A Randomized Three Arm Phase II Study of (1) Everolimus, (2)Estrogen Deprivation Therapy (EDT) with Leuprolide + Letrozole and (3) Everolimus + EDT in Patients with Unresectable Fibrolamellar Hepatocellular Carcinoma (FLL-HCC).

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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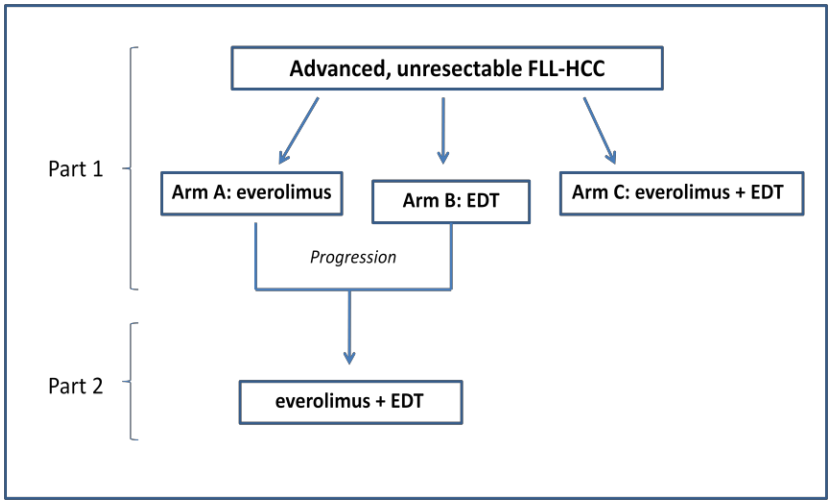
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Fibrolamellar hepatocellular carcinoma (FLL-HCC) is a rare primary liver malignancy affecting adolescents and young adults without an underlying history of chronic liver disease. While surgical resection offers the possibility of long-term disease control and prolonged survival, there are no effective systemic therapies for patients with unresectable disease, for whom median survival is 12 months or less. The paucity of patients with this disease has also made it extremely challenging to conduct clinical trials dedicated to FLL-HCC . As such, patients with FLL-HCC that cannot be resected represent an orphan population in need of novel, effective therapies.

The pathogenesis of FLL-HCC is largely unknown, though several potential drivers have been identified. FLL-HCC tumor overexpression of aromatase, in association with a hyperestrogenic clinical phenotype, as well as the PI3K/Akt/mTOR pathway have been reported by both immunohistochemistry and gene expression profiling. Based on the known interactions between estrogen and the PI3K/Akt/mTOR pathway in breast cancer, we hypothesize that suppression of central and peripheral estrogen production and mTOR inhibition will have antineoplastic activity in FLL-HCC. These hypotheses are the basis of the proposed clinical trial entitled: "A Randomized Three Arm Phase II Study of (1) Everolimus, (2)Estrogen Deprivation Therapy (EDT) with Leuprolide + Letrozole and (3) Everolimus + EDT in Patients with Unresectable Fibrolamellar Hepatocellular Carcinoma (FLL-HCC)."

This will be a 2-part protocol in which patients are initially randomized, in Part 1, to one of the three treatment arms shown in Figure 1 below. Upon disease progression, patients receiving everolimus alone, or EDT alone, may be treated with combined everolimus and EDT during Part 2 of the study as part of an exploratory analysis. The primary study endpoint is progression-free survival at 6 months (PFS6).

Figure 1: Protocol schema



2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.2 Primary efficacy endpoint (Arm A: everolimus vs. Arm B: estrogen deprivation therapy (EDT) with leuprolide + letrozole vs. Arm C: everolimus + EDT) of the study:

- Progression-free survival at 6 months (PFS6)

2.3 Secondary objectives:

- To evaluate median progression-free survival
- To evaluate median overall survival
- To evaluate objective response rate by RECIST 1.1 guidelines
- To evaluate rate of conversion to resectable status
- To evaluate safety/toxicity profiles.
- To evaluate correlative tissue and serum biomarkers.

2.4 Exploratory analysis for Part 2 (combined everolimus + EDT) of the study:

- PFS, measured as the time from the start of the combination therapy till progression, clinical progression or death, whichever occurs first, will be evaluated in patients who switch from either Arm A or B to combination therapy.

3.1 BACKGROUND AND RATIONALE

3.2 Fibrolamellar hepatocellular carcinoma (FLL-HCC): Background

FLL-HCC is an extremely rare malignancy. According to SEER data, only 68 cases of FLL-HCC were diagnosed between 1986 and 1999, comprising only 0.85% of all primary liver cancers [1]. International series have reported an FLL-HCC frequency ranging from 0.6% in Thailand [2] up to 5.8% in Mexico [3]. The incidence of FLL-HCC may be even higher given that a number of cases may be misdiagnosed as typical hepatocellular carcinoma (HCC) [1,4]. FLL-HCC is usually diagnosed in the 3rd to 4th decade of life and occurs equally in both sexes unlike typical HCC which has a male predominance [1,5-7]. In addition, FLL-HCC appears to occur mainly in Caucasian patients and is extremely rare in those of Asian descent [8,9]. Signs and symptoms are non-specific and include hepatomegaly and/or an abdominal mass with pain, weight loss, digestive symptoms and malaise [10-12]. FLL-HCC typically arises from normal liver parenchyma and is associated with normal α-fetoprotein (AFP) levels [13]. Serum markers that have been found to be elevated in patients with FLL-HCC include neurotensin, vitamin B12 binding capacity and plasma des-γ carboxy-prothrombin, and may represent potential tumor markers for this disease [5,14-17]. Radiographically, FLL-HCC appears as a well-defined lobulated, heterogeneous mass with central scarring, and is differentiated from typical HCC by the presence of normal surrounding liver tissue,

its tendency for unifocal disease, and the absence of vascular invasion [18]. On pathological examination, FLL-HCC is characterized by layers of fibrous stroma, and demonstrates an expanding growth pattern in contrast to the invasive pattern of typical HCC [12,16,19]. Locoregional lymph node metastases are present in up to 70% of patients at presentation and are associated with a high risk of relapse and poorer prognosis [5,11,20]. Distant metastases are less common.

3.3 Prognosis of patients with FLL-HCC

Historically, FLL-HCC has been perceived as the more indolent counterpart of typical HCC, but patients with metastatic, unresectable disease face a grim prognosis. While patients with resected disease can do extremely well, with 5-year and median survival outcomes of up to 76% and 112 months, respectively, those with unresectable disease fare much worse, surviving only 12-14 months [11-13]. The presence of lymph node metastases has also been significantly associated with shorter recurrence-free and overall survival times [4,11]. Growing evidence suggests that patients with FLL-HCC appear to have a prognosis similar to that of patients with typical HCC without cirrhosis [4,21,22], suggesting that absence of cirrhosis and not an intrinsically less aggressive disease biology, may drive the natural history of FLL-HCC [4]. A pediatric series found no significant differences in 5-year event-free and overall survival between 36 typical HCC and 10 FLL-HCC patients of all stages who were randomized to two different cisplatin-based chemotherapy regimens following surgery or biopsy [21]. Approximately 80% of all patients had advanced and/or unresectable disease, and survival was uniformly poor regardless of histologic subtype (13.6 months for FLL-HCC vs. 3.3 months for typical HCC, $p = 0.16$). The estimated progression-free survival at 6 months l in FLL-HCC and typical HCC patients were50% and 30%, respectively [21]. Of note, these values were derived from a treatment-naïve patient population and it is anticipated that the PFS6 for a heavily pretreated FLL-HCC would be lower at approximately 40%.

3.4 Therapy for FLL-HCC

Surgical resection is the mainstay of definitive therapy for patients with FLL-HCC, providing the opportunity for cure as well as prolonged survival. Unfortunately, the majority of patients relapse within 6-33 months [11,20,23]; in one series, the 5-year recurrence-free survival rate was only 18% [14]. The current management paradigm in this disease is an aggressive surgical approach with repeated resections of recurrent disease. When hepatectomy is contraindicated, liver transplantation may be an option although clinical experience with this approach is limited [5,24]. Among non-surgical candidates, doxorubicin-based hepatic artery chemoembolization has shown activity [25,26]. Once disease becomes so widespread that surgery and locoregional ablative therapies are no longer possible, systemic therapies are the only alternative.

Clinical experience with cytotoxic chemotherapy has not demonstrated substantial activity in FLL-HCC. Attempts to decrease the risk of post-operative relapses with adjuvant cisplatin, 5-fluorouracil or doxorubicin containing chemotherapy have been ineffective [5,23]. Chemotherapy in advanced FLL-HCC has also not shown any evidence of clinically meaningful activity [21]. The only notable exception is the combination of 5-fluorouracil and IFNα 2b which produced a 75% objective response rate, including one complete response, and a median survival of 23.1 months among 9 FLL-HCC patients in a phase II study that also included 34 patients with typical HCC [27]. These studies,

although limited by small sample sizes and highly heterogeneous study populations, underscore the need for better systemic therapies for patients with advanced, unresectable FLL-HCC.

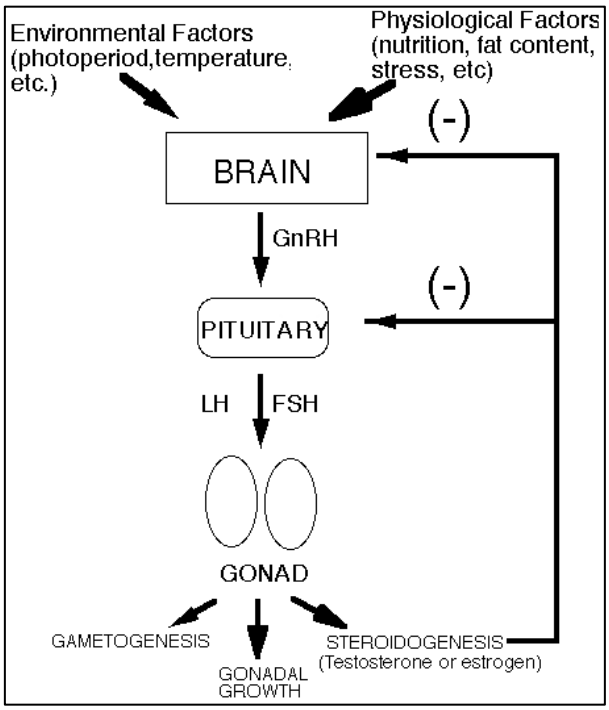
3.5 Estrogen and aromatase as therapeutic targets in FLL-HCC

Several case reports have described young males with FLL-HCC who present with elevated serum estrogen levels and gynecomastia that subsequently regresses following tumor resection [28-30]. Among women, FLL-HCC has been associated with pregnancy and oral contraceptive use [31-34]. Furthermore, immunohistochemical staining and gene expression profiling of FLL-HCC specimens has confirmed the presence of tumor aromatase overexpression [28-30,35]. These observations suggest that estrogen and aromatase may play a pathogenic role in FLL-HCC and represent potential therapeutic targets.

3.6 Estrogen deprivation therapy (EDT): Aromatase inhibitors and GnRH agonists

The hypothalamic-pituitary-gonadal axis governs reproductive physiology. Hypothalamic GnRH (also known as luteinizing releasing hormone or LHRH) secretion leads to pituitary release of gonadotropins which stimulate gonadal steroidogenesis. In both women and men, aromatase converts androstenedione and testosterone into estrone and estradiol, respectively [36]. Under normal circumstances, gonadal steroid hormones inhibit the hypothalamic and pituitary axis through a negative feedback loop (Figure 2) [37]. Aromatase inhibitors can cause a paradoxical increase gonadal steroidogenesis since the hypothalamus responds to the perceived lack of estrogen by secreting more GnRH. The differential effects of aromatase inhibition in men, premenopausal and postmenopausal women are described below. GnRH agonists recreate the normal negative feedback loop, ultimately leading to the suppression of gonadal steroidogenesis. These observations provide the basis for the co-administration of aromatase inhibitors and GnRH agonists.

Figure 2: The hypothalamic-pituitary-gonadal axis [37].



3.5.1 Premenopausal women

In premenopausal women, GnRH agonists cause an initial surge in pituitary gonadotropin release which is followed by GnRH receptor downregulation, inhibition of gonadotropin secretion and a sharp decline in ovarian estrogen production to postmenopausal levels [38,39]. The gonadotropin surge or "flare" occurs within the first week following administration of the GnRH agonist and chemical castration achieved by the fourth week [39-41]. Studies evaluating GnRH agonists in premenopausal women have demonstrated a more profound suppression in circulating estradiol levels when they are combined with an aromatase inhibitor rather than with tamoxifen [42,43]. Unlike aromatase inhibitors, tamoxifen is a selective estrogen receptor modulator but does not affect estrogen production itself.

