TITLE: A Phase 2 Study of Capecitabine or 5-FU with Pegylated Interferon alpha-2b in Unresectable/Metastatic Cutaneous Squamous Cell Carcinoma

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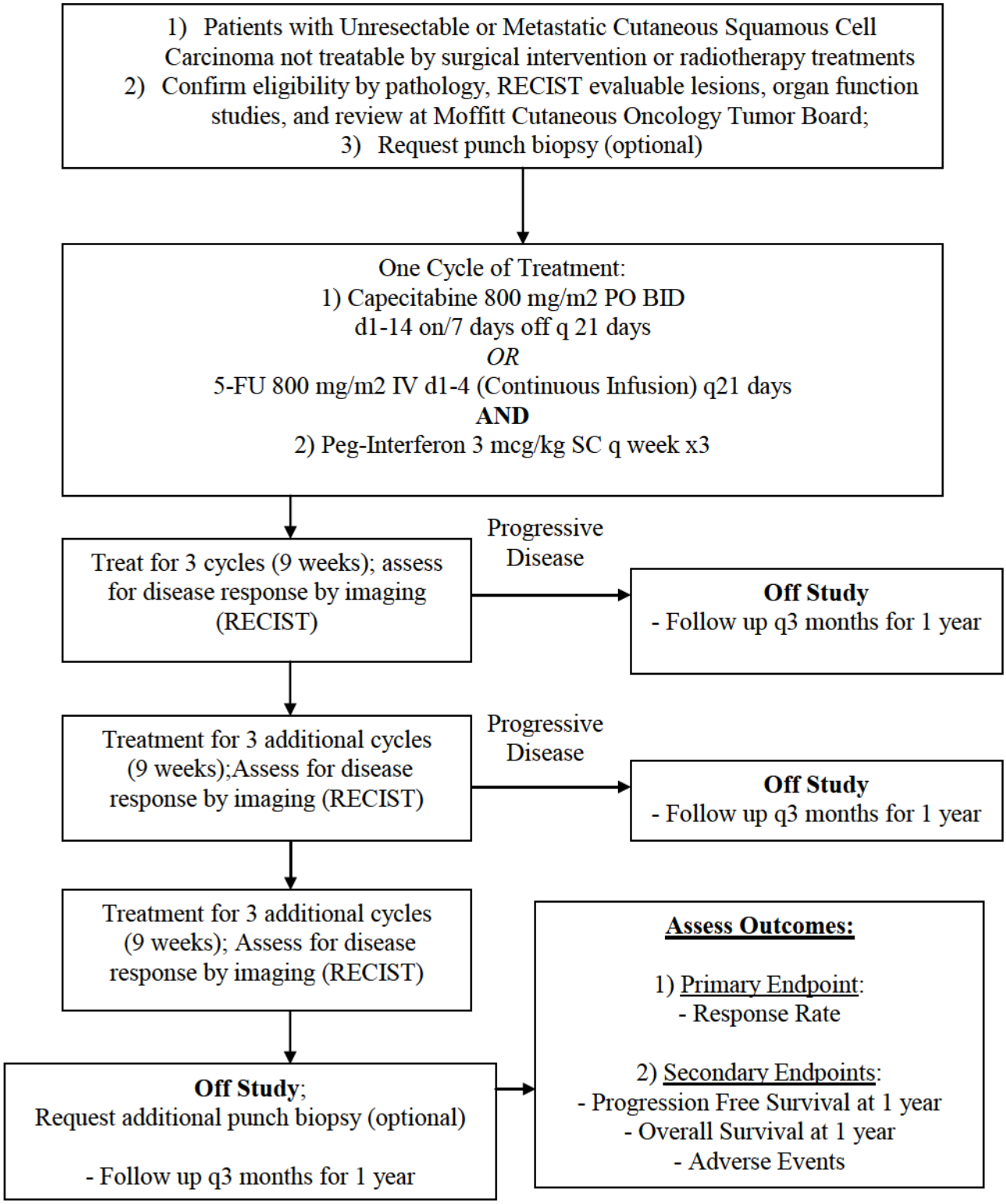
SCHEMA


1) Patients with Unresectable or Metastatic Cutaneous Squamous Cell Carcinoma not treatable by surgical intervention or radiotherapy treatments
2) Confirm eligibility by pathology, RECIST evaluable lesions, organ function studies, and review at Moffitt Cutaneous Oncology Tumor Board;
3) Request punch biopsy (optional)
One Cycle of Treatment:
1) Capecitabine 800 mg/m2 PO BID
d1-14 on/7 days off q 21 days
OR
5-FU 800 mg/m2 IV d1-4 (Continuous Infusion) q21 days
AND
2) Peg-Interferon 3 mcg/kg SC q week x3
Treat for 3 cycles (9 weeks); assess for disease response by imaging (RECIST)
Progressive Disease
Off Study
- Follow up q3 months for 1 year
Treatment for 3 additional cycles (9 weeks);Assess for disease response by imaging (RECIST)
Progressive Disease
Off Study
- Follow up q3 months for 1 year
Treatment for 3 additional cycles (9 weeks); Assess for disease response by imaging (RECIST)
Off Study;
Request additional punch biopsy (optional)
- Follow up q3 months for 1 year
Assess Outcomes:
1) Primary Endpoint:
- Response Rate
2) Secondary Endpoints:
- Progression Free Survival at 1 year
- Overall Survival at 1 year
- Adverse Events

