A Phase II Study of Total Skin Electron Beam Therapy (TSEBT) to dose of 12 Gy in stage IB-IIIA mycosis fungoides

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Agent: Total skin electron beam therapy

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**PROTOCOL SYNOPSIS**

<table>
<thead>
<tr>
<th>TITLE</th>
<th>Total Skin Electron Beam Therapy (TSEBT) to 12 Gy in mycosis fungoides (MF)</th>
</tr>
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<tbody>
<tr>
<td>STUDY PHASE</td>
<td>Phase II</td>
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<tr>
<td>INDICATION</td>
<td>Stage IB-IIIA MF</td>
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<tr>
<td>PRIMARY OBJECTIVES</td>
<td>To determine clinical response rate of TSEBT 12 Gy in IB-IIIA MF</td>
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</table>
| SECONDARY OBJECTIVES                                               | To determine: 1) duration of response and time to progression  
|                                                                 | 2) pruritus response and  
|                                                                 | 3) safety and tolerability of TSEBT 12 Gy in IB-IIIA MF | |
| HYPOTHESES                                                         | TSEBT 12 Gy produces clinically meaningful outcomes in IB-IIIA MF and is associated with minimal toxicities |
| STUDY DESIGN                                                       | Phase II, single arm, open-label study                                         |
| PRIMARY ENDPOINTS AND SECONDARY ENDPOINTS                         | Primary: objective response rate  
|                                                                 | Secondary: time to response, duration of response, time to progression, assessment of pruritus, frequency and severity of adverse events |
| SAMPLE SIZE BY TREATMENT GROUP                                      | 36 patients                                                                    |
| SUMMARY OF SUBJECT ELIGIBILITY CRITERIA                            | Inclusion Criteria  
|                                                                 | 1. Biopsy-confirmed mycosis fungoides in stage IB-IIIA  
|                                                                 | 2. Patients must have failed or have been intolerant to at least one prior systemic or topical therapy which may include topical steroids  
|                                                                 | 3. 18 years of age or older  
|                                                                 | 4. Life expectancy greater than 6 months  
|                                                                 | 5. Eastern Cooperative Oncology Group (ECOG) of ≤ 2  
|                                                                 | 6. Adequate bone marrow function: WBC> 2000/uL; platelet count> 75,000/mm3; ANC> 1000  
|                                                                 | 7. Required wash out period for prior therapies (Note: patients with progressive disease may be treated earlier than required washout period per Investigator’s decision)  
|                                                                 | • Topical therapy: 2 weeks  
|                                                                 | • Systemic biologic, monoclonal antibody or chemotherapy: 4 weeks  
|                                                                 | • Radiotherapy (excluding TSEBT) or phototherapy: 4 weeks  
|                                                                 | • Other investigational therapy: 4 weeks  
|                                                                 | 8. Ability to understand and the willingness to sign a written informed consent document.  
| Exclusion Criteria                                            |                                                                                                                                 |

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1. Prior courses of TSEBT (Note: localized skin-directed radiotherapy is allowed if administered at least 4 weeks prior to initiation on study)
2. Underlying medical condition including unstable cardiac disease, or other serious illness that would impair the ability of patient to undergo treatment
3. Prior malignancy (active within 5 years of screening) except completely excised non-invasive basal cell or squamous cell carcinoma of the skin, or *in situ* squamous cell carcinoma of the cervix
4. Pregnant or lactating
5. Initiation or change in dosage of topical corticosteroids within 3 weeks of study treatment (Note: topical steroid use within 3 weeks is allowed provided the strength and use has been stable for at least 1 month; “prescription strength”topical corticosteroids cannot be started during the study)
6. Any other medical history, including laboratory results, deemed by the Investigator to be likely to interfere with patient participation in the study

<table>
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<th>INVESTIGATIONAL PRODUCTS DOSAGE AND ADMINISTRATION</th>
<th>Total skin electron beam therapy (TSEBT) to total dose of 12 Gray (Gy)</th>
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<td>CONTROL GROUP</td>
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<td>STATISTICAL CONSIDERATIONS</td>
<td>Two-stage design: interim analysis will be performed when 12 patients have been observed for at least 2 months and are evaluable for response. If at least 6 have responded then trial will continue to accrue for a total of 36 patients.</td>
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1. OBJECTIVES

1.1. Primary Objectives

To determine clinical response rate to total skin electron beam therapy to a total dose of 12 Gray (TSEBT 12 Gy) in subjects with stage IB-IIIA mycosis fungoides (MF).