In women of reproductive age, pituitary release of follicle stimulating hormone (FSH) stimulates ovarian follicle recruitment and aromatization of androgens into estrogens [44]. In the presence of an aromatase inhibitor, estrogen production decreases, GnRH secretion increases and androgens accumulate. The potential adverse effects of using aromatase inhibitors as monotherapy in premenopausal women are illustrated by the clinical phenotype of females with congenital aromatase deficiency. These patients exhibit signs of virilization, pseudo-hermaphroditism, polycystic ovaries and hypergonadotropic hypogonadism [45]. These side effects may be mitigated by the co-administration of a GnRH agonist.

The efficacy and safety of EDT with a GnRH agonist such as goserelin or leuprolide, and an aromatase inhibitor in premenopausal women with hormone-receptor positive breast cancer has been demonstrated in multiple studies in both the adjuvant and metastatic settings [41-43,46-48]. The combination is generally well tolerated with the major side effects being hot flashes, fatigue and

arthralgias [41,46]. However, loss of bone mineral density is an important concern that warrants careful monitoring and consideration of prophylactic therapies (see section 3.5.6).

3.5.2 Postmenopausal women

In postmenopausal women, ovarian androgen production is diminished compared to the premenopausal ovary [49]. Ovarian and adrenal androgens are the major sources of substrate for peripheral aromatase which is found in adipose tissue, muscle, the liver and brain [36,50,51]. Aromatase inhibitor monotherapy is effective for the treatment of hormone receptor positive breast cancer in this population since there is no competing surge in ovarian androgen production.

Combined GnRH agonist and aromatase inhibitor therapy has been evaluated for its impact on bone mineral density in postmenopausal women [52]. Based on the hypothesis that increased FSH levels may contribute to increased postmenopausal bone resorption, patients were treated with letrozole and placebo or monthly leuprolide acetate for 3.5 months while serum markers of bone turnover were measured. Contrary to the study's hypothesis, patients treated with leuprolide acetate demonstrated significant increases in bone resorption markers although changes in markers of bone formation were more variable. Other adverse effects were not reported [52]. Combination therapy has not been evaluated in breast cancer patients, although GnRH agonists alone have been shown to be active and tolerable in disease that is refractory to prior hormonal therapies [53,54].

3.5.3 Men

In men, approximately 20% of endogenous estrogens are produced by the testes while the remaining 80% are the result of peripheral aromatization of testicular and adrenal androgens [55]. Although aromatase inhibitors can reduce estradiol to near undetectable levels comparable to those seen in postmenopausal women, the response is not complete in all patients [55]. Reasons for this observation are several-fold. First, as a function of having higher baseline androgen levels, men have higher estrogen levels compared to postmenopausal women [56]. In addition, aromatase inhibitors are ineffective against testicular estrogen production [57]. Furthermore, increased gonadotropins as a result of exposure to an aromatase inhibitor [58] may provoke an increase in androgen substrate which competes for aromatase, leading to secondary resistance [55]. These considerations provide the basis for adding a GnRH agonist to an aromatase inhibitor for the management of men with breast cancer. Experience with this combined regimen is mainly anecdotal thus far, and results have been mixed with respect to efficacy, possibly due to the uncertain effects of GnRH agonists on testicular estrogen production [59,60]. A phase II study of goserelin and anastrozole in men with advanced hormone receptor positive breast cancer has been completed and results are pending (NCT00217659, www.clinicaltrials.gov).

The side effects of prolonged androgen deprivation due to GnRH agonists are analogous to those associated with chemically induced menopause in premenopausal women. The most extensive experience with GnRH agonists in men comes from the prostate cancer literature. Common side effects include decreased libido, gynecomastia and hot flushes [61]. There is also a significantly higher risk of developing skeletal fractures, osteoporosis, and features of metabolic syndrome including diabetes and cardiovascular events [62,63]. Healthy lifestyle modifications and close

monitoring of glucose and lipid homeostasis as well as bone health (see section 3.5.6) are recommended as an integral part of the management plan [63].

3.5.4 Children and adolescents

The transition from childhood to adolescence is heralded by increases in luteinizing hormone (LH) and FSH, ultimately leading to bone and sexual maturation among other biologic and physiologic changes. Central precocious puberty is a pediatric condition caused by the premature maturation of the hypothalamic-pituitary-gonadal axis. GnRH agonists are the treatment of choice as they have been shown to be effective in slowing sexual maturation and improving the height attained in adulthood [64]. Long-term follow up data suggest that these agents do not significantly impair the recovery of normal reproductive function once stopped [65-67].

Aromatase inhibitors appear to hold promise in the management of precocious puberty caused by excess adrenal and gonadal sex hormone secretion (eg. familial male-limited precocious puberty) as well as other growth abnormalities, though their use is still investigational [68]. Reported side effects include increased vertebral abnormalities in boys with idiopathic short stature but not familial male-limited precocious puberty. No decreases in bone density have been reported in this population. Erythrocytosis has been reported in boys treated with aromatase inhibitors [69-71], though thrombotic events have not been reported. Mouse models suggest that estrogen deprivation as a result of aromatase knockout may adversely affect brain development [72,73]. In a recent study conducted in postmenopausal breast cancer patients, 1 year of tamoxifen was associated with a significant worsening in cognitive function, moreso in patients > 65 years old than in those $\leq$ 65 years old. In contrast, 1 year of exemestane was not associated with any cognitive decline [74]. Cognitive impairment due to aromatase inhibition has not been reported in the pediatric population.

The combination of an early generation GnRH agonist and aromatase inhibitor is reportedly active and tolerable in boys with familial male-limited precocious puberty [68,75]. In one series, the use of the aromatase inhibitor testolactone was associated with gastrointestinal upset which was self-limited and did not warrant a dose reduction [75].

Another setting in which EDT is used is in premenopausal females with endometriosis. GnRH agonists are accepted as safe and effective for relieving pelvic pain in premenopausal women with endometriosis [76]. In adolescents $\geq$ 16 years old with laparoscopically confirmed endometriosis, GnRH agonists can be used as a second-line strategy if NSAIDS and oral contraceptives fail to relieve symptoms. A GnRH agonist is typically given for 6 months, after which “add-back” therapy with a low dose progestin +/- estrogen is initiated to reduce side effects such as bone loss, while maintaining treatment efficacy [77,78]. Norethindrone acetate, a progestin-only oral contraceptive, is a preferred drug for add-back therapy and is effective at preserving bone mineral density in adolescents [79,80]. The role of aromatase inhibitors for endometriosis is less well established, but appears to be a promising approach for both pre and postmenopausal women when used alone or in combination with a GnRH agonist or norethindrone acetate [81-84]. The long-term effects and safety of EDT using these approaches, particularly in adolescents, are unknown.

3.5.5 Using EDT without knowledge of tumor estrogen/progesterone receptor status

In the setting of endometriosis, anti-estrogen therapies are used without knowledge of the hormone receptor status. The use of EDT is also justifiable in patients with tumors that do not express hormone receptors. In breast cancer, approximately 5-10% of patients with hormone receptor negative tumors still respond to anti-estrogen therapies. The reasons for this phenomenon are unclear, but may be due to technical limitations and/or molecular interactions. False negatives may occur as a result of inadequate sampling [85], poor tissue preparation/preservation, or receptor saturation due to prior tamoxifen therapy if binding assays are used [86,87]. In addition, there is evidence to suggest that the effects of anti-estrogens are not only mediated by hormone receptors. For example, tamoxifen has been shown to suppress insulin growth factor pathway signaling in breast cancer, reducing the risk of recurrence in high-risk patients [88,89]. For these reasons, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend a trial of endocrine therapy in patients with primarily soft tissue and/or bone breast cancer metastases, even if their disease appears to be hormone-receptor negative [90].

3.5.6 Effects of EDT on fertility

The effects of GnRH agonists on fertility and reproductive function are reversible in both men and women [91,92]. In girls with central precocious puberty, cessation of the GnRH agonist after a short course of treatment was associated with a normalization of gonadotropin and estradiol levels, as well as vaginal maturation index [93]. Menses reportedly return after a mean of 16 months [67]. Likewise, gonadal function appears to return to normal in boys treated with GnRH agonists; no differences have been noted compared to controls between the ages of 15-18 years [67]. Infertility has not been reported.

Letrozole and anastrozole are reversible aromatase inhibitors [94]. The long-term effects of aromatase inhibitors on reproductive function in prepubescent patients are unknown.

3.5.7 Maintenance of bone health during estrogen-deprivation therapy

Loss of bone mineral density with the consequent risks of developing skeletal fractures and osteoporosis is an important consideration in males and females undergoing endocrine therapy. Several studies have shown that oral or intravenous bisphosphonate therapy can prevent bone loss and potentially increase bone mineral density in women undergoing chemotherapy or endocrine therapy for breast cancer without bone metastases [95-97]. Similar findings have also been reported in men undergoing endocrine therapy for nonmetastatic prostate cancer [98-100]. Furthermore, there is growing evidence to suggest that intravenous zoledronic acid reduces the development of skeletal-related events (including fractures and additional sites of bone metastases) and may improve survival outcomes for patients with and without bone metastases in a variety of tumor settings [23,101-103].

According to the most recent ASCO clinical practice guidelines, postmenopausal women receiving aromatase inhibitors and premenopausal women with therapy-induced premature menopause are considered to be at high risk of developing osteoporosis [104]. Baseline bone mineral density screening is recommended, and a risk-guided algorithm for management has been proposed. The

guidelines do not recommend prophylactic intravenous bisphosphonates to maintain bone mineral density in breast cancer patients without bone metastases [104].

The National Comprehensive Cancer Network (NCCN) follows the National Osteoporosis Foundation (www.nof.org) guidelines for the screening and management of men receiving endocrine therapy for prostate cancer based on their risk of fracture [105]. Fracture risk is calculated using the World Health Organization Fracture Risk Assessment Tool (FRAX) calculator available at http://www.sheffield.ac.uk/FRAX/index.jsp.

3.5.7.1 Bone health in children and adolescents

In children treated with a GnRH agonist, bone maturation and normal skeletal development are the primary concerns. Consensus guidelines recommend monitoring of bone age during therapy. Routine monitoring of bone mineral density is not recommended as peak bone mass does not appear to be affected by the use of a GnRH agonist [67]. As previously mentioned, aromatase inhibitors have been associated with vertebral abnormalities in boys with idiopathic short stature but decreases in bone density have not been reported in the pediatric population [68]. Calcium and vitamin D supplementation as well as weight-bearing exercise are recommended to counteract the effects of EDT on bone health in children and adolescents [67,106].

3.6 The PI3K/Akt/mTOR pathway as a therapeutic target in FLL-HCC

Upregulation of PI3K/Akt/mTOR signaling may have a pathogenic role in FLL-HCC. A small series examining the immunohistochemical staining pattern for markers of mTOR activity in primary liver tumors included 13 FLL-HCC specimens. Approximately 25% of FLL-HCC tumors exhibited overexpression of total and phospho-mTOR [107]. Nuclear staining for S6 kinase, a downstream effector of mTOR, was also present [107]. The clinical relevance of these findings are unclear, and it is unknown whether immunohistochemical staining for mTOR activity will actually translate into sensitivity to therapeutic mTOR inhibition [107].

Another small series examined the gene expression profile of two primary and two metastatic FLL-HCC tumors [35]. The PI3K signaling cascade was found to be consistently upregulated in both primary and metastatic lesions [35].

