pathway is active in Yolk Sac Tumors (YSTs). mTORC1 is a central regulator of cell growth, proliferation, and differentiation. A variety of human cancers have been found to have activation of the mTORC1 signaling pathway, with activation of this pathway correlating with tumor progression and reduced survival in several cancer types[10, 11]. To date, however, mTORC1 signaling in GCTs has not been investigated. Recently mTORC1 was shown to control

the development of germline stem cells during development[12]. To assess the state of mTORC1 signaling in GCTs, we assembled a tissue microarray from 23 clinically-annotated childhood GCTs, and compared mTOR signaling in germinomas (GERs) and yolk sac tumors (YST). The cohort of yolk sac tumors included 14 cases, of which 8 were testicular, 4 were ovarian, 1 was sacral, and 1 was hepatic. The cohort of GERs included 9 cases, of which 1 was testicular (seminoma), 6 were ovarian (dysgerminomas), 1 was from an indeterminate gonad (dysgerminoma) and 1 was mediastinal (germinoma). Using phosphospecific antibodies, we determined that YSTs but not GERs express activated forms of mTOR and its downstream target, RPS6 (Fig 1). Furthermore, YSTs expressed higher levels of the mTORC1 target genes Cyclin D1, HIF1A (not shown). The results of immunohistochemistry indicate a robust activation of mTORC1 signaling in YSTs, the most common histology of pediatric germ cell tumors.



mTOR inhibitors suppress proliferation and survival of GCT cells *in vitro*. Our finding that YSTs frequently exhibit high levels of mTORC1 signaling activity suggested that the mTORC1 pathway may confer a survival advantage on the tumor cells, and that pharmacologic inhibitors mTORC1 signaling might have activity against GCTs. To test this idea, we exposed NTERA-2 and NCCIT cells (GCT derived embryonal carcinoma cell lines that have mTOR activity and express EGFR) to the mTORC1 inhibitor, sirolimus. 10 μ M sirolimus blocked phosphorylation of S6 and inhibited the proliferation of NTERA-2 and NCCIT cells. Higher doses of sirolimus impaired the viability of both cell lines. (Figure 2C, EC₅₀ 17 μ M for NTERA-2 and 19 μ M for NCCIT). While these results demonstrate the dependence of MGCT on mTORC1 signaling, these concentrations of sirolimus are not clinically achievable. Treatment of cancer cells with sirolimus and its analogs has been shown to cause a feedback upregulation of the PI3K/Akt and MAPK pathways, representing a possible source of resistance. Thus, we hypothesized that inhibition of feedback upregulation of upstream signaling components would sensitize MGCT to mTOR inhibitors.

EGFR is highly expressed in pediatric and adult GCT. Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase upstream of mTOR (Figure 3). Overexpression of EGFR has been demonstrated by immunohistochemistry in metastatic embryonal carcinomas (a form of GCT) in adult patients [13]. Thus, we interrogated EGFR expression by quantitative RT-PCR in a panel of pediatric germ cell tumors and found high expression in yolk sac tumors (the most common histology), but low expression in germinomas (Fig 4A). Consistent with EGFR activation in YST, we found high levels of phosphorylated ERK, a downstream marker of activity of the Ras/MAPK pathway in YST (Figure 1).

Combined EGFR and mTOR inhibition is synergistic in GCT *in vitro*. Given our finding that mTOR inhibitors show activity *in vitro* in germ cell tumor cell lines, we hypothesized that combined mTOR and EGFR inhibition may be synergistic by blocking two common mTOR resistance pathways, feedback upregulation of AKT and activation of the Ras/MAPK pathway (Figure 3). Consistent with this hypothesis we found that combined treatment of the relatively mTOR resistant NCCIT cell line with 1 μ M erlotinib and only 10 nM rapamycin demonstrated a synergistic reduction in viability (Figure 4B). This represents a 1000-fold sensitization to sirolimus over the EC₅₀ seen without EGFR inhibition.

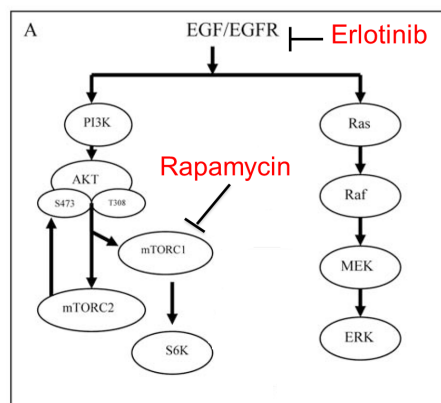


Figure 3. mTOR and EGFR pathway. EGFR is an upstream receptor tyrosine kinase that activates both the PI3K/AKT/mTOR pathway and the Ras/Raf/MEK/ERK pathways. The biologic effect of mTORC1 inhibition with sirolimus is limited by feedback upregulation of AKT and by activation of competing signaling pathways including Ras/MAPK. We have shown that EGFR inhibition with erlotinib is synergistic with mTOR inhibition in germ cell tumors *in vitro*, which we hypothesize is due to blocking this feedback upregulation as well as by inhibition of Ras/MAPK activation.

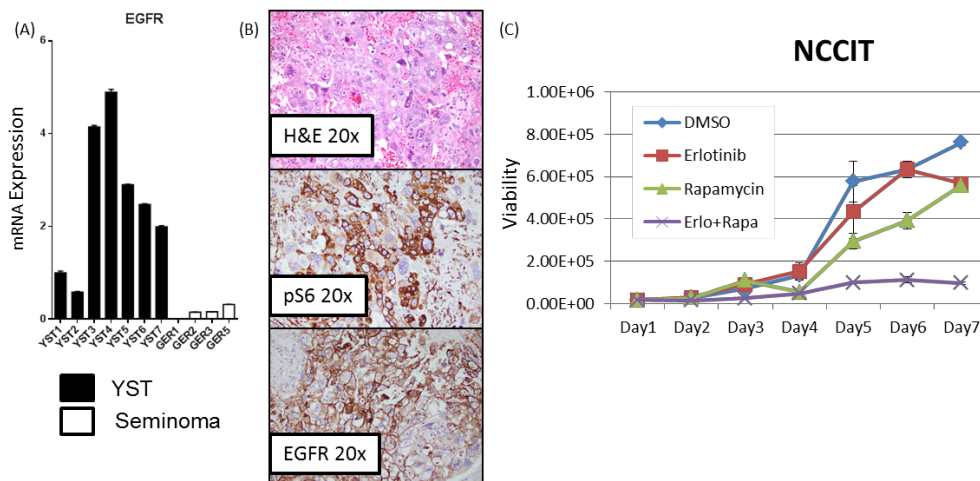


Figure 4. EGFR is highly expressed in Yolk Sac Tumors and EGFR inhibition is synergistic with mTOR inhibitors. (A) EGFR mRNA is highly expressed in primary yolk sac tumors compared with germinomas. (B) immunohistochemistry demonstrates mTOR pathway activation (pS6 expression) and EGFR expression in a patient with recurrent metastatic choriocarcinoma. Similar results were obtained from a case series of 14 pediatric patients with yolk sac tumors of which 13 had pS6 positivity. (C) The germ cell tumor cell line NCCIT was treated with 1uM erlotinib, 10nM rapamycin, or the combination of these drugs. Little effect is seen with treatment with either drug alone, but the combination results in synergistic growth inhibition. (Rakheja, et al, submitted)

Thus, there is robust pre-clinical rationale to test the combined inhibition of mTOR and EGFR in relapsed/refractory pediatric and adult germ cell tumors.

2.1 Toxicity and Pharmacokinetic Data

Sirolimus: Sirolimus (Rapamune) was FDA approved in 1999 for patients ≥ 13 years of age receiving renal transplants at doses of 5mg/day and 2mg/day for high and low immunologic risk patients. It is a generally well tolerated oral medication. In renal transplant patients, the most significant toxicities reported at a rate greater than in placebo were peripheral edema (54-58% vs 48% in placebo), lipid abnormalities: hypertriglyceridemia (45-57% vs 23% in placebo) and hypercholesterolemia (43-46% vs 23% in placebo), constipation (36-38% vs 31% in placebo), cytopenias: anemia (23-33% vs 21% in placebo) and thrombocytopenia (14-30% vs 9% in placebo), and rash (10-20% vs 6% in placebo). Rare but serious interstitial lung disease has been reported after treatment with sirolimus[14]. Its use in pediatric patients <13 years has been reported in patients as young as 1 year for auto-immune lymphoproliferative syndrome (ALPS) and for prevention of rejection in patients after liver transplant, including in two patients with hepatoblastoma and six with PTLT[15, 16]. Starting doses ranged from 0.8 - 3mg/m²/day with dose adjustment to achieve serum trough levels of 4-15 ng/mL [15, 17]. Toxicities potentially attributable to sirolimus were mild and similar to those seen in adults and included hyperlipidemia, leukopenia, thrombocytopenia, peripheral edema, and diarrhea. Additionally two of eight patients treated after liver transplant and two of six patients with ALPS were noted to have mouth ulcers or grade I-II mucositis and one patient had grade IV culture negative sepsis 16 months after starting treatment with sirolimus.