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1. OBJECTIVES

1.1 Primary Objective(s)

To establish the objective response rate, using RECIST criteria, to the combination Treatment of Interferon alpha-2b and 5-FU/Capecitabine in patients with unresectable and/or metastatic cutaneous squamous cell carcinoma of the skin

1.2 Secondary Objective(s)

To establish the progression free and overall survival at one year, adverse events, and safety profile of the combination treatment of Interferon alpha-2b and 5-FU/Capecitabine in patients with unresectable and/or metastatic cutaneous squamous cell carcinoma of the skin

2. BACKGROUND

2.1 Study Disease

While squamous cell carcinoma of the skin is a very common cancer, the true number of cutaneous squamous cell carcinoma (CSCC) cases are difficult to determine, as the national SEER database does not capture non-melanomatous skin cancers (NMSC)[1]. However, it has been estimated that there are over 1.5 million cases of NMSC (75% Basal cell carcinoma and 25% Squamous cell carcinoma) diagnosed annually in the US[2]. Besides the known risk factor of UV exposure, an increase in cutaneous squamous cell carcinoma (CSCC) has been noted as a result of rising rates of transplants (BMT and solid organ) and the widespread use of immunosuppressive agents.

The majority of CSCCs are local in origin and are therefore treated with focal therapies including surgery, cryotherapy, topical chemotherapy (imiquimod, topical 5-FU), photodynamic therapy, and radiation therapy. Local control with these therapies typically exceeds 90% and even in patients with recurrent local disease, local control rates remain quite high[3].

Seventy-five percent of recurrences occur in the first two years and typically recur locally or in regional lymph nodes placing patients at high risk for developing distant metastasis[4]. While metastatic squamous cell cancer of the skin is rare, its' consequences are profound. In one study, 34 of 695 cases of cutaneous squamous cell carcinoma developed metastases for a metastatic rate of approximately 5%. The overall mortality of all patients was 3.4%; however, the mortality rate in the metastatic group exceeded 70%[5]. Similarly, in CSCC patients with distant metastasis, Alam et al. described a 5-yr survival rate of less than 10%[6].

Thus, while many patients are cured with local therapy, those with unresectable locoregional disease or known sites of distant metastasis have an increased mortality rate. Presently there is no standard accepted treatment for unresectable or metastatic disease.

2.2 PEG Interferon alpha-2b

PEG Interferon (IFN) alpha-2b was approved in 2001 by the FDA for the adjuvant treatment of melanoma for those patients with residual microscopic or gross disease. Currently, IFN alpha-2b is also approved for use in patients with hepatitis C and used frequently in patients with renal cell carcinoma. The non-PEG formulation has been tested in a variety of tumor types including cutaneous squamous cell carcinoma.

The pegylated formulation of IFN alpha-2b was designed to protect IFN from proteolytic breakdown and extend the half-life of the protein. IFN alpha-2b is a protein produced by recombinant DNA techniques from a strain of *E. Coli* bearing a engineered plasmid containing

the interferon gene from human leukocytes. The drug comes in a lyophilized power in a single-use vial and reconstituted with 0.7 mL sterile water. Peg-IFN alpha-2b is given SQ on a weekly basis from doses of 3 mcg/kg (maintenance) to 6 mcg/kg (induction therapy) in the setting of melanoma and doses of 1-1.5 mcg/kg in hepatitis C patients. Treatment periods range from 24-48 weeks for hepatitis C and 1-5 years for melanoma. Of note, IFN alpha-2a and -2b are related protein products, but PEG IFN alpha-2b was selected as it is dosed by body weight, has a more rapid absorption, and a wider distribution within the body.

The mechanism(s) of action had not been fully identified; however, it is considered an immunomodulatory cytokine that enhances the phagocytic and cytotoxic activity of macrophages and leukocytes.

The drug has a half-life of approximately 40 hours with a peak plasma time of 15-44 hours. It is excreted renally and dose reductions of 25-50% are recommended for moderate to severe renal impairment (Cr Cl <50 or <29 ml/min respectively). The drug is contraindicated for patients with a known hypersensitivity to IFN, patients with autoimmune hepatitis, or hepatic decompensation.

Common adverse events include: headache, fatigue, injection site reactions, depression, emotional liability, suicidal ideation, insomnia, alopecia, fever, transaminitis, anorexia, GI irritation (abdominal pain, nausea, diarrhea), arthralgias, myalgias, chills, and rash. Severe adverse reactions include: neuropsychiatric reactions, arrhythmia, cardiovascular decompensation, retinopathy resulting in blindness, hepatic failure, and can result in new or worsening of endocrinopathies.

Currently there are no known drug interactions, however, data suggest possible impairment of CYP2C9 (increased activity) and CYP2D6 (decreased activity). When combined with drugs with narrow therapeutic windows, it is recommend to monitor those drug levels frequently.