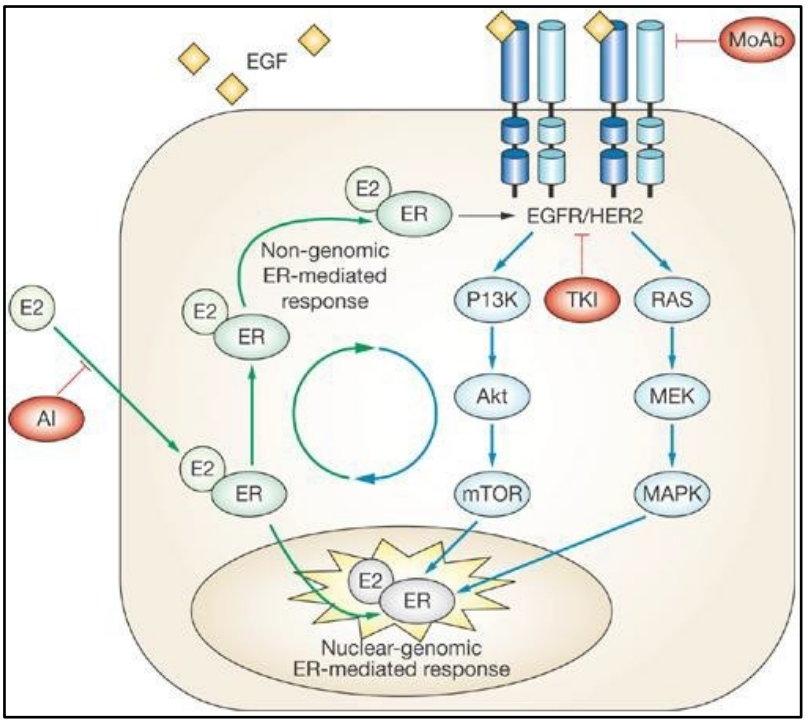
Inhibition of mTOR signaling is undergoing evaluation for the management of typical HCC. Interest in mTOR targeting was generated by observations that patients treated with sirolimus-containing immunosuppression following liver transplantation for HCC had considerably better survival outcomes compared to those treated with non-mTOR inhibitor-based regimens [108-112]. A phase II study of sirolimus in a mixed population of 21 patients with advanced HCC and 9 patients with cholangiocarcinoma reported one partial response, 5 with stable disease and a median survival of 6.5 months in the HCC group [113]. Currently, everolimus is being evaluated in advanced, typical HCC in several phase I/II clinical trials in the first-line setting (www.clinicaltrials.gov, NCT00828594), following failure of locoregional therapies (www.clinicaltrials.gov, NCT00390195) and after failure of prior systemic therapies (www.clinicaltrials.gov, NCT00516165). The EVOLVE-1 study is a large, multi-center, phase III placebo-controlled trial testing everolimus in advanced HCC that has

progressed on sorafenib (www.clinicaltrials.gov, NCT01035229). everolimus is also being tested in combination with anti-angiogenic therapies including bevacizumab (www.clinicaltrials.gov, NCT00775073) and sorafenib (www.clinicaltrials.gov, NCT01005199).

3.7 Interaction between the estrogen receptor and PI3K/Akt/mTOR pathway

The estrogen receptor and PI3K/Akt/mTOR pathways cross-communicate, and the former is capable of activating the latter (Figure 3) [114]. In breast cancer, selective downregulation of the PI3K/Akt/mTOR pathway is one of several mechanisms by which anti-estrogens exert their anti-mitogenic effects [115]. However, this pathway may eventually upregulate in response to prolonged estrogen-deprivation, allowing the cells to "escape" suppression and acquire resistance to anti-estrogens [116,117]. *In vitro* studies have demonstrated that breast cancer cells refractory to tamoxifen and aromatase inhibitors can be resensitized to these agents with the addition of the mTOR inhibitors everolimus and rapamycin [118,119]. This phenomenon has been reproduced in the clinical setting. In a phase I trial conducted in metastatic breast cancer patients with stable or progressive disease on letrozole, the addition of everolimus produced one complete response lasting 22 months, and 50% of patients had stable disease (lasting $\geq$ 6 months in a third of patients) [120]. Similarly, combination therapy with temsirolimus and letrozole has shown activity in heavily pretreated metastatic breast cancer patients [121]. Furthermore, a phase II study in treatment-naïve patients with operable breast cancer reported a significantly higher clinical response rate with neoadjuvant letrozole and everolimus compared to letrozole alone [122]. These findings support the use of dual aromatase and mTOR inhibition given either in sequence, or in combination upfront.

Figure 3: Cross-communication between the estrogen receptor and PI3K/Akt/mTOR pathway (AI = aromatase inhibitor, ER = estrogen receptor, E2 = estrogen) [114].



3.8 Dosing and safety of dual aromatase and mTOR inhibition in the clinical setting

Dual aromatase and mTOR inhibition was evaluated in a phase I trial of letrozole at the standard dose of 2.5 mg PO QD, with two different dose levels of everolimus at 5 mg PO QD or 10 mg PO QD [120]. Safety and pharmacokinetic studies revealed the combination to be safe, with no major interactions at either dose level of everolimus. Only one dose-limiting toxicity, grade 3 thrombocytopenia, occurred in the everolimus 10 mg PO QD cohort. A randomized phase II neoadjuvant breast cancer trial of letrozole 2.5 mg PO QD plus everolimus 10mg PO QD or placebo also reported an acceptable toxicity profile for the combination, with grade 3/4 toxicities occurring in $\leq$5% of patients receiving everolimus [122]. This included three patients who developed pneumonitis which resolved within two weeks of everolimus discontinuation.

EVOLVE-1 is a phase III trial of everolimus at 7.5 mg PO QD versus best supportive care in advanced typical HCC following failure/intolerance of sorafenib (www.clinicaltrials.gov, NCT01035229). The reduced dose of 7.5 mg PO QD was chosen given concerns about pneumonitis at the 10 mg PO QD dose, particularly in a patient population with abnormal hepatic drug clearance. Although most patients with FLL-HCC have normal hepatic parenchyma, hepatic reserve may be somewhat impaired by the presence of tumor. Thus, for the purpose of this trial, everolimus 7.5 mg PO QD will be administered.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a multi-institutional randomized three arms phase II clinical trial, consisting of two parts. In Part 1 of this study, patients with advanced (recurrent or metastatic), unresectable FLL-HCC will be randomized to one of three arms: Arm A (everolimus 7.5 mg PO QD); Arm B (EDT with letrozole 2.5 mg PO QD + leuprolide 7.5 mg IM monthly); or Arm C (everolimus + EDT). Upon disease progression, patients in Arm A or Arm B may proceed to Part 2 of the study in which they will receive combination therapy with both everolimus and EDT. Please refer to Figure 1 (page 4) for a schematic of the study design.

4.3 Intervention

Patients randomized to Arm A will receive everolimus 7.5 mg PO QD.

Patients randomized to Arm B (EDT) will receive leuprolide and letrozole to provide central and peripheral suppression of estrogen production, respectively.

- Leuprolide will be administered as a monthly depot injection of 7.5 mg IM.
- Bloodwork will be drawn 1 week after the first injection of leuprolide to measure serum estradiol levels in females and serum testosterone levels in males.
- Letrozole 2.5 mg PO QD will be started 1 week after leuprolide is given if serum testosterone and estradiol levels are found to be within the castration range. Otherwise, initiation of letrozole will be delayed until week 4, coinciding with the second dose of leuprolide.

Patients randomized to Arm C (EDT + everolimus) will receive everolimus, leuprolide and letrozole at the same doses and schedule as outlined for Arms A and B.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Everolimus

- Definition: everolimus is a rapamycin analog that inhibits the mammalian target of rapamycin (mTOR) serine-threonine kinase. everolimus binds intracellular FK506 binding protein-12 (FKBP-12) which subsequently complexes with mTOR, inhibiting its downstream effectors such as S6 kinase and 4E-BP1 [123-126]. everolimus is also a macrolide immunosuppressant that blocks mitogenic signaling in T cells [127]. everolimus has anti-proliferative and anti-angiogenic effects through its suppression of vascular endothelial growth factor (VEGF) and hypoxia inducible factor 1-α (HIF1-α) [124]. It is rapidly absorbed, reaching peak serum concentrations within 1.5-2 hours and has a half-life of about 30 hours [125,127]. everolimus undergoes extensive hepatic metabolism by CYP3A4 and is excreted fecally and, to a lesser extent, in the urine [128].

- For patients age 12-18, everolimus dose is reported as 5 mg/m2 [129,130]. Patients with a body surface area (BSA) $< 1.5\ m^2$ will receive everolimus 5 mg PO QD. Patients with a BSA $\geq 1.5\ m^2$ will receive everolimus 7.5 mg PO QD.

- Supply: Everolimus is manufactured by Novartis Pharmaceuticals. As an anti-neoplastic agent, everolimus is supplied as 2.5 mg or 5 mg oral tablets. Everolimus is supplied by Novartis for this study.

- Storage: Everolimus should be stored at an ambient temperature of 25 ^{o}C (77 ^{o}F) with brief temperature excursions ranging from 15 ^{o}C-30 ^{o}C (59 ^{o}F-86 ^{o}F) permitted. The drug should be stored in its original packaging, and exposure to light and moisture should be avoided [131].

- Administration: Everolimus is administered orally, once daily, with or without meals.

- Interactions:

  - Potent CYP3A4 inducers can decrease serum everolimus levels. If concomitant administration of a potent CYP3A4 inducer is required, this may warrant an increase in the dose of everolimus. The use of concomitant moderate CYP3A4 inducers requires close monitoring of everolimus but no dose modifications [132]. Please refer to Appendix 3 for a complete list of potent and moderate inducers of CYP3A4.

  - Potent CYP3A4 and/or P-glycoprotein inhibitors can increase serum everolimus levels and should not be given concurrently. Moderate inhibitors can produce mild-moderate increases in serum levels and may warrant a dose reduction in everolimus [132]. Please refer to Appendix 4 for a complete list of potent and moderate inhibitors of CYP3A4.

- Patients on everolimus should not be immunized with any live vaccines within 7 days of starting study therapy. They should also avoid close contact with individuals who have received attenuated live vaccines. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

5.3 Letrozole

- Definition: Letrozole is a type II (competitive) non-steroidal aromatase inhibitor.

- Mechanism of action: Letrozole binds the heme group of aromatase, blocking the conversion of androstenedione and testosterone to estrone and estradiol, respectively [94].

- Pharmacokinetics/dynamics: Letrozole has a half life of 2-4 days [133,134]. It strongly inhibits CYP2A6 and weakly inhibits CYP2C19. It is a minor substrate of CYP3A4 and CYP2A6, and is converted by hepatic metabolism into an inactive carbinol metabolite [135].

- The dose of letrozole in this study of 2.5mg po daily is the one used in for pediatric patients >25kg [68,136]. The weight range for a 12 years old being 30kg-60kg (5%-95%), it is expected that all pediatric patients would fall into that range.

- Supply: Letrozole is manufactured by Novartis Pharmaceuticals as a 2.5 mg oral tablet. Letrozole is supplied by Novartis for this study.

- Storage: Letrozole should be stored at an ambient temperature of 25 °C (77 °F) with brief temperature excursions ranging from 15 °C-30 °C (59 °F-86 °F) permitted. The drug should be stored in its original packaging, and exposure to light and moisture should be avoided [137].

- Administration: Letrozole is administered once daily at the standard dose of 2.5 mg/day.

5.4 Leuprolide

- Definition: Leuprolide is a synthetic nonapeptide GnRH analog with the chemical name 5-oxo-L-prolyl-L-histidylL-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl*N*-ethyl-L-prolinamide acetate. Leuprolide entrapped in polylactic acid polymer microspheres forms a biodegradable depot injection that is hydrolyzed by the body, allowing for sustained release over time [138-140].

- Mechanism of action: Leuprolide binds to GnRH receptors on the pituitary gland, causing an initial surge in gonadotropin and gonadal steroid hormone release. This is followed by GnRH receptor downregulation, and subsequent inhibition of pituitary-gonadal function in both men and women that is reversible. The gonadotropin surge or "flare" occurs within the first week following administration of the GnRH agonist and chemical castration achieved by the fourth week [38-41,141].

- Pharmacokinetics/dynamics: Leuprolide is available as a monthly depot injection of 7.5 mg monthly. This formulations is the one recommended for premenopausal ovarian suppression and in prostate cancer [142, 143]. After injection of 3-monthly leuprolide, peak plasma concentration is reached at approximately 3 hours after which steady state concentrations are achieved by Day 7, persisting until the next injection [141,144]. Excretion is primarily renal. No pharmacokinetic studies of leuprolide have been conducted in patients with hepatic or renal dysfunction.

- Supply: Leuprolide is manufactured by Takeda Pharmaceuticals for Abbott Pharmaceuticals. Leuprolide is supplied by Abbott for this study.

- Storage: Leuprolide should be stored at an ambient temperature of 25 °C (77 °F). Brief temperature excursions ranging from 15 °C-30 °C (59 °F-86 °F) are permitted. The drug should be stored in its original packaging, and exposure to light and moisture should be avoided [145].