Sirolimus exhibits wide inter and intra-patient variation in clearance and thus is typically dosed based on therapeutic drug monitoring. It is a substrate of the ABCB1 pump (p-glycoprotein) and metabolized by the CYP3A4 and CYP3A5 enzymes, and its metabolism is effected by polymorphisms in the IL-10 gene (1082G>A, [18]).

Erlotinib: Erlotinib (Tarceva) was FDA approved in 2004 and is now approved as maintenance therapy for adults with non-small cell lung cancer alone at a dose of 150mg/day and for pancreatic cancer at an oral dose of 100mg/day in combination with gemcitabine. The most common adverse events are skin rash and diarrhea, with nausea, anorexia, fatigue, and infection also reported. Rare but serious adverse events have been reported with erlotinib therapy, including interstitial lung disease, acute renal failure, hepatic failure and hepatorenal syndrome, GI perforations, bullous skin rash, thrombotic events and microangiopathic hemolytic anemia[19]. Erlotinib use in pediatric patients has been reported in a phase I trial of 46 patients aged 3-20 years with refractory solid tumors (in combination with temozolamide, [20]). Daily administration to a maximum tolerated dose (MTD) of 85mg/m²/day was well tolerated with one of six patients with dose limiting toxicity (painful grade II rash lasting >7 days). At a dose 110mg/m²/day, one of four patients developed a painful grade II rash and one developed grade III hyperbilirubinemia. An additional 17 patients were treated at the MTD and two had dose limiting toxicity - one developed a painful grade II rash and one had grade III diarrhea. Non-dose limiting toxicities included diarrhea in 56% of patients, rash in 43% of patients, and hyperbilirubinemia in 26%. Of note, the incidence of rash was age related with 10% of patients less than 12 years vs 92% of patients greater than 12 years developing a grade II or worse rash[20].

Erlotinib has also been studied concurrently with radiotherapy in a Phase I study of 23 children and young adults with high-grade glioma, ages 3.7-22.5 years [21]. In this study, the MTD was defined as 120mg/m²/day. One patient at the MTD developed grade III diarrhea. At 160mg/m²/day, one of six patients developed grade III skin rash and one developed grade III lipase elevation. Non-dose-limiting toxicities included grade III hypokalemia and hypophosphatemia that were readily reversed with oral supplementation, hyperbilirubinemia, and lymphopenia [21]. A third phase I trial of Erlotinib in patients aged 2-20 years with brain tumors determined an MTD of 125mg/m²/day [22]. Toxicities included one of six patients with grade 5 intratumoral hemorrhage at the MTD and one patient of four at 150mg/m²/day with grade III asthenia and one patient of four at 150mg/m²/day with grade IV intratumoral hemorrhage. One of eight additional patients enrolled at the MTD developed grade III hyperbilirubinemia[22].

Erlotinib is primarily metabolized by CYP3A4, with a minor component of its metabolism from other cytochrome p450 enzymes[23]. It is also a substrate of the ABCB1 transporter (p-glycoprotein). Approximately 5% of circulating erlotinib is the biologically active OSI-420 metabolite. Erlotinib pharmacokinetics are effected by CYP3A4 genotype and pharmacological inhibitors, with patients with the CYP3A4*1 allele having a 42% increase in clearance, patients with the ABCB1 2677G > T/A SNP having a 19% decrease in metabolism and patient's taking ketoconazole having a two fold increase in AUC[23, 24]. Thus, there is significant inter-patient variability in erlotinib exposure at a single dose level[21]. Erlotinib clearance has been found to be greater in children than adults, with the risk of skin rash and diarrhea correlating with exposure, possibly explaining the decreased risk of rash seen in young children[24, 25]. There are suggestions that exposure also influences anti-tumor efficacy with an increased percentage of EGFR wild-type patients with NSCLC demonstrating a response to therapy (38% in the highest quartile of exposure vs 5% in the remainder, p=0.058) [25]. Further, the development of rash on

erlotinib has been shown to correlate with prolonged overall survival and event free survival in patients with NSCLC, possibly as a biomarker of EGFR inhibition as EGF is involved in epidermal growth and healing[26].

Combination of sirolimus and erlotinib: A phase I dose escalation study and two phase II trials have reported on the combined administration of sirolimus and erlotinib. In the phase I study, 19 adult patients with malignant gliomas were treated at 3 dose levels, starting at 150 mg daily of erlotinib and 5 mg daily of sirolimus (11 patients) and escalating to 200 mg of erlotinib with 5 mg of sirolimus (3 patients) or 150mg of erlotinib with 10 mg of sirolimus (5 patients). Of note, the dose of sirolimus was not adjusted for trough concentrations in this study. 2 patients in each of the dose escalated arms developed DLT, with 1 of 11 patients in the 150mg/5mg arm developing DLT (1 each of grade III mucositis, rash, hyperphosphatemia, and altered mental status[27]).

In a phase II study, 24 adult patients with recurrent glioblastoma were enrolled in a study of sirolimus and erlotinib at 5mg and 150mg doses respectively ([28]). One heavily pretreated patient developed grade IV thrombocytopenia, 6 patients developed grade III rash, 2 patients each developed grade III mucositis, thrombocytopenia, and fatigue, and 1 patient each developed grade III hypertriglyceridemia, hypokalemia, hypophosphatemia, infection, and neutropenia. The remaining toxicities were grade II or lower and included rash (59%), mucositis (34%), diarrhea (31%), fatigue (28%), and hyperlipidemia (25%, [28]). No anti-tumor responses were observed; however the CSF penetration of erlotinib is $\leq 5\%$, and ascertainment of pathway inhibition was not performed[29]. Thus, there may have been insufficient drug exposure in these patients with intracranial tumors.

In a separate phase II study, 19 pediatric patients (age 3-16 years) with low-grade gliomas were treated with sirolimus 0.8mg/m²/day and erlotinib 65mg/m²/day [17]. This regimen was very well tolerated with 1 patient developing grade III cellulitis while not neutropenic and one patient developing grade III neutropenia. Grade I and II toxicities included rash (58%), aphthous ulcers (47%), and gastrointestinal symptoms (37%, [17]). There was no convincing anti-tumor responses in this group of patients with CNS tumors; however, the dose of erlotinib was below the established pediatric or adult MTD and CNS drug penetration may have been insufficient.

This will be the first study combining erlotinib and sirolimus for extra-cranial solid tumors. There have been no reported grade IV non-hematologic toxicities or grade V toxicities with this combination, and no reported cases of the development of interstitial lung disease. We hypothesize that these agents will show activity in this group of patients given the higher drug delivery extra-cranially, and the pre-clinical data showing synergy between these agents in germ cell tumors.

Drug interactions: Erlotinib and sirolimus are both metabolized hepatically by the CYP3A4 enzyme. There are significant differences in metabolism of both of these drugs with the concomitant use of enzyme inducing and inhibiting agents[18, 23]. The interaction between erlotinib and sirolimus metabolism has not been well studied. In the Phase I study in adult patients with gliomas, there was no significant difference in steady state trough sirolimus levels at doses of 150 and 200 mg of erlotinib (13 ng/mL and 10 ng/mL respectively, p=NS.[27]) However, only 3 patients were treated at the higher dose of erlotinib, limiting the power to detect a difference, and erlotinib levels were not measured, so the influence of sirolimus on erlotinib metabolism can not be determined.

2.2 Overview of the Proposed Study

This will be a phase II study to determine the response rate of children, adolescents, and young adults with relapsed / refractory germ cell tumors to the combination of sirolimus and erlotinib. Patients will be treated with these medications daily on a continuous schedule. The initial dose of sirolimus will be 1mg/m² daily (max 2mg) and adjusted to obtain trough concentrations of 10-15ng/mL. The initial dose of erlotinib will be 85mg/m² daily (max 150mg/day). The initial dose of erlotinib will be higher than used in the pediatric phase II study of sirolimus and erlotinib for low grade gliomas[17]. The dose of 65mg/m²/day used in the prior phase II study was empirically chosen and not a defined MTD. It was very well tolerated with no grade IV or V adverse events and only two grade III adverse events: cellulitis without neutropenia in one patient and neutropenia in one patient. The dose of 85mg/m²/day used in this study was chosen given that there are suggestions that erlotinib concentration correlates with efficacy in NSCLC patients, especially those with wildtype EGFR [25]. Further, erlotinib clearance is faster in pediatric patients and the incidence of the on target rash is lower, both again suggesting the need for a higher dose in this population[20, 24]. This dose was the pediatric MTD in the Children's Oncology Group phase I study of erlotinib in combination with temozolamide[20], and equivalent to the well tolerated adult dose of 150mg/day in the adult phase II study of sirolimus and erlotinib[28]. Note that the maximum dose of 150mg/day is equal to the adult phase II study and FDA approved dose, so this only represents a dose increase for pediatric patients.

There is significant inter-patient variability in the pharmacokinetics of erlotinib and drug exposure and the development of low grade rash have been shown to correlate with outcome in adult studies of this agent. Therefore, patients who do not develop grade II or greater drug-related rash (which is maximal at 2-3 weeks of therapy) or any dose limiting toxicities during cycle 1 will be dose-escalated to 120mg/m²/day (max 200mg) for the second and subsequent cycles (the MTD of erlotinib in combination with radiotherapy and approximately the MTD of single agent erlotinib (125mg/m²/day) in two studies pediatric brain tumor patients.) While dose escalation of erlotinib to 200mg/day when administered concomitantly with 5mg daily sirolimus was not tolerated in a phase I study in adults with the development of grade III DLTs in 2 of 3 patients (mucositis and rash), we hypothesize that this is due to inpatient variation in erlotinib and sirolimus metabolism[27]. Thus, in this study, sirolimus will be adjusted weekly based on trough concentrations, and only patients who do not show evidence of grade II or worse rash or mucositis in the first cycle of therapy will have the dose of erlotinib escalated.