1.2. Secondary Objectives

1.2.1. To determine duration of response and time to progression following course of TSEBT 12 Gy.
1.2.2. To determine pruritus response
1.2.2. To evaluate safety and tolerability of TSEBT 12Gy.

2. BACKGROUND

2.1 Study Disease

Mycosis fungoides (MF) and its leukemic variant, Sezary Syndrome, are extranodal non-Hodgkin’s lymphomas of CD4+ T-cell origin with primary cutaneous involvement. They comprise the most common of the cutaneous T-cell lymphomas, which have an overall annual incidence of approximately 6.4 per 1000,000 persons in the United States [1]. MF has a 2:1 male to female and has a peak age at presentation of 55 to 60 years, although it is rarely seen in the young (i.e. <35 years of age) with a similar presentation and disease course [2]. The cutaneous manifestations of MF are quite heterogeneous: patches and plaques in early disease, tumors and generalized erythroderma in more advanced disease. Staging of MF is based on a tumor-node-metastasis-blood (TNMB) classification system first developed and published by National Cancer Institute (NCI) in 1979 with recent revisions proposed via a joint report by International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) [3, 4]. The overall clinical stage is an important independent prognostic indicator as are the T classification (i.e. extent and type of skin involvement), presence of extracutaneous disease, and patient’s age. Other factors associated with poor prognosis include large cell transformation, high Sezary count, elevated LDH and peripheral eosinophilia, among others. The indolent nature of early stage MF is well-established, with life expectancy similar to that of a matched control population. On the other hand those who either present with or progress to have extracutaneous disease (i.e. stage IV) have poor outcomes, with median survivals of 1.5-3 years [5].

The therapeutic options for MF and Sezary syndrome are on a broad spectrum utilizing several modalities. The selection of a specific treatment regimen is made primarily on the basis of patient’s clinical stage. The National Comprehensive Cancer Network (NCCN) has recently published consensus guidelines for stage-adapted treatment of MF/SS which are followed by major institutions including Stanford University. In general the first line treatment of early stage MF (IA, IB, and IIA) consists of skin-directed therapies which include phototherapy, topically applied medications (including corticosteroids, chemotherapeutic agents, and retinoids), and
radiation therapy. At more advanced stages (i.e. IIB and higher) systemic therapies are often the mainstay of treatment. These include bexarotene, vorinostat, interferons, extracorporeal photopheresis, denileukin difitox, traditional chemotherapeutic agents (such as methotrexate, doxorubicin, gemcitabine, and chlorambucil among others), and new array of investigational agents. Furthermore, a number of combination therapies including skin-directed plus systemic as well as combination systemic agents have also been utilized for advanced or refractory disease [6]. Despite a wide array of available therapeutic options, MF remains incurable and the aim of therapy remains achievement of clinically meaningful responses, palliation of symptoms/improvement in quality of life, and prolongation of disease/progression-free and overall survival (OS).

2.2 Investigational Agent/Device/Procedure

Total skin electron beam therapy involves administration of ionizing radiation to the entire skin surface. At Stanford this treatment modality is utilized in accordance with NCCN guidelines and is thus offered as first line treatment for patients with T2 (generalized patch/plaque) and T3 (tumor) classified disease [7]. The efficacy and safety of conventional TSEBT (i.e. doses ≥ 30 Gy administered in 1.5-2 Gy fractions per 2-day cycles) in producing high clinical response rates in MF is well-documented through several retrospective reviews of large clinical cohorts over the past two decades [8-10]. In a recent retrospective review of the cohort of patients with T2 and T3-classified MF treated at Stanford with TSEBT doses ≥ 30 Gy an overall response rate of 100% was observed (i.e. all patients experienced ≥ 50% improvement in skin involvement) [11]. The complete clinical response (CCR) rate of this cohort was 60% (72% for T2 and 44% for patients with T3 disease) [11]. This is in line with CCR rates of approximately 80 to 90% for patients with T2 disease and 50-100% for patients with T3 disease reported by other major treating institutions using conventional doses of TSEBT [12]. Notably prior studies have demonstrated a dose-response relationship with TSEBT in treatment of MF. Published data from Stanford, for instance, showed a CCR rate of 18% for doses ≤ 10 Gy, 55% for doses of 10-20 Gy, 66% for doses 20-25 Gy, 75% for doses 25-30 Gy, and 94% for doses ≥ 30 Gy [13]. Furthermore, the Stanford data have shown an improvement in response duration with higher total doses of TSEBT. [13,14]. These and similar findings from other large retrospective studies have led to the general adoption of TSEBT ≥ 30 Gy as the standard prescribed dose by major treating institutions and endorsed by EORTC as part of their consensus guidelines [15].