- Administration: Leuprolide depot 7.5 mg will be administered intramuscularly monthly (+/- 7 days). This is the same dose used in premenopausal breast cancer patients. This is also the recommended dose for pediatric patients >25 kg [146]. Given that the weight range for a 12 years old being 30kg-60kg (5%-95%), it is expected that all pediatric patients would fall into that range.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Patients ≥ 12 years old.

- Pathologically confirmed diagnosis of advanced and/or unresectable FLL-HCC. This will be performed by the participating centers on submitted specimens. If the submitted material is insufficient for analysis, a repeat biopsy is recommended.

- ECOG performance status 0-2 (see Appendix 1); Lansky performance score of ≥ 60% for patients 12-16 years old (see Appendix 2)

- Adequate hematologic, renal and hepatic function defined as:

  - Hematologic: ANC ≥ 1.0 x 10^9/L, platelets ≥ 50 x 10^9/L.
  - Renal: creatinine ≤ 2 x upper limit of normal, or creatinine Clearance of ≥60 cc/mL/1.73 m^2 for patients > 16 years old. For patients ≤ 16 years of age, creatinine Clearance of ≥70 cc/mL/1.73 m^2 or serum creatinine based on the following chart:

Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 or serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

  - Hepatic: total bilirubin ≤ 2 mg/dL, alanine and aminotransferase levels ≤ 5 x upper limit of normal for age.

- Fasting blood glucose <1.5 x upper limit of normal . If fasting glucose ≥ 1.5 x upper limit of normal, adequate glycemic control (fasting glucose < 1.5 x upper limit of normal) for three weeks is recommended before starting protocol therapy.

- At least 1 target lesion measurable by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines**.**

  - Target lesion(s) must not lie within a previously resected, irradiated, ablated, or chemoembolized area. If a lesion does lie in such an area, there must be evidence of a ≥ 20% increase in diameter and/or the appearance of a new lesion on subsequent imaging in order for such a lesion to be considered a target lesion.

- Prior systemic therapy is allowed. Prior surgery, locoregional ablative or embolic therapies are also permitted provided that the criteria for measurable disease as outlined above are met.

- Concurrent antiviral therapy for hepatitis B is permitted.

- Women of childbearing potential must be practicing an effective method of birth control that may include intrauterine devices (both hormonal and non-hormonal are acceptable), double-barrier method, male partner sterilization or abstinence, before enrollment, and throughout the study and for 6 months after receiving the last dose of study drug. Men must agree to use a double barrier method of birth control and to not donate sperm during the study and for 6 months after receiving the last dose of study drugs. Sperm banking is acceptable for interested male patients enrolled on study prior to initiating treatment. Prescription oral contraceptives, contraceptive injections, and contraceptive patch are not approved methods of contraception and are not allowed in this study.

- Negative pregnancy test (serum hCG) result (applicable to women of child bearing potential) within 7 days before Cycle 1 Day 1 of study treatment.

6.3 Subject Exclusion Criteria

- Concurrent anticancer or radiation therapy. Patients must have completed all anticancer therapy > 4 weeks before the start of study therapy. The date of last palliative radiation must be > 2 weeks from the start of study therapy. Palliative radiation is permitted on protocol with MSK PI discretion on treatment modifications.

- Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) .

- Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.

- Concurrent oral contraceptive use or hormonal replacement therapy.

- Use of an aromatase inhibitor, GnRH agonist and/or tamoxifen within the past 30 days. Patients previously on fulvestrant or a q3 month GnRH agonist must have discontinued these medications for at least 3 months.

- Concurrent use of potent CYP3A4 and/or P-glycoprotein inhibitors or potent CYP3A4 inducers (please see Appendices 3 and 4). Where possible, otherwise eligible patients should be switched to alternative agents; otherwise, they will be excluded from the study.

  Potent CYP3A4 inducers decrease serum everolimus levels and should not be given concomitantly. Dose modifications of everolimus are not indicated in the presence of moderate CYP3A4 inducers [108]. Please refer to Appendix 3 for a complete list of potent and moderate inducers of CYP3A4.

  Potent CYP3A4 and/or P-glycoprotein inhibitors can increase serum levels of everolimus and should not be co-administered. Moderate inhibitors may mildly-moderately increase serum everolimus levels, though there is no definitive evidence supporting a dose reduction [108]. Please refer to Appendix 4 for a complete list of potent and moderate inhibitors of CYP3A4.

- Any investigational drug received within one month of study enrollment.
- Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases
- Other active malignancies that may influence outcome.
- Any severe, uncontrolled medical conditions that, in the opinion of the investigator, may be exacerbated by study therapy or affect with study participation including infection, diabetes,cardiopulmonary disease, active bleeding diathesis, infections including HIV, and gastrointestinal disease that could impair study drug absorption.
- Any psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant or nursing women.
- Patients with a known hypersensitivity to everolimus, letrozole, leuprolide and/or related compounds or their excipients.
- Patients who received any form of transplant and who are on any form of immunosuppressive therapy. However transplanted patients who are off immunosuppressive therapy for at least 4 weeks are allowed on the study, provided that any of their immunosuppressive-related toxicities have recovered to at least a grade 1.
- Known HIV positive with a CD4 count < 500 cells/mm3.
- Immunization with a live vaccine < 1 week of initiating study therapy or during therapy.
- BSA <1 m^2

7.0 RECRUITMENT PLAN

Subjects referred to any of the four participating centers: Memorial Sloan Kettering Cancer Center (MSKCC), the University of California San Francisco (UCSF), Johns Hopkins University (JHU) and the Dana- Farber Cancer Institute/Brigham and Women's Cancer Center and the Massachusetts General Hospital Cancer Center (DF/BWCC/MGHCC) who are deemed eligible by pre-screening will be invited to participate in the trial. Potential subjects will be identified from clinic consultation lists. A total of 84 patients are needed to meet the study endpoints. An accrual rate of 2 patients/month across all 4 study sites is anticipated, with the projected completion of enrollment within 42 months.

The trial will be announced on the NCI clinicaltrials.gov, the MSKCC, and the Fibrolamellar Cancer Foundation websites.

8.1 PRETREATMENT EVALUATION

8.2 Within 4 weeks of study treatment

- CT chest/abdomen/pelvis with contrast and triphasic liver.
    - Patients who are allergic to CT scan contrast despite premedication, or in whom a CT scan is clinically contraindicated, may undergo an MRI of the abdomen/pelvis and non-contrast CT chest instead.
- Baseline bone age radiographs in patients 12-15 years old interpreted using the Greulich-Pyle atlas [147].
- Baseline bone mineral density test for all patients ≥16 years old
- Routine screening for hepatitis B (including surface antigen and core antibody).

8.3 Within 2 weeks of study treatment including first day of treatment

- Complete medical history and physical examination, including ECOG performance status (Lansky performance status for patients 12-16 years old), height/weight/body surface area.
- Complete blood count (CBC) and differential, comprehensive metabolic panel (Na, K, Cl, HCO3, BUN, creatinine, AST, ALT, alkaline phosphatase, glucose), calcium, phosphorus, LDH, and ammonia
- Liver function tests (total bilirubin, albumin, INR/PTT)
- Fasting glucose and lipid profile including triglycerides and total cholesterol.
- Urinalysis.
- Electrocardiogram
- AFP
- Baseline plasma neurotensin, unsaturated vitamin B12 binding capacity, and des-γ-carboxyprothombin
- Baseline serum estrone, estradiol, testosterone and follicle stimulating hormone (FSH) in all patients.
- Quantitative PCR for hepatitis C and hepatitis B as applicable. If hepatitis B surface antigen and/or hepatitis B core antibody are positive, results must be reported **before** Cycle 1 Day 1 of study treatment. Hepatitis C and hepatitis B quantitative PCR, as applicable, will be repeated every 3 months.
- Patients known to be infected with hepatitis C will be monitored as clinically indicated.
- Patients will be asked to give a blood sample and have their biopsy specimen available for future research studies.

- Negative pregnancy test (serum hCG) result in women of child bearing potential within 7 days before Cycle 1 Day 1 of study treatment. Negative pregnancy test (serum hCG) on Cycle 1 Day 1 is adequate.

9.0 TREATMENT/INTERVENTION PLAN

The study drug leuprolide will be distributed to the all four participating institutions by a third party, Biologics, Inc. The study drugs letrozole and everolimus will be distributed to the all four participating institutions by Novartis Pharmaceuticals.

9.1 Part 1, Arm A: everolimus

- Everolimus will be administered by the respective institutions' pharmacies at the following doses:
  - Patients with a BSA < 1.5 m^2 will receive everolimus 5 mg PO QD.
  - Patients with a BSA $\geq$ 1.5 m^2 will receive everolimus 7.5 mg PO QD.
- Patients will be instructed to take everolimus at home, at the same time each day, consistently with food or without food, and swallowed whole with a glass of water.
- Patients unable to swallow whole tablets will be instructed NOT to crush or chew them. Instead, they should be completely dissolved in 30 cc of water by gently stirring immediately before swallowing. After swallowing, the glass should be rinsed with another 30 cc of water then swallowed again to make sure the entire dose was administered [131].
- If a dose is missed, they will be instructed to take it as soon as they remember up to 12 hours past the scheduled dose time. If it is almost time to take the next dose, they will be instructed to skip the missed dose and just take the scheduled dose. They will be instructed NOT to take 2 doses at the same time [131].
- If vomiting occurs after taking Everolimus, the subject should not take a replacement dose on that day. The subject should resume taking Everolimus at the next scheduled dose on the following day. If vomiting persists, the subject should be instructed to notify the investigator. If a subject vomits what appears to be an intact tablet(s), the subject should not take a replacement dose on that day because it is not possible to determine how much drug has actually been absorbed.
- Patients will be provided with a pill diary to record the date and time of day that everolimus is taken.
- Everolimus may be held for a maximum of 4 weeks for toxicity (see Section 9.5).
- Treatment will continue until disease progression, global clinical deterioration, unacceptable toxicity and/or consent withdrawal.

9.2 Part 1, Arm B: EDT (letrozole and leuprolide)

Day 1 of Cycle 1: Baseline serum estrone, estradiol, testosterone and follicle-stimulating hormone (FSH) level in all patients (if not already done). If estradiol is within postmenopausal range for women (≤ 30 pg/mL) and testosterone is within the castration range for men (≤ 50 ng/dL), patient does not have to have hormones retested at week 2 and may begin letrozole 2.5 mg po QD Week 2 of Cycle 1.

- Day 1 of Cycle 1: Leuprolide 7.5 mg IM will be administered by a nurse in clinic.
- Week 2 of Cycle 1 (+/- 7 days): Women with estradiol not within postmenopausal range (≤ 30 pg/mL) or men with testosterone not within the castration range (≤ 50 ng/dL), measure serum estradiol and testosterone; if estradiol is within postmenopausal range (≤ 30 pg/mL) and testosterone is within the castration range (≤ 50 ng/dL), begin letrozole 2.5 mg po QD. Otherwise,retest hormones on C2W1. Consult MSKCC PI if hormones are still not within range. to further discuss the letrozole start date.
- Letrozole will be dispensed by the respective instutions' pharmacies and will be taken at home. Patients will be instructed to take letrozole at the same time each day, consistently with food or without food, and swallowed whole with a glass of water.
    - If a dose is missed, they will be instructed to take it as soon as they remember up until 12 hours past the schedule dose time. If it is almost time to take the next dose, they will be instructed to skip the missed dose and just take the scheduled dose. They will be instructed NOT to take 2 doses at the same time [137].
    - If vomiting occurs after taking letrozole, the subject should not take a replacement dose on that day. The subject should resume taking letrozole at the next scheduled dose on the following day. If vomiting persists, the subject should be instructed to notify the investigator. If a subject vomits what appears to be an intact tablet(s), the subject should not take a replacement dose on that day because it is not possible to determine how much drug has actually been absorbed.
    - Patients will be provided with a pill diary to record the date and time of day that letrozole was taken.
- Continue leuprolide 7.5 mg IM every 4 weeks (+/- 7 days).
- One cycle of EDT corresponds to 4 weeks of treatment.
- Letrozole and leuprolide should be administered concurrently at all times.
    - Patients who are able to tolerate only leuprolide, but not letrozole, will undergo serum estradiol and testosterone testing at the start of every cycle. If serum estradiol remains within the post-menopausal range (females) or within the castration range (males), therapy on leuprolide will continue.