2.3 5-FU/Capecitabine

5-FU is an antineoplastic antimetabolite that blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, and in consequence, interferes with the synthesis of DNA and to a lesser extent RNA. Given the essential nature of DNA and RNA for cell growth, the generation of a thymine deficiency can result in cell death, most pronounced on rapidly growing cells, as found commonly in a variety of cancers[7].

In the US, 5-FU is given as a continuous infusion IV where it is partial excreted by the kidneys (20%) and the remainder is metabolized by the liver. Half-life is approximately 20 minutes and it can cross the blood-brain barrier. 5-FU is formally FDA approved in colorectal cancer, breast, stomach, and pancreatic cancers, but is widely used off label in a variety of cancers including mucosal squamous head and neck cancers and cutaneous squamous cell carcinomas.

Adverse events associated with 5-FU includes: stomatitis, nausea, diarrhea, neutropenia, neurotixicity, hand-foot syndrome, as well as risk of a hypersensitivity reaction in patients with a dipyrimidine dehydrogenase deficiency. 5-FU is teratogenic in lab animals and rated pregnancy class D.

Capecitabine,an oral pre-drug of 5-FU, was first approved for use in the United States by the FDA in 1988. It is presently approved for use in patients with metastatic breast cancer, both as monotherapy and in combination with docetaxel. It is also approved for both metastatic

colorectal cancer and as an adjuvant followers and resection of Dukes' Stage C colon cancer. Despite this rather limited FDA labeling, it is widely used both as a single agent and in combination for a multiplicity of other tumors including gastric, pancreatic, and squamous cell cancers of the head and neck.

While the standard FDA approved dose as listed in the package insert is 1250 mg per meter squared twice daily for two weeks followed by seven-day rest period, most clinicians have found this dose to be intolerable on a chronic basis. Therefore, it has become conventional to initiate dosing at 1000 mg per meter squared twice daily instead. The drug is presently available as Xeloda in two pill sizes, 150 mg and 500 mg. When the patent expires on Xeloda in 2013 is unclear when or if generic equivalents will become available and in what doses the pills will be manufactured. Should a generic version become available while this trial is open and accruing patients, the protocol will be modified accordingly.

The mechanism of action of capecitabine is conversion to 5-fluorouracil *in vivo*, occurring mostly in the liver. Cells subsequently metabolize 5- fluorouracil to FdUMP and FUTP. FdUMP inhibits thymidylate synthase, thereby decreasing pools of thymidine triphosphate available for DNA synthesis. FUTP can substitute for UTP during RNA synthesis, thereby disrupting protein synthesis from the abnormal RNA. Capecitabine is absorbed rapidly and conversion into 5-FU is rapid with peak levels reached within two hours post ingestion. Concomitant food consumption with capecitabine lowers both peak concentration and area under the curve concentration of capecitabine substantially. The elimination half-life of capecitabine and its metabolites is quite fast, on the order of approximately one hour. However, the cellular consequences of thymidylate synthase and RNA synthesis disruption are much more prolonged as they are dependent on regeneration of normal pools of the enzymes and RNA precursors.

Metabolism and bioactivation of capecitabine is hepatic, while excretion of capecitabine and its metabolites is predominantly accomplished by the kidneys with minimal fecal excretion. Therefore, dose adjustments for both renal insufficiency and hepatic insufficiency are warranted. In the case of mild renal impairment with a creatinine clearance greater than 50 mL/min, no dose adjustment is recommended. With moderate renal impairment (creatinine clearance 30-49 mL/min), a 20% dose reduction is recommended. While there is no defined dose adjustment for patients with hepatic dysfunction, caution should be used in administering capecitabine to patients with markedly abnormal hepatic function. Additional details on warnings and dose modifications for hepatic and renal dysfunction are available in the capecitabine package insert.

Common adverse events associated with capecitabine include diarrhea (stomatitis from gastrointestinal toxicity), coagulopathy, cardiotoxicity, fetal harm, hand-foot syndrome, hyperbilirubinemia, and bone marrow suppression, resulting in anemia, thrombocytopenia, and neutropenia.

There are known drug-drug interactions between 5-FU/capecitabine and coumadin anticoagulants, as well as 5-FU/capecitabine and phenytoin. While co-administration of these agents is not prohibited, frequent monitoring of prothrombin time and phenytoin levels in patients on concurrent 5-FU/capecitabine is warranted.

2.3 Rationale

There are no drugs presently approved by the US Food and Drug Administration for treatment of metastatic squamous cell carcinoma of the skin. However, several drugs are used off-label, based on a limited number of investigations in the medical literature. Prior case reports or case

studies have reported objective responses using cisplatin in combination with bleomycin, methotrexate, or doxorubicin[8-10]. Phase II data using retinoic acid and interferon-alpha alone or in combination with cisplatin demonstrated response rates of 34% and 43%, respectively[11,12]. A Phase I trial attempted to combine cis-retinoic acid, IFN alpha-2a, cisplatin, and 5-FU/Leucovorin; however, cytopenic toxicities limited the full administration of this regimen[13]. A more recent adjuvant Phase III trial in post-surgical patients with CSCC used cis-retinoic acid and interferon alpha versus observation, but failed to reduce the risk of recurrence[14].