To assess biological correlates of efficacy, we will assess banked tumor specimens (from the enrolled patients) for evidence of mTOR pathway activation by immunohistochemical staining for ERBB1 and ERBB2 receptors as well as phosphor-specific antibodies for (pERBB2, pAKT1, pERK1/2, pmTOR, p70S6, and pRPS6.) Expression of these targets will be correlated with response to therapy.

3.0 Eligibility Criteria

3.1 Inclusion Criteria

- Patients must be greater than 12 months and less than 50 years of age at the time of study enrollment.
- Patients must have had histologic verification of an extracranial germ cell tumor that is not a pure teratoma (mature or immature), pure germinoma, or pure seminoma.
- Patients must have relapsed or refractory disease following at least two prior platinum-containing chemotherapy regimens.
- Patients must have measurable disease, documented according to RECIST criteria, or evaluable disease with a standard tumor marker (AFP and/or HCG) greater than 10 times the upper limit of normal.
- Patients must have a Lansky or Karnofsky performance status score of ≥ 50 . Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
- Patients must have a life expectancy of greater than 8 weeks.
- Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy.
 - Patients must not have received myelosuppressive chemotherapy within 3 weeks of enrollment.
 - Patients must be >7 days since treatment with hematopoietic growth factors (>14 days for Neulasta).
 - Patients must be >7 days since therapy with a biologic agent and beyond the period for which adverse events of the biologic agent are known to occur if longer.
 - Patients must be >3 half-lives since therapy with a monoclonal antibody.
 - Patients must be >42 days since completion of any immunotherapy (i.e. tumor vaccines).
 - Patients must be greater than 2 weeks since most recent palliative XRT and greater than 6 weeks since substantial bone marrow irradiation.
 - Patients must be greater than 8 weeks since prior stem cell transplant or infusion and without evidence of active graft vs. host disease.
- Adequate bone marrow function defined as:
 - Peripheral absolute neutrophil count (ANC) of at least 1,000/ L
 - Platelet count of at least 100,000/L (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to enrollment)
 - Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions).
- Adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m² or
 - Maximum serum creatinine (mg/dL) based on age/gender as follows:

Age (yrs)	Male	Female
1-1.99	0.6	0.6
2-5.99	0.8	0.8
6-9.99	1	1
10-12.99	1.2	1.2
13-15.99	1.5	1.4
≥ 16	1.7	1.4
- Adequate liver function defined as:
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
 - SGPT (ALT) ≤ 2.5 x ULN (for the purpose of this study, the ULN for SGPT is 45 U/L)
 - Serum albumin ≥ 2 g/dL.

- Adequate central nervous system function defined as:
 - Patients with seizure disorder may be enrolled if receiving non-enzyme inducing anticonvulsants and well controlled.
- Serum cholesterol levels must be less than Grade 2 (< 300 mg/dL), and serum triglyceride levels must be less than Grade 2 (< 2.5 x ULN).

3.2 Exclusion Criteria

- Patients with active brain metastases are not eligible as lethal intratumoral hemorrhages have been reported with erlotinib therapy. Patients with brain metastases that have been treated and stable for ≥ 30 days following treatment will be eligible.
- Patients who are pregnant or breast feeding will not be entered into the study as erlotinib is teratogenic. Pregnancy tests must be obtained in females who are post-menarchal. Post-menarchal females with HCG secreting tumors will be excluded as pregnancy can't be excluded. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of the study.
- Concomitant medications
 - Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.
 - Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.
 - Anticonvulsants: Patients who are receiving enzyme-inducing anticonvulsants are not eligible (see Appendix 1 for a list of enzyme- inducing anticonvulsants).
 - Anticoagulants: Use of warfarin is not allowed while on study. Patients already on warfarin should use alternative anticoagulants while on this study. Warfarin must not have been administered within 7 days of enrollment.
 - Smoking: Smoking induces CYP3A4/5 enzymes and decreases exposure to sirolimus and erlotinib. Thus, patients must not smoke for 10 days prior to enrollment and for the duration of therapy.
- Infection: Patients who have an uncontrolled infection are not eligible.
- Drug interactions: Sirolimus and erlotinib are primarily metabolized by the CYP3A4/5 enzymes. Drug exposure is substantially effected by CYP inhibitors (increased exposure) and inducers (decreased exposure). Thus, concomitant administration of strong CYP3A4/5 inhibitors or inducers is prohibited while on therapy. See Appendix 1 for a list of these medications. Patients must not have received these medications for a minimum of 10 days prior to enrollment.
- Patients who have received prior therapy targeting EGFR with small molecule tyrosine kinase inhibitors or monoclonal antibodies are NOT eligible.
- Prior treatment with mTOR or TORC1/2 inhibitors (eg, rapamycin, temsirolimus, everolimus, deferolimus) is NOT allowed.
- Patients who have had major surgery within 3 weeks prior to enrollment are not eligible. Procedures such as placement of a central vascular catheter, or limited tumor biopsy, are not considered major surgery.
- Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.
- Patients who are unable to swallow erlotinib tablets are not eligible.

4.0 Treatment Plan

4.1 Overview

After enrollment and obtaining required baseline studies, therapy will consist of 28 day cycles of once daily sirolimus and erlotinib. These medications will be concurrently administered orally on an empty stomach (1 hour before or 2 hours after a meal.) Both medications will be purchased from commercially available supplies (erlotinib tablets and sirolimus tablets or oral solution).

	Cycle 1				Cycle 2		Subsequent cycles
Day	1	8	15	28	1	28	28
Erlotinib	Daily				Dose escalation if eligible		Daily
Sirolimus	Daily	Dose modification based on trough	Dose modification based on trough		Daily		Daily
Sirolimus level		X	X (weekly until in goal range twice)	X		X	X
Erlotinib level				X		X	
Erlotinib PK		X					

Study related procedures and observations may be adjusted for various logistical, scheduling, or patient preference reasons within a +/- 3 day window during cycle 1 of therapy. During subsequent cycles of therapy there is a +/- 7 day window for study related procedures and observations.

4.1.1 Sirolimus Dose and Escalation

The initial dose of sirolimus will be 1 mg/m²/day (maximum 2mg). The dose of sirolimus will be adjusted at least weekly to obtain a goal trough level of 10-15ng/mL. Trough levels will be measured locally at each treating institution. For patients able to take the tablet form of Sirolimus, up to 10% dose adjustment to the nearest tablet size is acceptable. A commercially available oral solution (1mg/mL) of Sirolimus may be substituted for patients who are unable to take the tablet form of the medication. The dosing instructions for the suspension are the same as for the tablets.

For patients 18 years and older, if the trough level is less than 10ng/mL or greater than 15ng/mL, the new sirolimus dose will be calculated by the following formula:

$$\text{New sirolimus dose (mg)} = \text{Current sirolimus dose (mg)} * \frac{12.5 \frac{\text{ng}}{\text{mL}}}{\text{Sirolimus trough} (\frac{\text{ng}}{\text{mL}})}$$

Note: The maximum new sirolimus dose is three times the current sirolimus dose. Further dose adjustment (increases or decreases) may be made based on subsequent trough levels on the new dose.

If the sirolimus trough is greater than 20ng/mL, one daily dose should be held prior to resuming dosing per the calculated dose above. If the sirolimus trough is greater than 25ng/mL, two daily doses should be held and a repeat sirolimus level obtained confirming a level less than 15ng/mL prior to resuming therapy per the calculated dose above.

Note: If the treating physician believes that lack of compliance with study medication has significantly affected the measured sirolimus trough, the current sirolimus dose may be continued with a repeat trough drawn within 1 week.

Note: Steady state sirolimus levels are not achieved until 3-6 days after dose adjustments. Care should be taken to avoid dose stacking if adjusting the dose more often than weekly.

For patients less than 18 years of age, the sirolimus dose will be adjusted at least weekly until in the goal range of 10-15ng/mL per the local institutional dose adjustment standards.

4.1.2 Erlotinib Dose and Escalation

Erlotinib Dose Level	Erlotinib Dose
0	65 mg/m ² /day, max of 100 mg/day
1	85 mg/m ² /day, max of 150 mg/day
2	120 mg/m ² /day, max of 200 mg/day

The initial dose of erlotinib for all patients will be 85mg/m²/day (maximum 150mg/day, dose level 1) and dose adjustment will be performed as below. Erlotinib will be administered as a tablet and the dose rounded to the nearest 25mg per the following table:

Calculated erlotinib dose	Rounded dose
12.5 mg to 37.5 mg	25 mg
>37.5 mg to 62.5 mg	50 mg
>62.5 mg to 87.5 mg	75 mg
>87.5 mg to 112.5 mg	100 mg
>112.5 mg to 137.5 mg	125 mg
>137.5 mg to 162.5 mg	150 mg

>162.5 mg to 187.5 mg	175 mg
>187.5 mg	200 mg

Inpatient dose escalation of erlotinib is planned for qualifying patients eligible to receive cycle 2 or higher of therapy provided the patient did not experience any of the following toxicities during cycle 1:

1. Grade II or greater rash or mucositis
2. Any grade III toxicity that is possibly, probably, or definitely attributable to study drugs with the exception of grade III electrolyte abnormalities that resolve to \leq grade II within 7 days or grade III nausea or vomiting that are controlled to less than or equal to grade II with anti-emetics within 5 days

For patients who meet these criteria, the dose of erlotinib will be increased to 120mg/m²/day (maximum 200mg, dose level 2) for the second and subsequent cycles.