- Patients who are able to tolerate letrozole, but not leuprolide, will be removed from the study. In very special circumstances (ie. postmenopausal female patient) study chair may allow continuation of letrozole alone pending the approval of the local IRB.

- Treatment will continue until disease progression, global clinical deterioration, unacceptable toxicity and/or consent withdrawal**.**

- EDT may be held for a maximum of 4 weeks to recover from toxicity (see Sections 9.6 & 9.7).

9.3 Part 1, Arm C: combined everolimus + EDT

- Day 1 of Cycle 1: Baseline serum estrone, estradiol, testosterone and follicle-stimulating hormone (FSH) level in all patients (if not already done). If estradiol is within postmenopausal range for women ($\leq$30 pg/mL) and testosterone is within the castration range for men ($\leq$50 ng/dL), patient does not have to have hormones retested at week 2 and maybe begin letrozole 2.5 mg po QD Week 2 of Cycle 1.

- Patients will begin leuprolide 7.5 mg IM and everolimus based on BSA:

  - Patients with a BSA < 1.5 m^2 will receive everolimus 5 mg PO QD.

  - Patients with a BSA $\geq$1.5 m^2 will receive everolimus 7.5 mg PO QD.

- Week 2 of Cycle 1 (+/- 7 days): Women with estradiol not within postmenopausal range ($\leq$30 pg/mL) or men with testosterone not within the castration range ($\leq$50 ng/dL), measure serum estradiol and testosterone; if estradiol is within postmenopausal range for women or testosterone is within the castration range for men, begin letrozole 2.5 mg po QD. Otherwise, retest hormones on C2W1. Consult MSKCC PI if hormones are still not within range. to further discuss the letrozole start date.

- Leuprolide 7.5 mg IM will be given every 4 weeks (+/- 7 days).

- Everolimus and letrozole will be administered continuously using the same dose, schedule and administration instructions as outlined in sections 9.1 and 9.2. Patients will be given a pill diary to record the date and time that everolimus and letrozole were taken.

- One cycle of combined everolimus + EDT corresponds to 4 weeks of treatment.

- Everolimus, letrozole and leuprolide should be administered concurrently at all times. However. patients who are only able to tolerate everolimus and leuprolide, but not letrozole, can continue on therapy but need to undergo testing of serum estradiol and testosterone every 4 weeks. If serum estradiol remains within the post-menopausal range (in females) or castration range (males), therapy with leuprolide and everolimus continue.

  - Patients who are able to tolerate everolimus and letrozole, but not leuprolide, will be removed

from the study. In very special circumstances (ie. postmenopausal female patient), study chair may allow continuation of everolimus with letrozole pending the approval of the local IRB.

- If everolimus or both EDT drugs must be completely discontinued, patient will be declared off trial. However, if a patient is able to tolerate either component of combined therapy (ie. Everolimus or EDT) but not both, and is experiencing clinical benefit, the study chair may allow continuation of everolimus or EDT pending the approval of the local IRB.
- Treatment will continue until disease progression, global clinical deterioration, unacceptable toxicity and/or consent withdrawal**.**
- Therapy may be held for a maximum of 4 weeks to recover from toxicity (see Sections 9.5 through 9.8)

9.4 Part 2: Combined therapy with everolimus and EDT after progression on either everolimus or EDT alone

- Patients who develop disease progression on either Arm A or B during Part 1 of the study will proceed to combined therapy.
    - At the start of Part 2 the last CT scan on Part I will be used as the baseline scan for RECIST 1.1 criteria.

Patients who were on everolimus (Arm A) during Part 1 will begin EDT with leuprolide 7.5 mg IM .

- Patients who required a dose reduction on Arm A during Part 1 will continue at the reduced dose level for Part 2.
- Day 1 of Cycle 1: Baseline serum estrone, estradiol, testosterone and follicle-stimulating hormone (FSH) level in all patients. If estradiol is within postmenopausal range for women ($\leq$30 pg/mL) and testosterone is within the castration range for men ($\leq$50 ng/dL), the patient does not have to have hormones retested at week 2 and maybe begin letrozole 2.5 mg po QD Week 2 of Cycle 1.
    - Week 2 of Cycle 1 (+/- 7 days): Women with estradiol not within postmenopausal range ($\leq$30 pg/mL) or men with testosterone not within the castration range measure serum estradiol and testosterone; if estradiol is within postmenopausal range (women) or testosterone is within the castration range (men), begin letrozole 2.5 mg po QD. Otherwise, retest hormones on C2W1. Consult MSKCC PI if hormones are still not within range. to further discuss the letrozole start date.
    - Leuprolide 7.5 mg IM will be administered every 4 weeks (+/- 7 days).

Patients who were on EDT (Arm B) during Part 1 will begin everolimus on Day 1 of Part 2 of the study at the following doses:

- Patients with a BSA ≤ 1.5 m^2 will receive everolimus 5 mg PO QD.
- Patients with a BSA > 1.5 m^2 will receive everolimus 7.5 mg PO QD.

- Patients should continue with their every 12 weeks hormone testing schedule from Arm B.

All Patients on Part II

- One cycle of treatment with combined therapy corresponds to 4 weeks.
- Everolimus, letrozole and leuprolide should be administered concurrently at all times. However, patients who are only able to tolerate leuprolide, but not letrozole, can continue on therapy but need to undergo testing of serum estradiol every 4 weeks. If serum estradiol remains within the post-menopausal range (in females), therapy with leuprolide and everolimus will continue.
  - Patients who are only able to tolerate leuprolide, but not letrozole, will undergo testing for both serum estradiol and testosterone every 4 weeks. If the levels of these hormones remain within the castration range, therapy on leuprolide will continue.
  - Patients who are able to tolerate everolimus and letrozole, but not leuprolide, will be removed from the study. In very special circumstances, (ie. postmenopausal female patient), study chair may allow continuation of everolimus with letrozole pending the approval of the local IRB.
- If everolimus or both EDT drugs must be completely discontinued, patient will be declared off treatment.
- Treatment will continue until disease progression, global clinical deterioration, unacceptable toxicity and/or consent withdrawal.
- Therapy may be held for a maximum of 4 weeks to recover from toxicity (see Sections 9.5 through 9.8)

9.5 Everolimus dose modifications and treatment interruptions/discontinuation guidelines

- Renal impairment: No dose adjustment necessary.
- Hepatic impairment: If total bilirubin > 2mg/dL, hold treatment for up to 4 weeks, then reduce dose to 5 mg PO daily once total bilirubin ≤ 2mg/dL.
- Everolimus will be held for any grade 3 hematologic adverse event, grade 2 pulmonary toxicity or any other grade 3 non-hematologic toxicity, excluding hyperlipidemia.

- If recovery (grade 2 or less for hematologic or non-hematologic toxicities) occurs within 4 weeks, everolimus will be resumed at a reduced dose of 5 mg PO daily.

- Any grade ≥ 3 pulmonary toxicity occurring at any time during therapy warrants discontinuation of everolimus and the study chair should be contacted.
- If BSA changes by > 10% at any time during the study, the dose of everolimus must be adjusted if needed and accordingly.
- Everolimus will not be reduced below 5mg.
- Everolimus may be held for a maximum of 4 weeks from the scheduled date of cycle commencement to permit recovery from toxicities/adverse events as outlined above. If more than 4 weeks are required for recovery, the study chair may allow continuation of everolimus pending the approval of the local IRB.

9.6 Letrozole dose modifications and treatment interruptions guidelines

If total bilirubin > 3mg/dL, hold treatment for up to 4 weeks, once total bilirubin ≤ 3mg/dL, continue letrozole at 2.5 mg PO QD every other day.

Otherwise no modifications required.

9.7 Leuprolide dose modifications guidelines

No dose modifications required.

9.8 Management of combined everolimus and EDT

Patients on everolimus + EDT who develop any grade 2 hematologic adverse event, grade 2 pulmonary toxicity or any other grade 3 non-hematologic toxicity (excluding hyperlipidemia) attributable to everolimus that warrants interruption of everolimus, may continue EDT. If everolimus or both EDT drugs must be completely discontinued, patient will be declared off treatment. In very special circumstances, study chair may allow continuation of everolimus or EDT pending the approval of the MSKCC IRB followed by the approval of the participating site's local IRB.

9.9 Ancillary medications/therapies

- Primary prophylactic G-CSF may be given as indicated.
- Anti-emetic therapy will be provided according to institutional guidelines.
- Erythropoietin and/or transfusions may be given according to institutional guidelines or investigator preference.
- Add back therapy with norethindrone acetate 5 mg PO QD will be initiated after 6 months of EDT in females < 18 years old.

- Calcium and vitamin D supplementation will be given according to the National Osteoporosis Foundation (NOF; www.nof.org) guidelines given the risk of decreased bone mineral density with EDT.
    - Calcium: 1000 mg/day for children and adults < 50 years old; 1200 mg/day for adults ≥ 50 years old. This represents total intake from supplements and food.
    - Vitamin D: 400 IU/day for children; 400-800 IU/day for adults < 50 years old; 800-1000 IU/day for adults ≥ 50 years old; maximum safe dose is 4000 IU/day total intake from supplements and food. Vitamin D2 (ergocalciferol) and D3 (cholecalciferol) are both acceptable.
    - Patients will be provided with a pill diary to record the date and time that calcium and vitamin D are taken.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Treatment/Intervention	Anytime before C1D1	Within 4 wks of Tx	Within 2 wks of Tx	C1D1[a]	C1W2[v]	C1W3[f]	C2W1 onwards[b]	C2W3 onwards[b]	Q4 wks	Q12 wks	4 wks after study
Study therapy											
Everolimus POQD[c]				x	Continuous administration						
Leuprolide 7.5 mg IM				x					x[d]		
Letrozole 2.5 mg PO QD					x[e]	Continuous administration					
Clinical											
History, physical exam, vitals, weight, ECOG versus Lansky as applicable, BSA			x		x[v]	x[f]	x	x[f]			X
Adverse event assessment				x	x[v]	x[f]	x	x[f]			x
Laboratory											
CBC +differential, metabolic panel[g], Ca^{2+}, PO_4, liver function tests[h], LDH			x			x[f]	x[i]	x[i,f]			x
Ammonia[w]			x[w]		x[w]	x[w]	x[w]	x[w]	x[w]	x[w]	x[w]
Hepatitis B sAg, cAb; +		x									
Quantitative PCR for hepatitis C and hepatitis B, (if known infection)			x[j]							x[j]	
Fasting glucose and lipid profile[k]			x				x[l]				x
Serum estrogens, testosterone, FSH			x		X[d,m,n]					x[o]	x
Plasma neurotensin, transcobalamin, DCP, AFP			x							x[o]	
Urinalysis[p]			x								
Serum pregnancy test			x[q]								
Imaging											
CT chest/abdomen/pelvis with contrast and triphasic liver[r]		x								x[s]	

Treatment/Intervention	Anytime before C1D1	Within 4 wks of Tx	Within 2 wks of Tx[a]	C1D1[a]	C1W2[v]	C1W3[f]	C2W1 onwards[b]	C2W3 onwards[b]	Q4 wks	Q12 wks	4 wks after study
Other											
Blood sample for future research			x								
Pathology specimen[t]	x			Repeat if patient undergoes surgery							
Bone mineral density scan (patients ≥ 16 years old)		x	Annually								
Bone age (all patients 12-15 yrs old)[u]		x	Every 6 months								
EKG			x	As clinically indicated							
Pulmonary function tests		As clinically indicated									
Psychiatric evaluation		As clinically indicated									