Capecitabine has also been used against CSCC with modest response rates, but the data is reported as two case series[15,16]. In virtually every disease studied in which 5- fluorouracil is clinically active, capecitabine has demonstrated similar activity. Previously, we have treated a number of skin squamous cell carcinoma patients with capecitabine off-label and have noted dramatic and prolonged antitumor effects in a number of these patients. Additionally, we found that with the ease of titrating the oral doses of capecitabine, we could reduce drug toxicity, and patients were able to tolerate therapy for an extended period of time. Furthermore, the use of an oral agent may be favored by patients rather than an IV infusion.

Unfortunately, the studies discussed above suffer from small patient numbers, combined squamous and basal cell cohorts, and the demonstration of chemotherapy-induced toxicity. While no standard therapy exists for CSCC, we propose that a cytotoxic drug with documented response rates in CSCC combined with an immunomodulatory agent, also known to have benefit in this patient group, may result in overall improved response rates.

Therefore, we intend to conduct a phase II, single arm trial of interferon alpha-2b and 5-FU/capecitabine in patients with advanced or recurrent squamous cell carcinoma of the skin for which local regional treatment would not be expected to be curative. Because there is no known first line standard of care treatment for these patients and because of the known activity of 5-fluorouracil analogues and interferon-alpha in this disease, our intention is to allow patients to be treated in the first line with the combination of interferon alpha-2b and 5-FU/capecitabine without regard to prior chemotherapy, other than prior systemic treatment with 5-fluorouracil analogues.

It is our intention to use commercially available PEG interferon alpha-2b and 5-FU/capecitabine for this trial. Based on prior experience, a high percentage of these patients are able to attain these drugs for off-label use in this situation. However, we have found in some cases, insurance companies have been reticent to approve coverage for capecitabine. We believe that by generating data showing that capecitabine in combination with interferon alpha-2b is safe and effective in this group of patients, its use will become more widely accepted based on this proposed clinical trial as well as to provide continued support of the benefit of immunotherapy in this disease. For patients that are not approved for oral capecitabine, we will use continuous infusion 5-FU as described above.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed squamous cell carcinoma of the skin. Patients who present with “squamous cell carcinoma of unknown primary lesions” at the time of diagnosis will be eligible if patients have a plausible primary skin site removed in the past. Similarly, patients with neck, parotid, or facial lymph nodes positive for squamous cell carcinoma with no identifiable mucosal primary would also be eligible.

3.1.2 Patients must have measurable disease, defined by RECIST v1.1 as at least one lesion that can be accurately measured in at least one dimension of ≥10 mm by CT, MRI, or calipers. See section 9.2 for the evaluation of measurable disease.

3.1.3 There is no limitation to prior treatments with local, regional, topical or systemic agents, except for prior systemic treatment with 5-fluorouracil or prodrugs thereof. Prior topical treatment with 5-fluorouracil is permitted. Patients who are on chronic daily doses of prednisone of greater than 10 mg are excluded. There is no restriction on timing of last treatments as long as patients have recovered from all expected toxicities and at least 21 days have passed since last administration.

3.1.4 Age >=18 years. Because no dosing or adverse event data are currently available on the use of 5-FU/Capecitabine or IFN alpha-2b in patients <18 years of age, children are excluded from this study.

3.1.5 Life expectancy of greater than 3 months.

3.1.6 ECOG performance status <=2 (Karnofsky >=60%; see Appendix A).

3.1.7 Patients must have normal organ and marrow function as defined below:

Absolute neutrophil count	>=1,500/mcL
Platelets	>=75,000/mcL
Total Bilirubin	< ULN or up to 2x ULN if patient has clinically documented Gilbert's syndrome (elevated unconjugated bilirubin from decreased UGT1A1 activity)
AST(SGOT)/ALT(SGPT)	≤2.5x institutional upper limit of normal or up to 5x ULN if known to be caused by liver metastasis
Creatinine Clearance	>=50 mL/min by either Cockcroft-Gault formula or 24 hr urine collection analysis.

3.1.8 Patients must not be candidates for curative locoregional treatments. Patients with recurrent locoregional disease following surgery and/or radiation for who a resection is unacceptably morbid and unlikely to be curative are eligible. Patients must be reviewed at the Moffitt Cutaneous Tumor Board prior to enrolling on trial to verify unresectability.

3.1.9 The effects of 5-FU/Capecitabine and IFN alpha-2b on the developing

human fetus at the recommended therapeutic dose are unknown. For this reason and because anti-metabolites are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 21 days (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to either 5-FU/Capecitabine or Interferon.

3.2.5 Uncontrolled, ongoing illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction <30 days, CVA/TIA <30 days, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Pregnant women are excluded from this study because 5-FU/Capecitabine is *an anti-metabolite* agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with 5-FU/Capecitabine, breastfeeding should be discontinued if the mother is treated with 5-FU/Capecitabine. Pregnancy testing will be completed on all female participants of child-bearing potential by urine analysis.