4.1.3 Erlotinib Dose Reduction

See section 4.5 for details of specific toxicities that would require dose reduction of erlotinib. If a dose reduction is necessary, the dose for patients assigned to receive 85mg/m²/day (dose level 1) will be reduced to 65mg/m²/day (maximum 100mg, dose level 0) and the dosage for patients assigned to 120mg/m²/day (dose level 2) will be 85mg/m²/day (maximum 150mg, dose level 1). If a patient requires dose reduction of erlotinib, the dose will not be escalated in the future even if there are no adverse events at the lower dose level.

4.2 Concomitant Therapy Restrictions

- Concurrent Anticancer Therapy: Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.
- The study chair must be notified prior to the use of growth factors that stimulate white cell number of function (eg GCSF, GM-CSF)
- Investigational Agents: No other investigational agents may be given while the patient is on study.
- Strong inducers or inhibitors of CYP3A4/5 (Appendix 1) change the pharmacokinetics of sirolimus and erlotinib. Administration of these medications must be avoided until treatment discontinuation. Smoking is a strong inducer of CYP3A4/5 and is not permitted while on therapy.
- The combination of mTOR inhibitors and angiotensin converting enzyme (ACE) has resulted in angioedema type reactions (including delayed reactions occurring up to 2 months after initiation of therapy). During treatment, the coadministration of (ACE) inhibitors should be avoided.
- Warfarin should not be used.

4.3 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has met laboratory parameters as defined in the eligibility section. Study drugs should not be interrupted between cycles unless required by Section 4.5.3 or 4.5.4 or Section 6.1.

4.4 Grading of Adverse Events

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

4.5 Definition of Dose-Limiting Toxicity

4.5.1 Definition of a Hematological Dose-Limiting Toxicity

Grade 4 neutropenia or thrombocytopenia.

4.5.2 Definition of a Non-Hematological Dose-Limiting Toxicity

Any Grade 4 or 5 non-hematologic toxicity

Any Grade 3 non-hematologic toxicity **EXCLUDING:**

- Grade 3 nausea or vomiting controlled to less than or equal to grade II with anti-emetics within 5 days
- Grade 3 hepatic transaminase (ALT, AST, GGT) elevation that returns to Grade ≤ 2 or baseline within 7 days of study drug interruption and that does not recur upon retreatment with study drugs
- Grade 3 febrile neutropenia of less than 5 days duration
- Grade 3 infection or fever while not neutropenic (ANC $>1000/\text{mm}^3$)
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia and/or hypomagnesemia that resolve to \leq grade 2 within 7 days (oral supplementation permitted)
- Grade 3 acneiform or maculopapular rash unless deemed intolerable by the patient or guardian.
- Non-fasting grade 3 hypercholesterolemia or hypertriglyceridemia. Such studies should be repeated while fasting within 1 week.

Grade 3 or worse bullous dermatitis if possibly, probably, or definitely drug related is a dose limiting toxicity.

4.5.3 Dose Modification for Hematological Toxicity

For patients who have grade IV neutropenia or thrombocytopenia, the treatment should be withheld. Complete blood counts should be obtained twice weekly until grade III or less. If toxicity resolves to meet on study parameters within 14 days of drug discontinuation, the patient may resume treatment with sirolimus at the previous dose and erlotinib at the next lower dose level. If toxicity does not resolve within 14 days of drug discontinuation, the patient must be

removed from protocol therapy. If dose-limiting hematological toxicity occurs in a patient on the lowest dose level (65mg/m²/day) of erlotinib, the patient must be removed from protocol therapy.

The days of the cycle should continue to be counted when drug is being held. The next cycle will start when criteria are met for that cycle. The day the next cycle is started will be day 1 of that cycle.

4.5.4 Dose Modification for Non-Hematological Toxicity

Dose modification for the first episode of AST and/or ALT elevations:

If a patient experiences grade 3 AST and/or ALT elevation, treatment will be withheld. Liver function tests will be repeated twice weekly until resolution to less than grade 3. If toxicity resolves to less than grade 3 within 7 days and the patient has not previously had grade 3 or worse AST and/or ALT elevation, the treatment may resume at the previous doses of sirolimus and erlotinib. If the patient experiences recurrent grade 3 or worse AST and/or ALT elevation at any time after resuming therapy, this will be considered a dose-limiting toxicity and the doses of study drugs should be modified as below.

Dose modification for other non-hematological toxicity and/or the second or greater episode of AST and/or ALT elevations:

If a patient experiences non-hematological dose-limiting toxicity, the treatment will be withheld.

4.5.4.1 When the toxicity resolves to meet on study parameters within 14 days of drug discontinuation, the patient may resume treatment with sirolimus at the previous dose and erlotinib at the next lower dose level.

4.5.4.2 If toxicity does not resolve to meet on study parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

4.5.4.3 If non-hematological dose-limiting toxicity recurs in a patient on the lowest dose level of erlotinib (65mg/m²/day), the patient must be removed from protocol therapy.

The days of the cycle should continue to be counted when drug is being held. The next cycle will start when criteria are met for that cycle. The day the next cycle is started will be day 1 of that cycle.

4.6 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary, taking care to avoid CYP3A4/5 inducers and inhibitors.

4.6.1 Rash:

An acneiform rash is a common toxicity with EGFR inhibitors, including erlotinib, with 9.4% being grade III or higher [30]. This rash typically begins 1 week after drug initiation and is at maximal severity after 2-3 weeks of therapy. The rash is thought to be due to inhibition of

EGFR in the skin (i.e. an on target effect) leading impaired keratinocyte migration and bacterial overgrowth [30]. The development of rash has been shown to correlate with prolonged survival in some studies of EGFR inhibitors [26]. The rash may improve despite continuation of anti-EGFR therapy [31]. Prompt symptomatic care of rash may improve patient tolerance of erlotinib. Thus, topical clindamycin 2% and hydrocortisone 1% lotion is recommended for any rash thought likely or definitely related to drug until improvement of the rash by at least 1 grade. For patients > 8 years of age, the addition of oral doxycycline 2.2mg/kg/day (maximum 100mg) as a single dose should be strongly considered for at least 1 month and until the rash resolves.

5.0 Observations

All enrollment/eligibility studies must be performed within 1 week prior to study enrollment (unless otherwise specified). If more than 7 calendar days elapse between the date eligibility studies were obtained and the start date of treatment, then the following studies must be repeated prior to treatment: CBC with differential, bilirubin, AST, ALT, serum creatinine, AFP, and HCG. If any of these repeat laboratory studies are outside the parameters required for eligibility (labs may again be repeated within 48-72 hours), then the patient is off protocol therapy. Imaging studies are required within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Study related procedures and observations may be adjusted for various logistical, scheduling, or patient preference reasons within a +/- 3 day window during cycle 1 of therapy. During subsequent cycles of therapy there is a +/- 7 day window for study related procedures and observations.

5.1 Studies to Be Obtained

	Baseline	During cycle 1 (and cycle 2 if erlotinib dose is escalated)	Before the start of subsequent cycles
History	X	Weekly	X
PE	X	Weekly	X
Height, weight, BSA	X	Before the start of cycle 2	X
Performance Status	X	Before the start of cycle 2	X
CBC, electrolytes including Ca, Mg, Phos, AST, ALT, bilirubin, creatinine	X	Weekly	X
Fasting Triglyceride, Cholesterol (Total, HDL, LDL)	X	Before the start of cycle 2	X
Urinalysis	X	Before the start of cycle 2	X
Albumin, total protein	X	Before the start of cycle 2	X
HCG, AFP	X	Before the start of cycle 2	X
CT/MRI of primary and metastatic sites	X	End of Cycle 2	End of even numbered cycles
Serum for Erlotinib level		Day 28 Prior to Starting Next Cycle	X ¹
Serum for Erlotinib pharmacokinetics		Days 8-9 of Cycle 1	
Sirolimus level		Weekly ²	X ²
Patient diary		End of each cycle	X
Tumor tissue	X ³		
Tumor cytogenetics ⁴	X		
Pregnancy test (if appropriate)	X		

1. Erlotinib trough levels will be obtained on day 28 of cycle 1 and day 28 of any cycle that includes an erlotinib dose change (escalation or reduction).
2. Sirolimus trough levels will be obtained at least weekly until two consecutive levels are within the goal range (10-15ng/mL). Levels will then be obtained at the end of each cycle. If subsequent dose adjustment is necessary, levels will be obtained at least weekly after dose adjustment and then weekly until two consecutive levels are within range. Sirolimus levels will be performed at the local institution.