[a] C1D1 = cycle 1 day 1; C1W2 = cycle 1 week 2
[b] Continue same for all subsequent cycles
[c] Patients with BSA < 1.5 m^2 receive everolimus 5 mg PO QD. Patients with BSA ≥ 1.5 m^2 receive everolimus 7.5 mg PO QD. If BSA changes by > 10% above or below the 1.5 m^2 cut-off at any time during the study, the dose of everolimus must be adjusted accordingly.
[d] May be done +/- 7 days
[e] If estradiol (females) and testosterone (males) are within castration range. Otherwise, delay start of letrozole until week 4, coinciding with 2nd dose of leuprolide.
[f] In exceptional circumstances, which must be approved by the MSKCC principal investigator, week 3 visit can be schedule with a local oncologists along with the week 3 bloods
[g] Includes Na, K, Cl, HCO3, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase.
[h] Total and direct bilirubin, albumin. INR/PT/PTT is required at screening. For weeks 1 and 3 of each cyle, only PT/INR is required.
[i] To be repeated during weeks 1 and 3 of every cycle.
[j] Only if Hepatitis B and/or C screening serologies are positive
[k] Total cholesterol, triglycerides, LDL and HDL
[l] To be repeated during week 1 of every cycle.
[m] For patients on EDT, serum estradiol and testosterone only (FSH and estrone excluded). The post menopausal cutoff level for serum estradiol is ≤ 30 pg/mL. See sections 9.2, 9.3, or 9.4 for further clarification.
[n] For patients on EDT, the castration cutoff for testosterone is < 50 ng/dL. See sections 9.2, 9.3, or 9.4 for further clarification.
[o] For patients on EDT, may be performed at same time as other blood draws on C4W1, C7W1, C10W1, etc.
[p] Includes specific gravity, color, turbidity, pH, albumin, glucose, ketones, bilirubin, blood, urobilinogen, leucocyte esterase, nitrite, and other findings
[q] To be completed within 7 days of starting study therapy.
[r] Or MRI abdomen/pelvis and non-contrast enhanced CT chest if patient allergic to CT contrast dye despite pre-medication, or other clinical contraindication.
[s] Imaging studies performed at 6 months (+/- two weeks) will be used to determine the primary endpoint (PFS6)

[t]Tumor aromatase and estrogen receptor expression, Ki67, and markers of mTOR activity (phospho-S6 kinase, phospho-Akt, cyclin D1) on biopsy specimens obtained before joining the study. For patients who undergo surgery on protocol therapy, tissue will be reexamined for same markers.
[u] Left hand and wrist radiographs using the Greulich-Pyle Atlas.
[v] If patient is randomized to Arm A, the Cycle 1 Week 2 visit can be scheduled with a local oncologist upon approval by the MSKCC principal investigator in exceptional circumstances.
[w]Ammonia testing should be tested within 2 weeks before or on Cycle 1 Day 1 and at every visit when blood work is required.

Summary of evaluation plan during treatment

- Patients will undergo clinical and laboratory evaluations on weeks 1, 2 and 3 of Cycle 1. For all subsequent cycles starting with Cycle 2, evaluations will take place on weeks 1 and 3.

- Only clinical and laboratory assessments performed at Memorial Sloan Kettering Cancer Center or participating sites will be used to determine if patient will proceed with protocol treatment using the parameters listed below. Protocol assessments performed at a local oncologist may be used to determine treatment decisions at discretion of treating investigator and local oncologist.

- Before treatment on week 1 and 3 of each cycle: CBC and differential, comprehensive metabolic panel (Na, K, Cl, HCO3, BUN, creatinine, AST, ALT, alkaline phosphatase, glucose), LDH, calcium, phosphorus, albumin, bilirubin, PT/INR, and ammonia. Treatment will only proceed if:

  - Hematologic: ANC $\geq$ 1.0 x 10^9/L, platelets $\geq$ 50 x 10^9/L
  - Renal: creatinine $\leq$ 2 x upper limit of normal or creatinine Clearance of $\geq$60 cc/mL/1.73 m^2 for patients > 16 years old. For patients $\leq$ 16 years of age, creatinine Clearance of $\geq$70 cc/mL/1.73 m^2 or serum creatinine based on the following chart:

Creatinine clearance or radioisotope GFR $\geq$ 70ml/min/1.73 m_2 or serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
$\geq$ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

  - Hepatic: total bilirubin $\leq$ 2 mg/dL, alanine and aminotransferase levels $\leq$ 5 x upper limit of normal for age.

- If hematologic, renal and hepatic function criteria are not met, treatment will be held and the patient will be reassessed weekly. Please refer to section 11.0 Toxicities/Side Effects for the

management of other adverse events during therapy.

- Fasting blood glucose and fasting lipid profile (total cholesterol, triglycerides, LDL, HDL) will be drawn on week 1 of each cycle beginning with cycle 2.

- Past FLL-HCC patients have also been referred for psychiatric services with depressive symptoms, immaturity and suicidal ideation as the most commonly observed symptoms. Participants on study will be psychiatrically evaluated as clinically indicated.

Follow-up after study therapy

Patients who have discontinued the study will be asked to return four weeks later for an exit visit consisting of a medical history, vital signs, physical examination, toxicity check and blood tests including a complete blood count, Na, K, Cl, HCO3, BUN, creatinine, glucose, AST, ALT, INR/PT/PTT, Ca, Mg, phosphorus, alkaline phosphatase, LDH, fasting blood glucose, fasting lipid panel, and ammonia. Patients who were on EDT will also be asked to provide blood to test serum estrogens, testosterone and FSH. After this exit visit, patients may be contacted every 3 months to monitor their survival. This information may also be checked through medical records or updated mortality lists of the institutions. Patients will also be encouraged to continue with periodic imaging after they have completed the study.

Correlative studies

Correlative studies are particularly important for rare diseases like FLL-HCC, and can be used to enhance the quantity and quality of information obtained from this study. Serum and tissue biomarker studies will be correlated with study outcomes to determine if they may have any predictive or prognostic value. Changes in biomarker expression in post-treatment specimens will also provide information about the precision of therapeutic targeting.

All specimens, including those procured at UCSF, JHU and DF/BWCC/MGHCC will be shipped to MSKCC or Labcorp and will be analyzed where the sample is sent.

- **Tissue biomarker analysis**

  Tissue procurement and processing

  - During screening, a block(s) of archived formalin-fixed paraffin-embedded FLL-HCC tumor tissue will be collected prior to the study and will be sent to the central laboratory facility at MSKCC along with the corresponding pathology report. Alternatively, approximately 20 unstained slides (if available) will be sent.

  - Adequate samples should be sent to the pathology core lab facility at MSKCC, preferably within 4 weeks of beginning the study to permit adequate time to evaluate the samples and determine if additional samples are required.

- **For MSKCC patients:** samples are to be sent to the attention of Dr Jinru Shia, Department of Pathology, 1275 York Avenue, New York, NY 10065.

- **For participating sites**: samples are to be sent to the attention of Study 11-211, Dr. Abou-Alfa, 300 East 66th St, 10th Floor, New York, NY 10065.

- The tumor block should be carefully selected by a pathologist or a skilled, experienced histology associate and should include a deep diagnostic section containing generous tumor tissue.

- If the adequacy of the tumor specimen is unclear, it is acceptable to submit more than 1 block or series of slide replicates containing tumor tissue. These must be accompanied by the pathology report, otherwise the submission will be considered incomplete.

- If insufficient tumor is available to perform biomarker analysis, patients will be offered the opportunity to undergo a repeat biopsy to obtain an adequate sample.

- Tumor slides taken from the tumor block to be submitted to the MSKCC core laboratory facility should be prepared according to the following preferred specifications:

  - Approximately 20 slides in 5 micron thick slices should be cut from the same block onto the charged slides.

  - The slides should be labeled by etching or using an indelible histology marker with the block ID number to match the pathology report.

- Subject identifiers (e.g. name, social security number) should be blacked out on the pathology report to protect subject identity. However, the subject ID number should be written on the report. The specimen collection date and block ID numbers should be visible and legible.

- No additional invasive procedures to obtain tumor tissue are required for this study. However, if a patient undergoes surgery or another biopsy during the study as part of the routine investigations of the subject's disease, a fresh formalin-fixed paraffin-embedded tumor tissue sample (block or unstained slides) may be submitted of the central laboratory for additional immunohistochemical analysis.

- Participating sites will notify the Multicenter Trial Research Staff at MSKCC or medmctcore@mskcc.org) when samples are shipped by using a sample requisition form. The Research Staff will contact the receiving laboratory to confirm receipt of the specimens. In addition to the information noted above, the following information will be recorded: (1)MSKCC CRDB protocol participant #, (2) patients initials, (3) sample type (slides or block), (4) date specimen was obtained, (5) shipping date.

Immunohistochemical analysis

- Immunohistochemical analysis will be performed on formalin-fixed paraffin embedded tumor specimens. Tumors will be assayed at baseline using monoclonal antibodies to stain for:

  - Aromatase
  - Estrogen receptor expression
  - Ki67
  - Phospho-S6 (phosphorylated ribosomal protein S6)
  - Phospho-Akt
  - Cyclin D1

- Evaluation of the tumor specimens and description of staining intensity will be performed by Dr. Jinru Shia.

- The baseline staining pattern for the various markers will be correlated with progression-free survival at 6 months (PFS6).

- Immunostains will be repeated on tumor specimens obtained from patients who undergo surgery on protocol therapy. Changes in tissue biomarkers from baseline to surgery will be summarized descriptively.

Blood biomarkers

Blood samples for future research

- Two tubes of blood for plasma and serum to be used in future research studies at MSKCC will be collected from all patients
  - Kits for these samples will be provide to each participating site by MSKCC and collected plasma and serum samples will be bulk shipped to MSKCC every six months.
  - Instructions for processing these samples, as well as shipment information, are in the Lab Manual.

Putative FLL-HCC tumor biomarkers to be measured within 2 weeks of initiating study therapy and every 12 weeks during the protocol in all patients.

- **AFP**
  - AFP will be collected and resulted at respective site's laboratory.
- **Plasma neurotensin**
  - **Patients should be fasting 10 - 12 hours prior to collection of specimen. Patients should not be on any antacid medication or medications that affect gastro entero-intestinal function, if possible, for at least 48 hours prior to collection.**
  - A 10mL sample will be drawn into an EDTA z top tube provided by the Interscience Institute through LabCorp. The serum should be separated from the whole blood as soon as possible to maintain the integrity of the sample. Once the serum has been

separated it should be frozen immediately until the sample is ready to be shipped. All neurotensin samples will be processed at Inter Science Institute 944st Hyde Park Blvd Inglewood CA, 90302. Further details regarding sample preparation, packaging, and shipping are found in the study lab manual.

- **Serum unsaturated vitamin B12 binding capacity (transcobalamin)**
  - **Must draw before Schilling test, transfusions, or B_{12} therapy is started.**
  - A 0.5 mL sample will be drawn into a red-top, gel-barrier, or EDTA tube provided by LabCorp. The serum should be separated and put into a plastic transfer tube and frozen immediately until it is ready to be shipped. All unsaturated vitamin B12 binding capacity samples will be processed at LabCorp 1447 York Court Burlington, NC 27215. Further details regarding sample preparation, packaging, and shipping are found in the study lab manual.

- **Serum des-γ-carboxyprothrombin (DCP)**
  - No special patient preparations are necessary.
  - A 2 mL sample will be drawn into a red-top or gel-barrier tube provided by LabCorp. The serum should be separated, put into a plastic transfer tube, and frozen immediately until it is ready to be shipped. All unsaturated serum DCP samples will be processed at LabCorp 1447 York Court Burlington, NC 27215. Further details regarding sample preparation, packaging, and shipping are found in the study lab manual.

Serum hormones

- All serum hormones will be processed and resulted at the respective site they were drawn at. Patients on the EDT-containing study arms (Arms B and C) will have blood drawn for the following serum hormones:
  - Serum estrone
  - Serum estradiol
  - Serum follicle stimulating hormone (FSH)
  - Serum testosterone

- Serum hormones will be measured within 2 weeks of initiating study therapy. Serum estradiol and testosterone will be measured again during Week 2 of therapy if required per protocol. All hormones (estrone, estradiol, FSH, testosterone) will be measured every 12 weeks thereafter.

- **Sample storage and destruction**

Blood and tumor samples collected for biomarker analysis and any other components from the cells may be stored for up to 20 years for future scientific investigations related to FLL-HCC. Study subjects maintain the right to have the sample material destroyed at any time by contacting the principal investigator. MSKCC will be the exclusive owner of any data, discoveries or derivative materials form the sample materials and is responsible for the destruction of the sample(s) at the request of the research subject through the principal investigator, at the end of the storage period, or as appropriate (e.g. the scientific rationale for experimentation with a certain sample type no longer

justifies keeping the sample). The principal investigator will provide MSKCC with the required study and subject numbers so that any remaining blood and tumor samples and any other cell components can be located and destroyed.