3.2.8 Any heart or lung transplant patient on immunosuppressive agents. Renal transplant patients are allowed if patient is willing to reduce immunosuppressive agents and understand risk of rejection and possible need to return to dialysis. Patients with CLL or other hematologic malignancies are allowed as long as they meet other criteria listed above.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

3.4 Patient Registration

Once clinical eligibility is confirmed, patients must sign an informed consent prior to registration indicating awareness of the investigation nature of the study and its inherent risks in keeping with the policies of the hospital and Federal regulations (Code of Federal Regulations Part 1X, Subpart B, Sections 50.20-50.27).

3.5 Removal of Patients From Study

- Patients may be removed from the study for any of the following reasons:
  - Progression of disease
  - Significant protocol violation
  - Patient non-compliance: defined as any deviation from the protocol without prior agreement of the principal investigator
  - Investigator non-compliance: defined as any significant medical or non-medical deviation from the protocol without agreement of the sponsor
  - Patient's request to withdraw from the study or refusal of further therapy
  - Unacceptable toxicity. A patient may be removed from the study for any complication of treatment that the investigator feels is life threatening.
  - If patient does not meet eligibility criteria

4. TREATMENT PLAN

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Interferon alpha-2b and 5-FU/Capecitabine are available commercially and a commercial supply will be used for this study.

4.1 Capecitabine Administration

Drug administration will be on an outpatient basis. Capecitabine will be administered at an initial dose of 800 mg/m2 by mouth twice daily on days 1-14 of a 21 day cycle with days 15-21 off. This cycle will be repeated every 21 days during the study for a maximum of 9 cycles as tolerated. Administration via feeding tube in patients unable to swallow is permitted. For severe side effects, dose reductions are listed in Table 5. Reported adverse events and potential risks are described in Section 6.

Capecitabine tablets should be swallowed with water within 30 min after a meal. The calculated dose by body surface area (BSA) will be rounded down to allow as close to as total daily dose of 1600 mg/m2 divided as closely as possible into AM and PM doses of 800 mg/m2 using a combination of 150 mg and 500 mg tablets. There will be no modification of BSA calculation based on idealized body weight or other corrective factor.

4.1.1 Storage: Capecitabine tablets should be kept a room temperature

4.1.2 Pill Diary: The patient will be requested to maintain a medication diary for review at the end of each cycle of treatment and reconciled with a pill count.

If the patient is clinically stable after 3 cycles, then a diary review and pill counts may be discontinued.

4.1.3 Supportive Care Guidelines

Capecitabine has a low emetogenic potential. Routine anti-emetics are not recommended but may be used at the treating physician's discretion. Standard use of anti-diarrheal agents is permitted.

4.2 5-FU Administration

If patients are not able to acquire oral capecitabine, then we will start patients on infusional 5-FU which can be delivered via standard of care. Patients will need to have a port placed for continuous infusion treatments. 5-FU pumps will be activated in the infusion center at Moffitt Cancer Center with a starting dose of 800 mg/m2 days 1-4, with pump removal on day 5 at the infusion center. 5-FU pumps will be attached every 21 days (1 cycle) for a maximum of 9 cycles. For severe side effects, dose reductions are listed in Table 5. Reported adverse events and potential risks are described in Section 6.

4.2.1 Storage

Drug stored in pharmacy per manufacturer's instructions.

4.2.2 Supportive Care Guidelines

5-FU has a low-medium emetogenic potential. Routine anti-emetics may be used at the treating physician's discretion. Standard use of anti-diarrheal agents is permitted.

4.3 Interferon Administration

Drug administration will occur on an outpatient basis at the infusion center at Moffitt Cancer Center. Dose will be weight-based. Starting treatment doses of 3 mcg/kg will be given SC injection in the thigh, abdominal wall, or upper arm every week for a total of 27 weeks as tolerated. Patients will be premedicated with 650 mg of acetaminophen or 400 mg of ibuprofen as tolerated. For severe side effects, dose reductions are allowed as discussed in Section 5. Reported adverse events and potential risks are described in Section 6.

4.3.1 Storage: Drug stored in pharmacy per manufacturer's instructions.

4.3.2 Supportive Care Guidelines

Anti-pyrectics such as ibuprofen and acetaminophen can be used as directed to manage low grade fevers and muscle/joint pains. Anti-nausea and anti-diarrheal agents can be used at the treating physician's discretion.

4.4 **Duration of Therapy**

In the absence of treatment delays due to adverse event(s), treatment may continue for 9 cycles or until one of the following criteria applies:

- X Disease progression,
- X Concurrent illness that prevents further administration of treatment,
- X Unacceptable adverse event(s),
- X Patient decides to withdraw from the study, or

X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.5 Duration of follow up

Patients will be followed for up to one year after removal from study or until death. Patients removed from the study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1 5-FU/Capecitabine

A dose reduction will be instituted upon any grade 3 or 4 toxicity that is attributable to 5-FU/capecitabine. For all grade 3 or 4 toxicities related to 5-FU/capecitabine, the study treatment will be withheld for up to 3 weeks until the toxicity has resolved to CTCAE grade 1 or better (or back to baseline), and then treatment may be restarted. Dose reduction/re-challenge for each toxicity criterion will be managed as discussed in the sections that follow. Patients will be withdrawn from the study if toxicity does not resolve to ≤ CTCAE grade 1 (or to baseline) within 3 weeks.