3. Required if available. Dr. Laetsch must approve enrollment if no tumor tissue is available.
4. Tumor cytogenetic reports to be collected if available, including karyotypes and SNP arrays.

5.2 Tumor Sample for Correlative Biology Studies

Submission of a tumor sample from diagnosis or relapse for correlative biology studies is required for study entry if available. Enrollment of patients without archival tumor tissue must be approved by Dr. Laetsch, the PI of the study.

5.2.1 Description of Assay

Archival tumor tissue must be submitted if available. If multiple biopsies have been performed, tissue from the most recent biopsy is preferred. Tumor tissue will be analyzed by immunohistochemistry for AFP, EGFR, AKT, ERK, and mTOR pathway activation and banked for other future studies.

5.2.2 Sampling Schedule

Either a paraffin-embedded tissue block or unstained slides are required for enrollment. Tumor tissue or slides from the most recent resection or biopsy with available tissue are required. If there have been multiple procedures, samples from the initial diagnostic biopsy or resection are also requested if available. A block or slides from any resections or biopsies occurring after the start of protocol therapy are also requested.

5.2.3 Sample Collection and Handling Instructions

A paraffin-embedded tissue block should be submitted. If a tissue block is unavailable, at least 15 unstained standard sections of 3 to 4 μ M thickness must be sent (20 slides are recommended).

5.3 Serum for Erlotinib Levels

1 mL of blood will be drawn into a heparinized tube (green top) between 0 and 60 minutes before the next scheduled daily dose of erlotinib. Blood will be centrifuged within 30 minutes of collection for 10 minutes at 1500g and the plasma removed and frozen at -80° C. Samples will be shipped on dry ice and stored at -80° C until analysis. Samples will be analyzed for levels of erlotinib and its active metabolite OSI-420 by HPLC with tandem MS as previously described[32].

5.4 Serum for Erlotinib Pharmacokinetics

2 mL of blood will be drawn into a heparinized tube (green top) between 0 and 60 minutes before, and 1 hour (+/- 15 minutes), 2 hours (+/- 15 minutes), 4 hours (+/- 30 minutes), 8 hours (+/- 60 minutes), and 24 hours (+/- 2 hours and before the next scheduled erlotinib dose) after the scheduled day 8 dose of erlotinib. Blood will be centrifuged within 20 minutes of collection for 10 minutes at 1500g and the plasma removed and frozen at -80° C. Samples will be shipped

on dry ice and stored at -80° C until analysis. Samples will be analyzed for levels of erlotinib and its active metabolite OSI-420 by HPLC with tandem MS as previously described[32].

5.5 Removed from Protocol Version 1.3

5.6 Central Review

Patients enrolled on study will have their pathologic diagnosis centrally reviewed by the UTSW pathologist Dr. Dinesh Rakheja after study entry.

6.0 Criteria for Removal From Protocol Therapy and Off Study Criteria

6.1 Criteria for Removal From Protocol Therapy

- a) Progressive disease.
- b) Adverse Events requiring removal from protocol therapy.
- c) Patients who receive concurrent anticancer or investigational therapy.
- d) Refusal of further protocol therapy by patient/parent/guardian.
- e) Completion of 25 cycles of therapy.
- f) Physician determines it is in patient's best interest.
- g) Repeat eligibility studies (if required) are outside the parameters required for eligibility.
- h) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
- i) Patients who develop a second malignant neoplasm.

Patients who are removed from protocol therapy (except for g) are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

6.2 Off Study Criteria

- a) Death.
- b) Lost to follow-up.
- c) Entry into another research study with tumor therapeutic intent (e.g., at recurrence) or initiation of another systemic therapy with tumor therapeutic intent
- d) Withdrawal of consent for any further data submission.
- e) The fifth anniversary of study entry.

7.0 Statistical Considerations

7.1 Sample Size and Study Duration

The University of Texas Southwestern Medical Center / Children's Medical Center has averaged 10 newly diagnosed pediatric malignant germ cell tumor patients per year over the last 6 years

(CCDB Tumor Registry). With approximately 20% of patients expected to relapse, this will result in 2 eligible pediatric patients per year at UTSW/CCDB. For this rare tumor, we plan to submit this protocol for approval through the MaGIC (Malignant Germ Cell Tumor International Collaborative) consortium and 4-5 additional large pediatric cancer centers, including the Boston's Children's Hospital, Children's Hospital of Philadelphia, Children's Healthcare of Atlanta, and Texas Children's Hospital (Houston). Between these sites, we expect to accrue 5-10 response evaluable patients per year. A minimum of 11 patients and a maximum of 30 patients are anticipated to account for possible ineligible and inevaluable patients. Thus, we expect this study to complete accrual in 2 - 4 years.

7.2 Study Design

PFR, defined as the proportion of response evaluable patients free of objective disease progression after 4 cycles (16 weeks), will be the primary endpoint. Response evaluable patients who demonstrate a best response of CR or PR and are removed from protocol therapy prior to completion of cycle 4 for any reason other than death or progressive disease will be considered free of objective disease progression. The PFR will be examined using Simon's two-stage design[36]. The null hypothesis, $H_0: p \leq p_0$, that the PFR p is less than or equal to $p_0 = 10\%$ will be tested against the one-sided alternative, $H_1: p \geq p_1$, that the PFR p is greater than or equal to $p_1 = 35\%$. In the first stage, 11 response evaluable patients will be evaluated. If there is less than or equal to 1 patient free of objective disease progression at 16 weeks (4 months) among these 11 patients, the study will be stopped early for futility. Otherwise, 16 additional response evaluable patients will be accrued for a total of 27. The null hypothesis will be rejected if greater than or equal to 6 patients free of objective disease progression are observed in 27 patients. This design yields a type I error rate of 5% and power of 90% when the true response rate is 35%.

7.3 Methods of Analysis

Aim 1.1.1: A responder is defined as a patient free of objective disease progression 4 cycles (16 weeks) of therapy. Response rates will be calculated as the percent of evaluable patients who are responders, and confidence intervals will be constructed accounting for the two-stage design. A secondary analysis will be reported including only patients with a best response of CR or PR as responders.

Aim 1.1.2: Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. The relative frequency of each type of toxicity will be quantified as the number of toxicity-evaluable patients in which the AE was noted and considered by the treating physician to be possibly, probably or definitely related to one of the agents in the regimen divided by the number of toxicity-evaluable patients enrolled on the trial. The proportion of patients who experience dose-limiting toxicity on the first cycle and at any time during protocol therapy will be calculated. The analytic population for these analyses will be all patients considered evaluable for toxicity (see below).

Aim 1.2.1: Expression for activation of the listed pathways will be scored as 0 = negative; 1+ = weak staining; 2+ = moderate staining; and 3+ = strong staining. The proportion of patients falling into each category (relative to the total number of patients evaluated) will be calculated. If 10% or more of patients demonstrate a response, the response status of each patient will be cross-tabulated with expression of the proteins of interest.

Aim 1.2.2: Patients evaluable for response will be included in analysis of progression free survival as a secondary outcome measure. Progression-free interval (PFI) will be calculated as the date of enrollment until the end PFI date, where that date is calculated as the date of disease progression, date of death, date of removal of all tumor by surgery or last patient contact, whichever occurs first. Patients whose end PFI date is disease progression or death will be considered to have experienced an event. Patients whose end PFI date is date of removal of all tumor by surgery will be considered removed from the analytic set at that time by a competing event. Patients whose end PFI date is the date of last patient contact will be considered censored for PFI analysis. The probability of remaining progression-free as a function of days since enrollment will be calculated according to the method of Gray accounting for censoring and the competing events. The data for those patients with immunohistochemically defined mTOR pathway activation (grades 2 and 3+ staining for pS6) will be compared to those without pathway activation (grades 0 and 1+ staining for pS6) by the method of Gray.

Aim 1.2.3: Blood samples drawn between 0 and 60 minutes before, and 1, 2, 4, 8, and 24 (before the next scheduled erlotinib dose) hours after the scheduled day 8 dose of erlotinib will be analyzed for levels of erlotinib and its active metabolite OSI-420 by HPLC with tandem MS as previously described[32]. The pharmacokinetics of erlotinib in subjects on this trial will be analyzed by a non-compartmental method using WINNonlin and compared to prior published data for pediatric subjects not taking sirolimus [20].

7.4 Evaluation Criteria

This study will use the Response Evaluation Criteria in Solid Tumor (RECIST) from the NCI v 1.1. and the response of initially elevated tumor markers (AFP and/or B-HCG). Tumor markers must be initially elevated to >10X the upper limit of normal (ULN) to be used for response determination.

7.5 Definitions

7.5.1 Evaluability for Response

Any patient who is enrolled and receives at least one dose of sirolimus and erlotinib will be considered evaluable for response provided: (1) the patient demonstrates progressive disease or death while on protocol therapy; (2) the patient is observed on protocol therapy for at least one cycle and the tumor is not removed surgically prior to the time complete response or partial response is confirmed; or (3) the patient is observed on protocol therapy for at least four cycles and the tumor is not removed surgically prior to the time stable disease after 4 cycles is confirmed. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule above. All other patients will be considered non-responders. All patients considered to have a response (CR or PR) according to the institutional investigator must have imaging studies reviewed centrally.

7.5.2 Evaluability for Toxicity

Eligible patients who receive at least one dose of sirolimus and erlotinib will be included in analysis of toxicity.