11.1 TOXICITIES/SIDE EFFECTS

All toxicities will be graded using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

11.2 Anticipated adverse events

- Everolimus:
    - Likely: stomatitis, xerostomia, nausea/vomiting, diarrhea, anemia, leucopenia, thrombocytopenia, increased transaminases, fatigue, dysglycemia, hyperlipidemia, hypophosphatemia, low bicarbonate, upper respiratory symptoms or infection, asthenia, peripheral edema, epistaxis, pruritus
    - Less likely: rash, , dysgeusia, anorexia, weight loss, pneumonitis, dyspepsia, arthralgia, myalgia, hyperkalemia, hyponatremia, hypomagnesemia, hand-foot syndrome
    - Rare but serious adverse events: chest pain, cardiac arrhythmias, cardiac arrest, pancreatitis, renal failure, a secondary malignancy, diabetes, bleeding and hepatitis B reactivation
- Letrozole:
    - Likely: hot flashes, edema, hyperlipidemia, arthralgia, weakness, decreased bone mineral density, night sweats, headache, fatigue, dizziness, constipation, weight loss or gain, back pain, dyspnea, chest pain, nausea, vomiting, vaginal bleeding, renal failure, infection
    - Less likely: cough, hypertension, diarrhea, anorexia, breast tenderness/soreness
    - Rare but serious adverse events: cerebrovascular accident, venous thrombosis, myocardial infarction, and secondary malignancies
- Leuprolide:
    - Likely: hot flashes, headache, depressed mood, pain or bruising at injection site, hyperhidrosis, insomnia, decreased bone mineral density, edema, hyperlipidemia, weight gain or loss, decreased libido, hypogonadism, acne, breast tenderness/soreness, breast enlargement, dysglycemia, hyperuricemia, infection at injection site, paresthesias, erectile dysfunction, pelvic or urinary tract discomfort
    - Less likely: nausea, vomiting, dizziness, fatigue, arthralgia, myalgia, epistaxis, osteoporosis
    - Rare but serious adverse events: chest pain, arrhythmia, thrombosis, fever, seizure, renal failure, hypersensitivity reaction, hemoptysis, hepatic failure

11.3 Reproductive risks

- Patients must not become pregnant or father a child while receiving protocol therapy due to potential risks to the unborn baby. Intrauterine device, double-barrier method, male partner sterilization or abstinence must be used during the duration of protocol therapy and until three months after the last dose of study therapy.

- Prescription oral contraceptives, contraceptive injections, and contraceptive patch are not approved methods of contraception in this study.
- Prepubescent patients have been shown to regain normal reproductive function after therapy with a GnRH agonist [67]. The long-term effects of aromatase inhibitors on reproductive function in prepubescent patients is unknown.

- Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported by the MSKCC Principal Investigator to Novartis within 24 hours of learning of its occurrence and/or receiving from the participating sites. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

11.4 Effects on bone health

Decreased bone mineral density with the increased risk of fractures and osteoporosis is a well known side effect of hormonal deprivation therapy in men and women. The 2003 ASCO guidelines on the use of bisphosphonates in women with breast cancer state that all postmenopausal women receiving aromatase inhibitors and premenopausal women with treatment induced menopause are considered at high risk of developing osteoporosis and should undergo a bone mineral density test [73]. Regardless of the result, healthy lifestyle modification should be encouraged and all patients should receive calcium and vitamin D supplementation. Oral bisphosphonates will be prescribed to women with osteoporosis as defined by a T score of $\leq$ - 2.5. Prophylactic IV bisphosphonates are not indicated to maintain bone health in women without bone metastases [73]. Similar recommendations apply to men based on guidelines of the National Osteoporosis Foundation (www.nof.org) and fracture risk as determined by the World Health Organization Fracture Risk Assessment Tool (FRAX) calculator available at http://www.sheffield.ac.uk/FRAX/index.jsp.

Bone mineral density in children and adolescents is not known to be affected by the use of aromatase inhibitors or GnRH agonists. Vertebral abnormalities have been reported in a specific population of boys with idopathic short stature who were treated with letrozole [68] but not other pediatric patient populations treated with aromatase inhibitors. Consensus guidelines recommend that children and adolescents receive daily calcium and vitamin D supplementation as well as engage in skeletal-loading exercise while receiving a GnRH agonist [67]. The guidelines also state that bone age should be followed periodically during therapy [67].

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Tumor responses will be evaluated using the revised RECIST version 1.1 guidelines [148].

12.2 Measurement of tumors

All lesions should be measured and recorded using metric notation. The same assessment method and technique should be used to characterize each identified and reported lesion at baseline and on follow-up.

12.2.1 Measurable disease

- Tumor lesions must be accurately measurable in at least one dimension (longest diameter in plane of measurement recorded) and have a longest diameter of $\geq$ 10 mm by CT (slice thickness $\leq$ 5 mm) or MRI.
- Pathologically enlarged, measurable lymph nodes are $\geq$ 15 mm in the short axis on CT (slice thickness $\leq$ 5 mm) or MRI. Only the short axis is to be measured at baseline and on follow-up scans.
- Lytic or mixed lytic-blastic bone lesions with a soft tissue component are considered measurable disease if the soft tissue component is measurable by CT or MRI and meets the size criteria for measurability.
    - Bone scan, PET and plain films are inadequate techniques to measure bone disease, but can be used to verify the presence or disappearance of bony lesions.
- Lesions representing cystic metastases are considered measurable if they meet the size criteria for measurability. Where possible, non-cystic lesions are preferred as target lesions.
- Lesions sitting in an area previously irradiated or treated with locoregional therapy are only considered measurable if there has been evidence of progression in those lesions.

12.2.2 Non-measurable disease

- Includes all lesions < 10 mm in longest diameter or pathological lymph nodes $\geq$ 10 or < 15 mm on short axis and truly non-measurable lesions (leptomeningeal metastases, ascites, pleural/pericardial effusions, lymphangitic skin or lung involvement, abdominal masses/organomegaly found on physical exam that is not reproducibly measurable by imaging studies, osteoblastic metastases).

12.2.3 Reporting of target lesions

- The sum of the longest diameter of all measurable non-lymph node target lesions and the short axis of all measurable target lymph nodes equals the baseline sum diameters. This value will be used for future comparisons with subsequent imaging to evaluate objective tumor responses.

12.2.4 Reporting of non-target lesions

- All non-target lesions, disease sites, and pathological lymph nodes do not require measurement, but should be recorded at baseline. Non-target lesions can be described as "present", "absent", or showing "unequivocal progression." Multiple non-target lesions in the same organ can be reported as a single item.

12.2 Response criteria

12.2.1 Evaluation of target lesions

- Complete response (CR): disappearance of all target lesions and regression of all pathological lymph nodes (target and non-target) to < 10 mm in short axis diameter.
- Partial response (PR): $\geq$30% reduction from baseline in the sum of diameters all target lesions.
- Progressive disease (PD): $\geq$20% increase in the sum of diameters of all target lesions from the smallest sum on study AND an absolute increase of at least 5 mm. Also includes the appearance of any new lesion(s).
- Stable disease (SD): Meeting neither criteria for PR or PD using the smallest sum on study as the reference.

12.2.2 Evaluation of non-target lesions

- Complete response (CR): disappearance of all non-target lesions. All lymph nodes must be < 10 mm in short axis diameter (i.e. non-pathological).
- Progressive disease (PD): unequivocal progression of existing non-target lesions or the appearance of new lesion(s).
- Non CR/non PD: Persistence of $\geq$1 non-target lesion(s).

12.2.3 Evaluation of patients with both measurable (target) and non-measurable (non-target) disease

- In order to have PD based on non-target lesions, there must have been sufficient growth of the non-target lesions such that, even in the presence of SD or PR of target lesions, the overall tumor burden has increased enough to warrant discontinuation of therapy.
- A modest increase in the size of $\geq$1 non-target lesions, in the presence of SD or PR of target lesions, is insufficient to define unequivocal disease progression.

12.2.4 Best overall response

- This is the best response documented from the start of treatment to disease progression or recurrence according to the table below.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	none	CR
CR	Non CR/non PD	none	PR
CR	Not evaluated	none	
PR	Non PD or not all evaluated	none	
SD	Non PD or not all evaluated	none	SD
Not all evaluated	Non PD	none	Not evaluable
PD	Any	Yes/no	PD
Any	PD	Yes/no	
Any	Any	Yes	

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

- Patients with a global deterioration of health status warranting discontinuation of therapy without objective disease progression at that time will be reported as "symptomatic deterioration." Every effort should be made to document disease progression even after discontinuation of therapy.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Study therapy will continue until/unless there is:

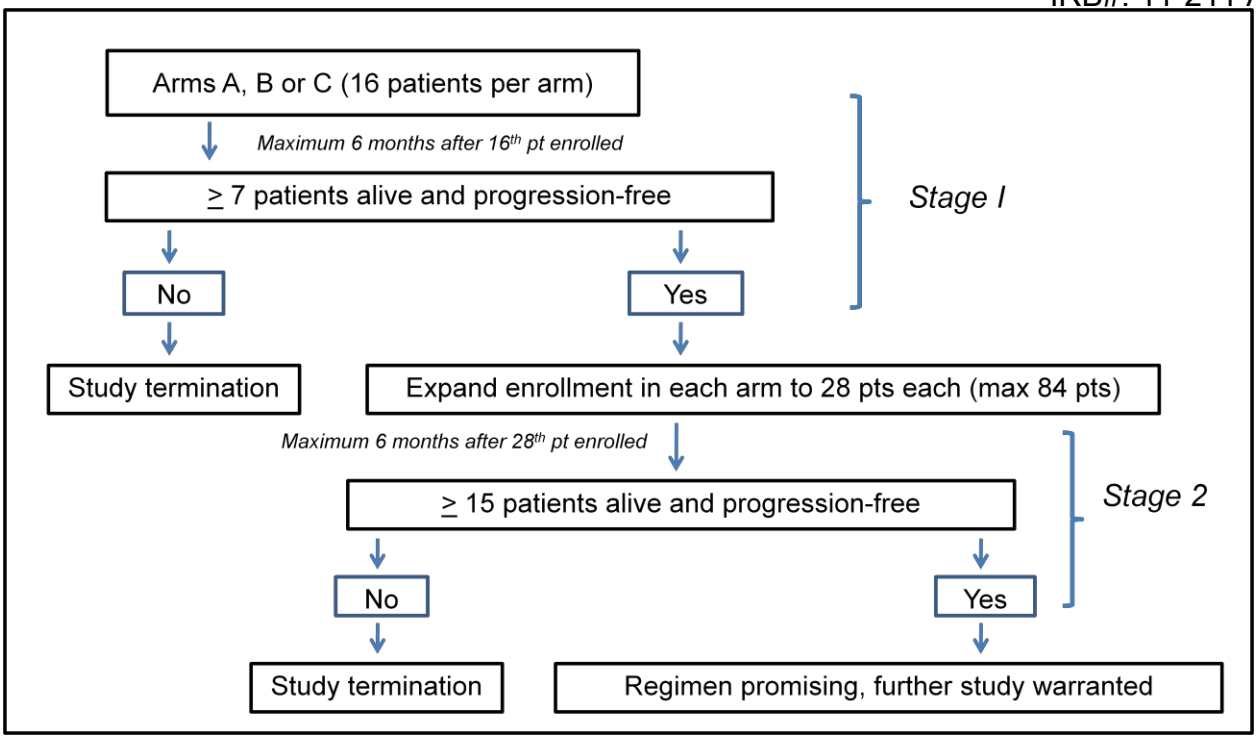
- Disease progression as defined by RECIST 1.1 criteria
- Clinical progression
- Unacceptable toxicity
- Patient withdrawal of consent
- Patient noncompliance
- Intercurrent illness that prevents further administration of treatment. Inability to take EDT and everolimus simultaneously for patients who receive combination therapy. In very special circumstances, study chair may allow continuation of everolimus or EDT pending the approval of the local IRB.
- General or specific changes in the patient's condition rendering him/her unacceptable for further treatment in the judgment of the investigator. Delay of therapy for > 4 weeks. If more than 4 weeks are required for recovery, the study chair may allow continuation of everolimus or EDT pending the approval of the local IRB.
- Patients who are removed from the study for any of the above reasons will continue to be monitored for survival every 3 months unless consent for continued follow-up is withdrawn.