Myelosuppression

On Day 1 of each cycle, if the neutrophil count is < 1000/mm^3, or the platelet count is < 75,000/mm^3, then treatment with 5-FU/capecitabine will be held until the neutrophil count is ≥ 1000/mm^3, and platelet count is ≥ 75,000/mm^3. Once restarted, 5-FU/Capecitabine will be dose reduced per Table 1. If treatment is required to be held for ≥ 3 weeks, then study treatment will be discontinued.

GI Toxicity

Nausea, vomiting, or both may be controlled with antiemetic therapy. Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits.

Dose modifications for **diarrhea** will be as follows:

If ≥ grade 3 diarrhea refractory to oral anti-diarrheal medication occurs, treatment will be held until the toxicity is < grade 2, then the 5-FU/capecitabine dosage will be reduced according to Table 2 shown below. If treatment must be withheld for more than 3 weeks for resolution of diarrhea, the patient will not restart treatment and the patient will be withdrawn from the study.

Mucositis or Hand/Foot Syndrome (HFS)

If ≥ grade 3 mucositis or HFS occurs, 5-FU/capecitabine will be interrupted for a minimum of 1 week. If the toxicity has not improved to < grade 2, the treatments will be held for up to 2 additional weeks. Once restarted, the dose of capecitabine will be reduced according to Table 2. If treatment is required to be held for ≥ 3 weeks, then study treatment will be discontinued.

Other toxicities

If ≥ grade 3 toxicities directly attributable to 5-FU/capecitabine other than those discussed above occur (except fatigue, alopecia, or nausea/emesis in the absence of anti-emetics), therapy will be discontinued until the toxicity is < grade 2. If there is no evidence of tumor

progression, therapy may resume with a dose reduction according to Table 1. If treatment is required to be held for ≥ 3 weeks, then study treatment will be discontinued.

TABLE 1: Capecitabine dose levels

Dose Level	5-FU/***Capecitabine*** **Dose**
-2	*400 mg/m2 per 21 day cycle*
-1	*600 mg/m2*
0 (starting dose)	*800 mg/m2*

5.2 Interferon Alpha-2b

A dose reduction will be instituted upon any grade 3 or 4 toxicity that is attributable to Interferon alpha-2b. For all grade 3 or 4 toxicities related to IFN, the study treatment will be withheld for up to 3 weeks until the toxicity has resolved to CTCAE grade 1 or better, and then treatment may be restarted. Dose reduction/re-challenge for each toxicity criterion will be managed as discussed in the sections that follow. Patients will be withdrawn from the study if toxicity does not resolve to ≤ CTCAE grade 1 within 3 weeks.

Fatigue

If patient complains of severe fatigue (>gr3), IFN will be held for the remained for the cycle. Upon starting the next cycle, patient will be placed in the dose "-1" group and managed according to table 2. If patient is unable to receive IFN for greater than 3 weeks, they will be withdrawn from the study.

Arthralgias/Myaglias

Pain management will initially be done with acetaminophen or ibuprofen as tolerated, or opiates as indicated. For severe toxicity, IFN will be held for 3 weeks and dose reduced according to Table 2. If not resolved to CTCAE grade 1 or better, patient will be removed from the study.

Weightloss

If patient weightloss occurs >10% of initial body weight, then IFN alpha will be held for 3 weeks. Weight gaining medications such as megace, marinol, and mirtazapine are acceptable. Patients will be dose reduced according to Table 2. If weight does not stabilize or start to recover within 3 weeks, patients will be withdrawn from the study

Depression

For moderate depression grade 1 or 2, patients may be started on SSRI therapy as necessary. Any acute grade 3 or 4 reaction (psychosis, mania, suicidal ideation), IFN alpha will be stopped for 3 weeks. Patients can be restarted at reduced doses according to Table 2. If toxicities do not resolve to CTCAE grade 1 or better within 3 weeks, patients will be withdrawn from the study. Referral for acute hospitalization or psychiatric consultation will be placed for any life-threatening events.

GI Toxicity

Nausea, vomiting, or both may be controlled with antiemetic therapy. Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits. For persistent Gr3/4 adverse events, pt will be dose reduced according to Table 2.

TABLE 2: IFN alpha-2b dose levels

Dose Level	IFN alpha-2b
-2	*1 mcg/kg SQ q week per 21 day cycle*
-1	*2 mcg/kg SQ q week per 21 day cycle*
0 (starting dose)	*3 mcg/kg SQ q week per 21 day cycle*

6. PHARMACEUTICAL INFORMATION

5-FU/Capecitabine and IFN are commercially available and will be used from commercial suppliers.