7.5.3 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm. With spiral CT scan or clinical exam using calipers, lesions must be at least 5 mm. All tumor measurements will be recorded in millimeters (or decimal fractions of centimeters). The investigator will identify up to 5 measurable lesions to be followed for response.

Serial measurements of lesions are to be done with CT or MRI. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable only if there is unequivocal evidence of disease progression at that site following irradiation, or if there is histologic proof of viable tumor at that site following irradiation.

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 no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

7.5.4 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, ascites, pleural or pericardial effusions, 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.

7.5.5 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 that 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.

7.5.6 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.

7.6 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. 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.

Conventional CT and MRI: The 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). 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-holding techniques if possible.

7.6.1 Quantification of Disease Burden

The sum of the longest diameter (non-nodal masses) and shortest axis (lymph nodes) for all target lesions will be calculated and reported as the disease measurement.

7.6.2 End-of-Cycle Response

a) Complete Response (CR)

Disappearance of all target lesions if present and normalization of tumor markers if elevated. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

b) Partial Response (PR)

Either at least a 30% decrease in the disease measurement, taking as reference the baseline sum diameters, OR a decline of at least 90% of initially elevated tumor markers (>10X ULN) in the absence of progressive disease by criteria below. If the patient initially has evaluable disease without measurable target lesions, a reduction of >90% but less than normalization of tumor markers qualifies as a partial response.

c) Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest disease measurement recorded since the start of treatment OR an increase in tumor markers by greater than 50% from the smallest measurement since immediately prior to or after the start of treatment and to greater than 10 times the upper limit of normal qualifies as progressive disease. The sum of diameters must also demonstrate an absolute increase of at least

5 mm. In addition, the appearance of one or more new lesions is also considered progressive disease.

d) Stable Disease (SD)

Neither sufficient shrinkage or tumor marker decline to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

7.6.3 Overall Best Response Assessment

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described in Section 7.7.

7.6.4 Evaluation of Non-Target Lesions

(a) Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. 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.

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

(c) 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.

If a patient has evaluable disease without measurable target lesions, an increase in tumor markers by greater than 50% from the smallest measurement since immediately prior to or after the start of treatment and to greater than 10 times the upper limit of normal qualifies as progressive disease.

7.7 Best 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. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable disease; if the first objective status is unknown, only one such determination is required. Patients with an objective

status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

8.0 Safety and Adverse Events

8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

8.1.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild

- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A “Serious adverse event” is by definition an event that meets *any* of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The term “unanticipated problem” is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets *each* of the following criteria:

- Unexpected (in terms of nature, severity or frequency) AND
- Definitely, or probably, related to participation in the research AND
- In the opinion of the PI, suggests that the research places subjects or others at a greater risk of harm (including physical, psychological economic or social harm) than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

8.1.2 Reporting

The UTSW IRB requires reporting of all UPIRSOs according to the guidance below. For participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. All SAEs occurring during the protocol-specified monitoring period should be submitted to the UTSW study team within 2 business days of the center learning of the event.

UPIRSOs occurring on the study require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB by the UTSW study team and to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the UTSW study team and will be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent documentation that is available are also submitted to the DSMC Chair who determines if further action is required. (See

Appendix IV of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).

All local serious adverse events which occur on research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW. Simmons Cancer Center, the DOT Manager or the lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to:

Theodore Laetsch, MD
Principal Investigator
214-648-5475

UTSW SCC Data Safety Monitoring Committee Coordinator (if fax report is not available)
within 2 working days to 214-648-7097.

Written reports to:

Theodore Laetsch, MD
Mail Code A3.01
Department of Pediatrics - Oncology
5323 Harry Hines Blvd.
Dallas, TX 75390
Fax: 214-648-5475
Email: ted.laetsch@utsouthwestern.edu

UTSW SCC Data Safety Monitoring Committee Coordinator
Email: SCCDSMC@utsouthwestern.edu
Fax: 214-648-7018 or deliver to NB 2.418

UTSW Institutional Review Board (IRB)
Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. SAEs

Serious adverse events (SAEs) for studies where SCCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness or as described in the protocol.

2. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

Local Serious Adverse Event UPIRSOs require reporting to the UTSW IRB within 48 hours of PI awareness of the event (life threatening or fatal events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction).

Local UPIRSOs (non-serious events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction) require reporting to the UTSW IRB within 5 business days of PI awareness.

External UPIRSOs including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf>

8.3 Data Safety and Monitoring

The PI at each participating center will monitor the clinical outcome of each patient treated on the trial, and UTSW (Overall PI Theodore Laetsch, MD), as the coordinating center will monitor the overall safety and efficacy of the treatment. The UTSW PI, responsible research nurse, data manager, and study team will meet on an at least bi-weekly schedule to review enrollment and observed toxicities. Documentation of the study team meetings will be maintained along with other protocol related documents and will be reviewed during internal audit.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the study team, which includes but is not limited to accuracy of case report forms, protocol compliance, timeliness and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Individual patient dose escalations will be reviewed and monitored by the treating physician. After data has been submitted for the first two cycles of therapy for the first 5 pediatric patients, the trough based dose adjustment of sirolimus in pediatric patients will be reviewed. Toxicity and efficacy review will be performed after enrollment of the first eleven response evaluable patients (prior to opening the second stage). This review will be documented in an Excel spreadsheet that will be maintained along with other protocol documents.

The UTSW Simmons Comprehensive Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events

and UPIRSOs in real time as they are reported. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

Further detail may be found in the SCC-DSMC Plan.

8.4 Protection of Subjects

Complementing the safety measures noted above, additional procedures will be followed to protect the safety of the research subjects. Potential Subjects will be screened for medical illnesses that would preclude the use of sirolimus or erlotinib. Subjects selected for the study will be evaluated weekly while receiving study drug treatments for the first cycle and then at least every 4 weeks. AEs will be monitored weekly and a study physician will be available at all times to evaluate and treat adverse effects of the medication. Significant AEs will result in exclusion from the study (see Clinical Trial Discontinuation Criteria). Venipuncture or blood draws from central venous catheters (CVCs) will be carried out with good aseptic technique by an experienced phlebotomist, registered nurse, nurse practitioner or physician. Venipuncture sites will be monitored carefully for signs of infection. The PI or treating physician will clinically follow all subjects who are discontinued due to a serious AEs until the AE resolves and becomes completely stable, unless a referral to another physician (i.e. specialist) is clinically indicated or requested by the subject.

8.5 Stopping Rules

The study will pause enrollment after the first 11 response evaluable patients are enrolled until efficacy (cycles 1-4) and toxicity (cycles 1 and 2) data are complete for these patients. A toxicity and efficacy review will occur at this time point prior to opening enrollment for an additional 16 response evaluable patients (see section 8.2). Only dose limiting toxicities occurring during cycles 1 and 2 will be considered for these stopping rules. If greater than 25% of toxicity evaluable patients experience a dose-limiting toxicity as defined in section 4.5 of this protocol, the study will be stopped early for toxicity. If less than or equal to 1 of 11 response evaluable patients demonstrate a response to therapy (as per section 7.2), the study will be stopped early for futility. If neither of these conditions are met, the study will open to accrual of an additional 16 response evaluable patients.

9.0 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Information Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- The personal health information (PHI) to be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- To whom the data may be disclosed and the reasons for this disclosure
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.0 Consent Procedures

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Appendix 2 for a copy of the Subject Informed Consent Form. This consent form will

be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

The PI or study physician will obtain informed consent from all patients and/or their parents or legal guardians before any study procedures occur, explaining all procedures in detail in an individual session. The consent form and explanation will include; detailed information about sirolimus and erlotinib, the rationale for why they are being studied, frequency of dosing, and length of treatment, potential side effects and risks, safeguards and emergency procedures. The collection of all lab specimens will be described in detail. Subjects will be assured that their participation is voluntary and that withdrawal from the study would not jeopardize current or future treatment. All subjects will be informed of potential risks and benefits involved in the study, including side effects of sirolimus and erlotinib.

11.0 Study Management

11.1 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the UT Southwestern Pediatric Oncology Clinical Research Office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.2 Registration Procedures

All subjects must be registered with the UT Southwestern Pediatric Oncology Clinical Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the UT Southwestern Pediatric Oncology Clinical Research Office Study Coordinator. To register a subject, call 214-456-8138 Monday through Friday, 9:00AM 5:00PM, Central Standard Time.

11.3 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.3.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

11.3.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Violations: Study personnel should report violations within two (2) weeks of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems and to their local IRB according to institutional guidelines.

11.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.5 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki.

The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

Appendix 1: CYP3A4/5 Inducers and Inhibitors

The following medications are not permitted for 10 days prior to study enrollment or at any time while receiving protocol therapy due to their effect on sirolimus and erlotinib pharmacokinetics.