14.0 BIOSTATISTICS

Primary efficacy endpoints for Part 1 of protocol

- The primary efficacy endpoints for Part 1of the study is progression-free survival at 6 months (PFS6).
- A progression event refers to the first evidence of radiographic disease progression, clinical progression as determined by study investigators, or death.
- Imaging performed in 6 months will be used to determine PFS6.
- PFS6 will be defined as the percentage of patients who are alive and have not experienced a progression event as defined above at 6 months from the date that study therapy was initiated. Patients that come off study before the 6 months scan will be considered events for the primary endpoint analysis.
- PFS6 will be assessed using a Simon's minimax two stage design, hypothesizing an improvement in PFS6 from 40% to 64% with the study regimen. Sixteen patients will be enrolled onto each of Arms A, B and C for a total of 48 patients in the first stage. Accrual will stop till the progression status at 6 months is obtained on all 16 patients in each arm. If 6 or less patients in one arm are progression free at 6 months the regimen in that arm will be terminated; otherwise, if 7 or more patients are alive and progression free at 6 months, enrollment will be extended in that arm to 28 patients (maximum total of 84 patients). At the end of stage 2, the respective regimens will be declared promising if 15 or more of the 28 patients in each arm are alive and progression free at 6 months. The design assumes a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) both set to 10%.

Figure 4: Simon's minimax 2 stage design (schematic applicable for each study arm)



- The probability of early termination due to drug inefficacy is 53%. In the event that 2 or more arms show promising activity, we will use the "pick the winner" format based on the randomized phase II clinical trials approach proposed by Simon et al. In this case, the regimen that has at least 15 patients progression free at 6 months and exceeds by at least 2 patients the number of progression free patients in the second best arm would be declared the winner. The probability of selecting the better regimen is 85%; the probability that no regimen is selected is 7%, while the probability of a tie is approximately 6% [149].

Secondary endpoints

- Secondary endpoints are:
  - Median PFS
  - Median overall survival (OS)
  - Objective response rate by RECIST 1.1 guidelines
  - Rate of conversion to resectable status
  - Safety and toxicity
  - Correlative serum and tissue biomarker studies.
- Kaplan-Meier PFS will be measured from the date that study therapy is initiated until the date of

first evidence of radiographic disease progression, global clinical deterioration as determined by study investigators, or death.

- Kaplan-Meier OS will be measured from the date that study therapy was commenced until the date of death.
- Objective responses will be reported using RECIST guidelines (version 1.1). Objective response will be estimated using binomial proportions and exact 95% CIs will be provided.
- Conversion to resectable status to be determined by hepatobiliary surgeons in conjunction with radiological assessment of response to therapy.
- Adverse events/toxicity will be monitored and recorded using the CTCAE version 4.0 and summarized descriptively.
- Baseline serum measurements will be correlated with PFS6 (binary endpoint) using Fisher's exact test for categorical serum measurements and using Wilcoxon rank sum test for continuous measurements. For each time point at which serum measurements are collected, changes in the different binary serum markers from baseline will be correlated with PFS6 using conditional logistic regression to account for the paired nature of the data while Wilcoxon signed-rank test will be used for continuous measurements.
- Associations between baseline tissue biomarkers and PFS6 will be assessed using Fisher's exact test for categorical biomarkers, trend tests for ordinal biomarkers and Wilcoxon rank-sum test for continuous biomarkers. For patients undergoing surgery, changes in tissue biomarkers from baseline to surgery will be summarized descriptively in an exploratory fashion.

Exploratory analysis for Part 2 of protocol (combination therapy).

- PFS will be evaluated for patients who were on Arm A (everolimus) or Arm B (EDT) during Part 1 of the study who subsequently received combined everolimus + EDT during Part 2.
- PFS will be measured as the time from the start of the combination therapy till progression or death whichever comes first.

Biomarker analysis and data interpretation

- Baseline tissue biomarkers will be correlated with PFS6.
- Baseline levels of hormones will be correlated with PFS6.
- Baseline levels of tumor markers will be correlated with PFS6.
- Following initiation of EDT, castration will be considered effective if serum estrogens are in the postmenopausal range, serum testosterone is in the castration range and FSH below the detection threshold as per the cutoffs established at the respective study site laboratories. The achievement of chemical castration will be correlated with PFS6.

- The maximum change in levels of tumor biomarkers from baseline will be correlated with PFS6.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.1.1 For participating sites

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to email registration/eligibility documents to the Multicenter Trials Core at medmctcore@mskcc.org .

The following documents must be sent for each enrollment within 24 hours of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good

standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

15.2 Randomization

In Part 1 of the study, patients will be randomized to Arm A (everolimus), Arm B (EDT) or Arm C (everolimus + EDT). Randomization will be performed centrally. Study investigators and participants will not be blinded to therapy assignment. Patients will be stratified by study site.

Patients will be registered and randomized using the Clinical Research Database (CRDB) and assigned an MSKCC CRDB number. This number is unique to the patient and must be written on all data and correspondence for the patient. This protocol patient number and the treatment arm assignment will be relayed back to the study staff at the registering site via email and will serve as enrollment and treatment arm confirmation.

16.1 DATA MANAGEMENT ISSUES

Data to be collected include documentation from all inpatient and outpatient visits, pathology, imaging, laboratory, pharmacy and treatment records.

A research project coordinator (RPC) will manage the data from all patients enrolled at MSKCC. Data from patients enrolled at MSKCC, UCSF, JHU, and DF/BWCC/MGHCC will be sent to the Multicenter Trial Center. The responsibilities of the research project coordinator will include coordination of patient enrollment, quality assurance and serious adverse event reporting.
A Research Study Assistant (RSA) will be assigned to the study at each of the participating sites (MSKCC, UCSF, JHU, DF/BWCC/MGHCC). The responsibilities of the RSA include confirmation of patient eligibility, project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. The data collected from each site for this study will be entered into a central, secure clinical research database maintained at MSKCC. Source documentation will be available to support the computerized patient record.

16.1.1 Data and Source Documentation for Participating Sites

16.1.1.1 Data

Electronic Report Forms (eCRFs), directions for use and sign off requirements have been generated

for this study. The MSKCC Principal Investigator or designee will provide eCRFs to the participating sites. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

16.1.1.2 Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. CT or MRI)
- Treatment records
- Toxicities/adverse events not previously submitted with SAE Reports
- Response designation

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter

16.1.1.3 Data and Source Documentation Submission for Participating Sites

Participating sites are responsible for data entry using the Electronic Data Capture (EDC) system. Instructions for EDC access and guidelines are provided in the study procedure manual.

All source documents should be e-mailed to the research study assistant at medmctcore@mskcc.org.

16.1.1.4 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to the chart below:

	Baseline	***Cycle 1***	***Cycle 2***	***Cycle 3***	***Cycle 4+***	***SAE***	***Long-term Follow-Up***	***Off Study***
SUBMISSION SCHEDULE								
Source Documentation	**Within 24 hours (see section 15.1.1)**	**within 14 days of *end of Cycle***				**Within 3 days of event (see section 17.2); updates to be submitted as available**	**Every 3 months**	**Within 14 days of visit**
eCRFs	**Within 7 days of visit**							
Required Forms								
Demographics Form	**X**							
Medical History Form	**X**							
Concomitant Medications Form	**X**	**X**	**X**	**X**	**X**			**X**
Physical Exam Form	**X**	**X**	**X**	**X**	**X**			**X**

Treatment Form		**X**	**X**	**X**	**X**			**X**
Laboratory Form	**X**	**X**	**X**	**X**	**X**			**X**
RECIST Form					**X**[1]			**X**
Adverse Event Form		**X**	**X**	**X**	**X**	**X**		**X**
Serious Adverse Event Form						**X**		
Disease Status							**X**	
Off Study Form								**X**

16.1.1.5 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

Teleconferences will be held approximately once a month to update investigators on the progress with the study and to discuss toxicity observed to date. Frequency of calls may be adjusted as indicated by the study progress. The Principal Investigator and staff will make arrangements with investigators for the teleconferences.

16.1.1 Quality Assurance for Participating Sites

Each site accruing participants to this protocol will be audited by the staff of the MSK study team for protocol and regulatory compliance, data verification and source documentation.

Audits will be conducted annually during the study (or more frequently if indicated) and at the end or closeout of the trial. Ideally the first audit will occur shortly after the first patients are enrolled.The number of participants audited will be determined by auditor availability and the complexity of the protocol. Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the

participating sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site

- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for *3 years.*

16.4 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges and/or contract payments maybe withheld may be suspended until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Patient participation in this protocol is completely voluntary. Patients will be provided with documentation explaining the protocol rationale and objectives, as well as its potential risks, benefits, toxicities/side effects, inconveniences and financial costs/burdens. Alternative options for therapy will also be discussed. Patients who choose to participate will sign an informed consent conforming to the MSKCC IRB guidelines. The protocol will protect the rights and privacy of all participants.

The cost and supply of letrozole and Everolimus will be covered by Novartis Pharmaceuticals. The cost and supply of leuprolide will be covered by Abbott Pharmaceuticals. The tissue and serum biomarker studies will be research non-billable costs. All other costs will be billed to the patient.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of

protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

Patient privacy at UCSF and JHU will be protected according to those institutions' policies.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

Pregnancy Reporting

Any pregnancy or fathering that may occur while on study or within 4 weeks after completion of therapy, must be reported as detailed in sections 11.2 and 17.3.

17.2.1 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for reporting all SAEs and pregnancies while on treatment and within 4 weeks after completion of therapyvia email within 3 calendar days of learning of the event.
- Participating sites should notify the MSKCC PI and study team of any grade 5 event immediately Participating sites should use the electronic case report form to report all SAEs to MSKCC.

SAE contact information:
Email: medmctcore@mskcc.org to the attention of **Protocol 11-211** Research Staff

AND

Email: abou-alg@mskcc.org

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2 and to the funding entity as described in 17.3
- The MSKCC PI is responsible for informing all participating sites about all deaths and unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.3 Novartis instructions for MSKCC for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (888-299-4565), to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence and/or receiving from the participating sites. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be

reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

17.4 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites upon receipt.
- MSKCC must submit outside safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.1 INFORMED CONSENT PROCEDURES

During the initial conversation between the investigator/research staff, patients may also be asked to provide certain health information which will also be used towards assessing eligibility. Eligibility will be determined based on review of portions of the patient's medical records and the review of the study chair. Patients who are eligible will be contacted for study enrollment. It a patient is deemed ineligible to participate, research staff will destroy all information obtained during the initial conversation and medical record review except for any information that must be retained for screening log purposes.

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. The protocol design, rationale and objectives will be discussed, and a copy of the protocol summary written in layman's terms will be provided. The summary will also include a description of the benefits, risks, potential side effects and inconveniences of the study therapy. Participation is voluntary, and patients will be advised of any appropriate therapeutic alternatives. Participants will also be informed that they are free to withdraw from the study at any time.

All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.2 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

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20.0 APPENDICES

Appendix 1: Eastern Cooperative Oncology Group (ECOG) performance status [150].

Appendix 2: Lansky performance score for patients < 16 years old [151]

Appendix 3: Potent and moderate CYP3A4 inducers

Appendix 4: Potent and moderate CYP3A4 and/or P-glycoprotein inhibitors

Appendix 5: Serious adverse event report form for non-MSKCC sites.

Appendix 1: Eastern Cooperative Oncology Group (ECOG) performance status [150]

0	Fully active, able to carry on all pre-disease performance without any restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg light house work or office work)
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
4	Completely disable. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead

Appendix 2: Lansky performance score for patients ≤ 16 years old [151]

100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quieter activities
30	In bed, needs assistance for even quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Note: Patients who are evaluated using Lansky performance at study entry, will be assess using the same throughout the study, even if the patient becomes older than 16 years old while on study.

Appendix 3: Potent and moderate CYP3A4 inducers

Potent inducers	*Moderate inducers*
Rifampin	Dexamethasone
Carbamazepine	Ethosuximide
Nevirapine	Primidone
Phenobarbital	
St. John's Wort	

Potent inducers of CYP3A4 can lower serum everolimus levels; as such, their concomitant use should be avoided. Investigators should be aware of moderate inducers but dose adjustments are not required.

Appendix 4: Potent and moderate CYP3A4 and/or P-glycoprotein inhibitors

Potent inhibitors	*Moderate inhibitors*
Clarithromycin	Verapamil
Voriconazole	Erythromycin
Nelfinavir	Fluconazole
Ketoconazole	Phenobarbitol
Indinavir	Cyclosporine
Itraconazole	
Nefazodone	
Ritonavir	
Saquinavir	
Phenytoin	

Potent inhibitors of CYP3A4 and/or P-glycoprotein can increase serum everolimus levels; as such, their concurrent use should be avoided. Investigators should be aware of moderate inhibitors but dose adjustments are not required.