6.1 Expected potential toxicities of 5-FU/Capecitabine:
Hematologic: anemia, neutropenia, thrombocytopenia
Constitutional: fatigue, pyrexia, edema, pain, chest pain
Dermatologic: hand-foot syndrome, dermatitis, skin discoloration, alopecia, nail disorders
Gastrointestinal: diarrhea, nausea, vomiting, stomatitis, abdominal pain, gastrointestinal motility disorder, constipation, oral discomfort, upper GI inflammatory disorders, gastrointestinal hemorrhage, ileus
Hepatic: hyperbilirubinemia
Infections: bacterial or viral
Metabolic: appetite decreased, dehydration
Musculoskeletal: back pain, arthralgia
Neurologic: peripheral sensory neuropathy, headache, dizziness, insomnia, taste disturbance
Ocular: eye irritation, vision abnormal
Psychiatric: mood alteration, depression
Pulmonary: dyspnea, cough, pharyngeal disorder, epistaxis, sore throat
Vascular: venous thrombosis
Cardiac: myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy.
Dihydropyrimidine Dehydrogenase Deficiency: Rarely, unexpected, severe toxicity (eg, stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity.

6.2 Expected potential toxicities of IFN alpha-2b:
General: "Influenza-like" symptoms (mainly fever, headache, chills, myalgia, and fatigue)
Gastrointestinal: anorexia, nausea, diarrhea, vomiting, altered taste, abdominal pain, constipation, gingivitis, loose stools, dyspepsia
Hepatic: elevated SGOT, right upper quadrant pain
Psychiatric: depression, anxiety, nervousness
Dermatologic: alopecia, rash, pruritus, dry skin, dermatitis, hair discoloration
Respiratory: dyspnea, coughing, pharyngitis, sinusitis, nonproductive cough, nasal congestion, and bronchitis
Nervous system: headache, somnolence, dizziness, irritability, paresthesia, impaired concentration, amnesia, confusion, insomnia, hypoesthesia, vertigo, and decreased libido

Musculoskeletal: myalgia, musculoskeletal pain, and arthralgia
Immunologic: nonspecific infection, viral infection, and herpes simplex
Hematologic: neutropenia, anemia, thrombocytopenia, bleeding, and purpura
Genitourinary: Amenorrhea, polyuria
Cardiovascular: hypertension. Angina, arrhythmia, atrial fibrillation, bradycardia, cardiac failure, cardiomegaly, cardiomyopathy, coronary artery disorder, extrasystoles, heart valve disorder, hematoma, hypotension, palpitations, phlebitis, postural hypotension, pulmonary embolism, Raynaud's disease, tachycardia, thrombosis, and varicose vein have been reported in less than 5% of patients.
Endocrine: aggravation of diabetes mellitus, goiter, hyperthyroidism, and hypothyroidism in less than 5% of patients.
Metabolic: Hypertriglyceridemia, dehydration, hypercalcemia, hyperglycemia, and
Ocular: Ocular side effects have included abnormal vision, blurred vision, diplopia, dry eyes, eye pain, lacrimal gland disorder, lacrimation, nystagmus, and photophobia in less than 5% of patients.
Renal: increased BUN and renal insufficiency in less than 5% of patients.
Hypersensitivity: Hypersensitivity side effects have included allergic reaction
Local: injection site inflammation

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse Event: Any untoward medical occurrence in a patient of clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment. An adverse event (AE) can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Event Characteristics:

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Hematologic and metabolic toxicities of Grade 1 and 2 will not be reported.

Expedited Serious Adverse Event (SAE) Reporting:

A SAE is any sign, symptom or medical condition that emerges during treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling

- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

All SAEs should be recorded on a MedWatch 3500a Form and delivered to:

The study coordinator will submit the SAE for review to the PI and to the institutional IRB (per the SOP of the Moffitt Cancer Center clinical trials office).

Routine Adverse Event Reporting

All adverse events **must** be reported in routine study data submissions using the data forms completed for each cycle of 5-FU/capecitabine and IFN treatment for entry by the study coordinator into the Oncore system.

8. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 week prior to administration of protocol therapy. Scans and x-rays must be done <=4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Estimated time per treatment visit is 1 hour.

		Cycle 1			Cycle 2			Cycle 3			
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Off Study[c]
Capecitabine		X	X		X	X		X	X		
5-FU[d]		**X**			**X**			**X**			
IFN alpha-2b		X	X	X	X	X	X	X	X	X	
Informed consent	X										
Pregnancy Testing	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X									
Physical exam	X	X			X			X			X
Vital signs[a]	X	X			X			X			X
Height	X										
Weight	X	X			X			X			X

ECOG/Performance status	X	X			X			X			X
CBC w/diff	X	X			X			X			X
Serum chemistry[b]	X	X			X			X			X
EKG (as indicated)	X										
Adverse event evaluation		X----------X									X
Tumor measurements	X	Tumor measurements and imaging are repeated every *nine* weeks. Documentation must be provided for patients removed from study for progressive disease. If treatment is held for adverse event recovery thereby extending cycle length, then imaging and tumor measurement intervals may be correspondingly altered so that the patient is imaged every third cycle.									
Radiologic evaluation	X										

a= Blood Pressure, Heart Rate (Pulse), Temperature,
b= Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, , potassium, total protein, SGOT[AST], SGPT[ALT], sodium
c= Off-study evaluation to be conducted within 30 days of last dose (+/- 7 days).
d= patients will be on either 5-FU infusion treatments or capecitabine, not both

9. MEASUREMENT OF EFFECT

Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for **response every *nine* weeks.** If treatment is held for adverse event recovery thereby extending cycle length, then imaging and tumor measurement intervals may be correspondingly altered so that the patient is imaged every third cycle.