Inhibitors:

- Antibiotics: clarithromycin, telithromycin, troleandomycin, roxithromycin
- Protease inhibitors: ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir
- Antifungals: itraconazole, ketoconazole, voriconazole
- Antidepressants: nefazodone

Inducers:

- Glucocorticoids for greater than 2 weeks duration: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamazepine, phenobarbital, oxcarbazepine, primidone, fosphenytoin
- HIV antivirals: efavirenz, nevirapine, tipranavir
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentine
- Miscellaneous: St. John's Wort, modafinil, pioglitazone

Appendix 2: Sample Consent Form

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research: A Phase II Study of Sirolimus and Erlotinib in
Recurrent/Refractory Germ Cell Tumors

Funding Agency/Sponsor: UT Southwestern Medical Center

Study Doctors: [Insert Study Doctors]

You may call these study doctors or research personnel during regular office hours at [insert phone number]. At other times, you may call them at [insert phone number].

Note: If you are a parent or guardian of a minor and have been asked to read and sign this form, the “you” in this document refers to the minor.

Instructions:

Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?

This study is being done to find out how effective the combination of sirolimus and erlotinib is at treating relapsed and refractory germ cell tumors. Sirolimus is a drug that is an FDA approved drug to prevent rejection of kidney transplants in patients over 13 years of age. Erlotinib is an FDA approved drug to treat adults with some types of lung and pancreatic cancers. We are using this combination of drugs because they work together to inhibit a growth pathway that is felt to be important in how germ cell tumors grow. This combination of drugs has been administered to both adults and children who have brain tumors, but have never been given to participants with germ cell tumors. The dosages of sirolimus and erlotinib given in this study may be higher than given in the previous studies.

Research blood tests will be conducted before and while you are taking these drugs. These research tests include measurement of the concentration of the drugs in your blood and measurement of the effect of the drugs on your white blood cells. We will also obtain research blood tests over a 24-hour period to determine whether these drugs have an interaction in how they are metabolized by your body. Further, we will do special stains on tissue from a previous biopsy of your tumor to determine the degree of activation of pathway that these drugs inhibit. Finally, using tissue from a previous biopsy of your tumor, we will look for genetic mutations in this pathway. You will not need to have a new biopsy of your tumor to participate in this study.

Why is this considered research?

This is a research study because this combination of erlotinib and sirolimus has never been given together to patients with germ cell tumors. We will collect data on the safety and effectiveness of these drugs on patients with relapsed germ cell tumors.

The following definitions may help you understand this study:

- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center at Dallas and its affiliated hospitals and at your treating institution.

Why am I being asked to take part in this research study?

You are being asked to take part in this study because you have a malignant germ cell tumor that has come back (relapsed) after or failed to respond to at least two standard therapies.

Do I have to take part in this research study?

No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?

This study also is planned at a number of other medical facilities around the country. There will be a total of between about 11 and 30 people participating in this research study throughout the United States. Of these, about [insert expected accrual] people will take part in this study at [insert local institution].

What is involved in the study?

If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this study.

	Baseline	During Cycle 1	Before the Start of Following Cycles
Medical History & Physical Exam	X	X	X
Blood Test	X	X	X
MRI/CT scan	X		End of even numbered cycles
Patient Diary		X	X
Pregnancy Test	X	X	X
Urine Test	X	X	X
Research Blood Tests	X	X	Only if erlotinib dose changes
Sirolimus Levels (to adjust dose)		X	X
Receive Study Drug	X	X	X

Screening Procedures

To help decide if you qualify to be in this study, the researchers will ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have to fill out certain forms or have the following exams, tests or procedures:

- Physical exam and medical history;
- Vital signs;
- Blood tests;
- Urine tests;
- Pregnancy test;
- Demographic information (age, sex, ethnic origin);
- A CT or MRI of your tumor(s)

Study Medication/Intervention

Each treatment cycle lasts 4 weeks during which time you will be taking both of the study drugs daily:

- Sirolimus tablets or suspension at a starting dose of 1mg/m² daily

- During Cycle 1, the amount of this drug will be measured in your blood each week on Day 1, Day 8, Day 15 and Day 28. Your dose will be increased or decreased if necessary to achieve the desired amount in your blood. During Cycle 2 and any cycles after that, the drug will be measured in your blood at the end of the cycle only on Day 28.
- Erlotinib tablets at a starting dose of 85mg/m² daily (maximum dose 150mg)
 - Your dose of this drug will be increased if you do not have significant side effects after the first 28 days of therapy. Your dose may be decreased if you have significant side effects from this drug.

Procedures and Evaluations during the Research

You will have the following tests and procedures during the study. They are part of standard cancer care.

- Physical exam and medical history;
- Vital signs;
- Blood tests;
- Urine tests;
- Pregnancy test;
- A CT or MRI of your tumor(s)

Clinic visits will occur every week for the first one to two 4-week cycles of the study. After the first 8 weeks, clinic visits will occur monthly. Clinic visits are expected to take 1-2 hours. You will have a CT or MRI of your tumor every 8 weeks while on this study.

You will be asked to keep a diary of the time and dose of the drugs that you take and any symptoms that you experience while participating in this research study.

You will have the following additional research blood tests during the study. These will occur before you take the first dose of drug and at the end of each 28 day cycle of therapy. These blood tests will occur at the same time as blood is being drawn for other standard laboratory tests. These are done to help better understand the effect of these drugs on your body and the way your body metabolizes these drugs.

- Blood tests for drug levels (1/2 teaspoon of blood)

Additionally, on the eighth day after you start taking the study drugs, you will have 5 research blood tests over an 8-hour period and an additional blood test on the ninth day. In total, we will draw about 2.5 teaspoons of blood for these tests. These tests may be drawn from a central line if you have one. If you do not have a central line, an IV will be placed and your blood drawn for the IV for these tests. These tests will help us understand the pharmacokinetics of erlotinib (how your body metabolizes the drug.)

The research blood tests in this study are designed for research, not for medical purposes. They are not useful for finding problems or diseases. Even though the researchers are not looking at your blood tests to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because the research blood tests done in this study are not for medical purposes, the research results will not be sent to you or to your regular doctor.

Procedures for storing of extra or left over samples

At the time of your enrollment on this study, leftover tissue from at least one biopsy of your tumor must be supplied to us by the hospital where your biopsy was obtained. We will use this sample to look for activation of the metabolic pathways inhibited by sirolimus and erlotinib and to test for mutations in the genes that may make some tumors more or less sensitive to these drugs. The principal investigators of this study will keep your remaining samples in a research laboratory at the UT Southwestern Medical Center until they are all gone, become unusable or until they decide to discard the sample. If you withdraw from the study, you may request that any unused samples from your tumor be destroyed.

Your samples will be stored labeled with a unique identification number. A table that links this identification number to your personal information will be kept in a secure facility with limited access and password protection. The computer maintained by UT Southwestern is protected by a firewall which prevents unauthorized access to the information. Any results collected will not be released in a personally identifiable manner, and thus no information will be given to your insurance provider, employer, family, etc. without your permission.

When you provide a sample for purposes of this study your sample becomes the property of The University of Texas Southwestern Medical Center and may be used for future studies or provided to other investigators at other medical research facilities without any identifiers. The principal investigators of this study will decide which researchers at this medical center and at other medical centers may receive samples. Your samples may be used in other research only if the other research has been reviewed and approved by an Institutional Review Board (IRB).

If your sample remains stored beyond your lifetime, your sample will be used as described in this document.

How long can I expect to be in this study?

You may be in the study for up to 24 months if you are responding to therapy. Your doctor may decide to take you off study if any of the following occur:

- The side effects of the combination of sirolimus and erlotinib are too harmful for you
- You need a treatment that is not allowed on this study
- Your tumor does not improve or worsens
- You are not able to follow study-related treatment instructions
- New information becomes available
- The study is not in your best interest
- The study is stopped

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?

Study Drugs

Because of your participation in this study, you are at risk for the following side effects. You should discuss these with the researchers and your regular health care provider.

Sirolimus and erlotinib may cause some, all or none of the side-effects listed below. Because there is limited information about the use of these drugs in combination, other unexpected side-effects, which may be serious, may also occur.

	Sirolimus	Erlotinib
Frequent (≥20% of subjects)	<ul style="list-style-type: none"> • High blood pressure • Nausea/vomiting • Diarrhea and/or constipation • Increased risk of infection that may be serious or life-threatening • Fever <ul style="list-style-type: none"> • Liver problems: Abnormally high levels of enzymes produced by the liver that are found in the blood and indicate that your liver is not functioning properly. The high enzyme levels can cause fatigue and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, 	<ul style="list-style-type: none"> • Rash, itching, dry skin • Diarrhea • Nausea/vomiting • Pancreatitis (elevated enzymes in the pancreas which may cause pain, nausea and vomiting.) • Mouth sores • Conjunctivitis (pink eye) • Irritation to the liver • Shortness of breath or cough <p>Increased risk of infection which may be serious or life-threatening</p>

	<p>this can be serious or life threatening</p> <ul style="list-style-type: none"> Abnormal kidney function tests, which means the kidneys aren't working properly. When the kidneys do not work properly, wastes can build up in your blood, leading to swelling in the arms and legs, tiredness and weakness. This could become severe, requiring hospitalization and dialysis to clean the wastes out of your blood. If the wastes are not removed from your blood, this could cause seizures and be life threatening. Weight gain Muscle pain High cholesterol <p>Acne</p>	
Occasional (5-20% of subjects)	<ul style="list-style-type: none"> Chest pain Insomnia (unable to sleep) Shortness of breath Low blood counts which may increase your risk of infection (low number of white blood cells) or increase your risk for bleeding (low number of platelets) Skin rashes or hives <p>Slow wound healing</p>	<ul style="list-style-type: none"> Weight loss <p>Inflammation of the lung tissue that may cause difficulty breathing and can be</p> <ul style="list-style-type: none"> life-threatening Scarring of the lungs <p>Severe skin rash</p>
Rare (<5% of subjects)	<ul style="list-style-type: none"> Low blood pressure this may cause dizziness Lung problems, including asthma Loss of appetite Serious infections Blood clots Skin problems (serious peeling, redness and itching) Kidney failure Secondary cancers <p>Bone degeneration (break down)</p>	<ul style="list-style-type: none"> Liver problems or failure which can cause fatigue, and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening and may require hospitalization and surgery. Kidney failure which is when both of your kidneys fail and your body holds fluid which can be serious or life threatening. Your blood pressure rises and harmful wastes build up in your body. You may experience

		<p>fatigue, nausea, and loss of appetite. When this happens, you need treatment to replace the work of your failed kidneys such as dialysis.</p> <ul style="list-style-type: none"> • Hearing loss <p>Bleeding in the gastrointestinal tract</p>
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Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Males: Being in this research may damage your sperm, which could cause harm to a child that you may father while on this study. If you take part in this study and are sexually active, you must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

- (1) surgical sterilization (vasectomy), or
- (2) a condom used with a spermicide (a substance that kills sperm).