9.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with conventional techniques (CT, MRI, x-ray). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis,, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

9.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

9.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.2 Guidelines for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require

specific protocols.

9.3 Response Criteria

9.3.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

9.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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

9.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 9.3.1).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR

CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:
1) Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration."

2) In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 9 weeks (see section 9.3.3).

9.4.2 Duration of overall response

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

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

9.4.3 Duration of Stable Disease

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

9.5 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10. REGULATORY AND REPORTING REQUIREMENTS

10.1 Expedited Adverse Event Reporting

The PI of this study has primary responsibility for the overall study, including patient welfare, data integrity, and monitoring of adverse events.dverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

10.2 Data Reporting

10.2.1 Institutional Review Board

The protocol, the proposed informed consent, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the IRB and Moffitt Cancer Centers' Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators. No subject is to be enrolled on this protocol until the Center's Institution Review Board has approved it.

10.2.2 Data Reporting

Moffitt Cancer Center's Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

10.2.3 Informed Consent

The investigator is responsible for patient care and for obtaining consent by the patient. Written informed consent must be obtained prior to entry of any patient.

10.2.4 Hospital/Clinic Records

Hospital records for patients on this study are the responsibility of the investigator. They will be available for review by the sponsors of the trial, health care personnel involved in this study, the IRB, DHHS, and the FDA.

10.2.5 Investigator Study Files

The Principal Investigator is responsible for maintaining study files for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. The following documents should be kept in the study files:

A completed, signed FDA Form 1572 (Statement of Investigator) and copies of all current curricula vitae of all sub investigators listed on the Statement of the Investigator.

- The original protocol and all amendments
- Final IRB approval, annual renewals and all IRB correspondence
- Blank Case Report Forms
- Copy of all IRB approved Informed Consent forms with applicable version date
- Updated laboratory certification and laboratory values (covering entire time of study)
- Copy of all patient's signed informed consent forms
- The final completed case report form for all patients

10.2.6 **Data Management Plan**

Electronic case report forms for specified protocol related information on each trial patient, using the Oncore system, will be created. Electronic data will be kept secure within the Oncore password protected system. Paper copies of the documentation from the medical record which support the data entered into Oncore will be kept in patient specific binders in a secure, locked, and HIPPA compliant environment.

10.3 **Reporting and Exclusions**

Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with 5-FU/capecitabine and IFN alpha-2b. Adverse events that occur during screening will not be captured. Adverse events will only be captured until 30 days after the last dose of any investigational drug.

11. STATISTICAL CONSIDERATIONS

11.1 Study Endpoints

11.1.1 Primary Objective

To establish the objective response rate to IFN alpha-2b and 5-FU/capecitabine using RECIST criteria in patients with unresectable/metastatic CSCC after 3 cycles of treatment (9 weeks).

11.1.2 Secondary Objective

To establish the progression free survival (PFS), overall survival (OS), and safety profile (AEs) of the combination of IFN alpha-2b and 5-FU/capecitabine in this patient population at 6 months and 1 year.

11.2 Statistical Design

This is a single arm, Phase II trial using a Simon's two-stage design to evaluate the RECIST response rate to 5-FU/capecitabine and interferon alpha-2b in patients with

unresectable or metastatic squamous cell carcinoma of the skin after 3 cycles of treatment[17,18]. Patients must have received at least one cycle of 5-FU/capecitabine and PEG-IFN alpha in order to be evaluable for response. We wish to distinguish between a response rate of 10%, which would be uninteresting, and a response rate of >30%, which would merit further testing. Choosing an alpha type error probability of 0.1 and a beta type error probability of 0.1 would mean that in order to proceed beyond the first stage, at least 2 of first 16 patients would have to have responses, and at least 5 of 25 patients (statistics based on 25 evaluateable patients with a total enrollment of 30 patients) would have to respond in order declare this a regimen of interest.

11.3 Sample Size/Accrual Rate

We anticipate enrolling 1 patient every 1-2 two months for approximately 6-12 patients per year. We would like to enroll a total of 30 evaluable patients on trial for robust statistical analysis and to allow for a 20% drop out rate. Enrollment would occur over a three-year period to achieve the enrollment goals.

11.4 Analysis of Secondary Endpoints

Overall survival (OS) (the time from registration to death or date of last contact) and progression free survival (PFS) (patients alive without RECIST progression) are secondary objectives of the study. Kaplan-Meier estimates of overall and progression-free survival rates will be calculated, along with their corresponding 95% confidence intervals. The median, 6-month and 12-month overall and progression free survival rates will be estimated. Adverse events will be collected according the study calendar and tabulated for cumulative evaluation.

[redacted]

[redacted]

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