Females: If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If you can become pregnant, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you participate in this study. If you take part in this study and you are sexually active, you and any person that you have sex with must use medically-acceptable birth control (contraceptives) during the study. Medically-acceptable birth control (contraceptives) includes:

- (1) surgical sterilization (such as hysterectomy or “tubes tied”),
- (2) approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera, Implanon),
- (3) barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm), or
- (4) an intrauterine device (IUD).

If you do become pregnant during this study, you must tell the researchers immediately.

If your parents or guardian asks, we will tell them the results of your pregnancy test or that you are using birth control.

Risks of MRI

There are no known risks from exposure to magnetic fields. You may experience nervousness and/or anxiety due to the loud banging made by the machine while it is taking pictures and from confinement in a tight space (claustrophobia). If you become anxious, you can stop the procedure at any time

You may also experience some discomfort and fatigue from lying still during imaging.

If you have any metal clips or plates in your body, you should tell the investigator.

MRI may not be appropriate if you are pregnant or are trying to become pregnant. MRI may not be appropriate if you have permanent eyeliner or eyebrows or any pieces of metal in your body, such as the following:

- heart pacemaker, heart valve replacement, or aortic clips
- metal fragments in your eyes, skin, or elsewhere in your body
- brain clips or pieces of metal used in aneurysm surgery or intercranial bypass
- venous umbrella
- pieces of metal in the body resulting from work as a sheet-metal worker or welder
- clips placed in an internal organ
- prosthetic devices, such as middle ear, eye, joint, or penile implants
- joint replacement.
- hearing aid that cannot be removed
- neurostimulator
- insulin pump
- intrauterine device (IUD)
- shunts or stents
- metal mesh or coil implants
- metal plate, pin, screws, or wires, or any other metal implants

Risks of Radiation – Diagnostic Test

The radiation dose that you will get from diagnostic tests is medically indicated for your condition and it is the same that you would get if you were not involved in this research study.

Risks of Blood Drawing

Risks associated with drawing blood from your arm include minimal discomfort and/or bruising. Risks associated with drawing blood from a central line are rare but a central line infection is possible, although unlikely.

You will have approximately 2 tablespoons of blood collected because you are in this research study.

Other Risks

There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?

Potential risks and discomforts must be minimized to the greatest extent possible. All personnel conducting this study will be appropriately trained. You will be closely monitored with physical exams, medical histories, and blood tests during the time you are participating in this study. If the researchers determine that the study drugs are causing you too much harm, they may instruct you to stop taking the drugs for a period of time, reduce your dose, or stop your participation in this study. If any of these side effects of therapy require treatment that the researchers or your oncologist are unable to provide, you will be referred to an appropriate physician. If your cancer grows despite the study drugs, your participation in the study will be stopped to limit the risk of the drugs causing you harm.

What will my responsibilities be during the study?

While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Store study tablets in a secure place at home away from anyone who is unable to read and understand labels, especially children.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Carry information about sirolimus and erlotinib in your purse or wallet.
- Report to the researchers any injury or illnesses while you are on study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?

If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?

If you agree to take part in this study, there may be direct benefits to you. The potential benefit of the treatment with the combination of sirolimus and erlotinib is that it may cause your cancer to stop growing or to shrink for a period of time. It may lessen the symptoms, such as pain, that are caused by the cancer. Because there is no information about the effect this combination on germ cell tumors in humans, we do not know if you will benefit from taking part in this study. The researchers cannot guarantee that you will benefit from participation in this research.

We hope the information learned from this study will benefit others with germ cell tumors in the future. Information gained from this research could lead to better treatment of relapsed disease.

What options are available if I decide not to take part in this research study?

You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:

- Receive standard chemotherapy or radiation
- Participate in a research study of another therapy
- Choose to not receive treatment at all

Please talk to the researchers or your personal doctor about these options.

Will I be paid if I take part in this research study?

No. You will not be paid to take part in this research study. There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Will my insurance provider or I be charged for the costs of any part of this research study?

Yes. The costs of sirolimus and erlotinib tablets and sirolimus drug levels will be billed to you or your insurance provider.

What will happen if I am harmed as a result of taking part in this study?

It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or Children's Medical Center or your local treating institution.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?

Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor may be a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?

Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.

- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?

Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The UT Southwestern study committee;
- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people;
- The Institutional Review Board at your treating institution; and
- The UT Southwestern Institutional Review Board.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Are there procedures I should follow after stopping participation in this research?

Yes. If you, the researchers, or the sponsor stops your participation in the research, you may be asked to do the following:

- Let the researchers know immediately that you wish to withdraw from the research.
- Return to the research center for tests that may be needed for your safety.
- Discuss your future medical care, if any, with the researchers and/or your personal doctor.

Whom do I call if I have questions or problems?

For questions about the study, contact [insert local PI] at [insert phone number] during regular business hours and at [insert phone number] after hours and on weekends and holidays.

For questions about your rights as a research participant, contact the Institutional Review Board (IRB) Office at [insert phone number].

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

SIGNATURES:

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers and authorized persons including your insurance company.

Name of Participant (Printed)

Signature of Participant

Date

Time

AM / PM

Legally Authorized Representative's Name (Printed)

Legally Authorized Representative's Signature

Date

Time

AM / PM

Name of Person Obtaining Consent (Printed)

Signature of Person Obtaining Consent

Date

Time

AM / PM

ASSENT OF A MINOR:

I have discussed this research study with my parent or legal guardian and the researchers, and I agree to participate.

_____	_____	_____ AM / PM
Participant's Signature (age 10 through 17)	Date	Time

Interpreter Statement (if applicable):

I have interpreted this consent form into a language understandable to the participant and the participant has agreed to participate as indicated by their signature on the associated short form.

Name of Interpreter (Printed)		
_____	_____	_____ AM / PM
Signature of Interpreter	Date	Time

Appendix 3: References

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Appendix 4: Patient Diary

Patient: _____ Institution : _____

Complete each day with the time and dose of sirolimus and erlotinib given. Make note of other drugs and supplements taken. Please note if a dose was missed or if there was vomiting after any dose of medication and whether the medication was given again. Add the dates to the calendar below and return the completed diary to your institution after each treatment cycle. Your institution will send this form to the UTSW study team after each treatment cycle.

Notes: If a dose is missed and you remember within 8 hours of when the dose was supposed to be taken, take the dose immediately. Resume your usual schedule the following day.

If you throw up a dose of medication within 30 minutes of taking it, the dose should be given again. You may take a medication for nausea first and allow 30 minutes to 1 hour for this to work prior to redosing the medication(s).

Example:

WEEK 1	Date	Time	Sirolimus Dose (mg)	Sirolimus Dose (mL)	Erlotinib Dose (mg)	Comments
Day 1	9/1/13	7:00 AM	2 mg		150 mg	Felt nauseated an hour after drugs, but did not vomit. Had mildly itchy rash on arms.

Diary:

Cycle #: _____ Erlotinib Dose: _____ Start Date: ____/____/____ End Date: ____/____/____						
WEEK 1	Date	Time	Sirolimus Dose (mg)	Sirolimus Dose (mL)	Erlotinib Dose (mg)	Comments
Day 1						
Day 2						
Day 3						
Day 4						
Day 5						
Day 6						
Day 7						

WEEK 2	Date	Time	Sirolimus Dose (mg)	Sirolimus Dose (mL)	Erlotinib Dose (mg)	Comments
Day 8						
Day 9						
Day 10						
Day 11						
Day 12						
Day 13						
Day 14						

WEEK 3	Date	Time	Sirolimus Dose (mg)	Sirolimus Dose (mL)	Erlotinib Dose (mg)	Comments
Day 15						
Day 16						
Day 17						
Day 18						
Day 19						
Day 20						
Day 21						

WEEK 4	Date	Time	Sirolimus Dose (mg)	Sirolimus Dose (mL)	Erlotinib Dose (mg)	Comments
Day 22						
Day 23						
Day 24						
Day 25						
Day 26						
Day 27						
Day 28						