2.3 Rationale

Despite this high efficacy of conventional TSEBT, responses are transient in nature and the majority of patients experience an eventual recurrence of their disease following completion of their TSEBT course. For the Stanford cohort, for instance, the median freedom from relapse (FFR) in complete responders was 29 months for patients with T2 disease and 9 months for patients with T3 disease although the progression free survival (defined as increase in TNMB stage or death) in all responders was 8.5 years for T2 patients and 2.9 years for T3 patients [11]. In addition, TSEBT is associated with significant side effects and the treatment is inconvenient for many patients due to the duration of therapy (4 days per week for 9-10 weeks). Patients develop acute erythema, with occasional blistering. They experience near complete (and often permanent) alopecia. They lose their fingernails and toenails (although they regrow). Patients
develop abnormal sweat patterns and may suffer from chronic xeroderma. These effects are dose-related.

In an attempt to prolong disease-free interval as well as PFS, several studies have investigated the use of agents known to be active in MF as adjuvants to TSEBT. Previously, we reported the Stanford results using adjuvant topical nitrogen mustard in patients receiving TSEBT as initial management of their T2 and T3 mycosis fungoides [8]. Other investigators have reported outcomes with the use adjuvant IFN-alpha [16], PUVA [10], oral etretinate [17], extracorporeal photophoresis [18], and systemic chemotherapy [19]. The reported outcomes are mixed and there is no consensus on the role of these agents as adjuvants.

An alternative radiation-based treatment strategy would center on utilization of lower than conventional doses of TSEBT. The advantage of such a regimen is reduction of radiation-induced toxicities, allowing more frequent re-treatment to extend the duration of benefit of total skin irradiation over a longer time span. Recently Kamstrup et al. reported on a prospective study of TSEBT at total doses of 4 Gy in stage IB-II MF previously treated with PUVA [20]. Of the 10 treated patients 2 achieved CCR and 6 achieved PR. Responses, however, were short-lived with median time to relapse of 2.7 months. In an attempt to identify a lower than conventional dose-range of TSEBT with a more favorable clinical outcome profile than previously reported, we recently updated the long-term experience at Stanford utilizing TSEBT at doses \( ≤ 30 \) Gy (data not yet published). While we confirmed a general trend toward improved response with increasing doses, some of the outcome measurements were not significantly different between the >10-20 Gy cohort and >20-30 Gy cohort. For example, in the T2 subgroup CCR rate was 41% in the >10-20 Gy cohort vs. 44% in the >20-30 Gy cohort while PR rate was 59% vs. 56% in the two cohorts, respectively. Similar outcomes were seen with the T3 subgroup. Importantly the overall response (OR) rates for the >10-20 Gy cohort were 100% for the T2 and 97% for the T3 subgroups, compared to 87% and 94% in the 5-10 Gy cohort. We also noted a significant prolongation of FFR among complete responders in the >10-20 Gy cohort compared to the 5-10 Gy cohort (FFR of 30 mo vs. 12 mo, p= 0.02). Finally, we attempted to analyze a clinically relevant “duration of benefit”, which we defined as the interval between completion of TSEBT and initiation of another systemic or total skin-directed therapy. Here we again noted a significantly longer outcome in the >10-20 Gy vs. 5-10 Gy cohort (96 mo vs. 11 mo, p= 0.02).

In light of these findings there is sound rationale to explore further the outcomes of low dose (>10-20 Gy) TSEBT.

In this study we aim to examine prospectively the clinical outcomes of 12 Gy TSEBT in the treatment of mycosis fungoides. This dose was selected based on the data noted above. In addition, this dose of TSEBT may be administered over a period of just 3 weeks, a convenient duration of therapy for patient participation. We hypothesize that this is an adequate dose to achieve clinically meaningful outcomes while minimizing radiation-associated toxicities.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix B.

3.1 Inclusion Criteria
3.1.1 Biopsy-confirmed mycosis fungoides in stage IB-IIIA

3.1.2 Patients must have failed or have been intolerant to at least one prior systemic or topical therapy which may include topical steroids

3.1.3 18 years of age or older

3.1.4 Life expectancy greater than 6 months

3.1.5 Eastern Cooperative Oncology Group (ECOG) of ≤ 2

3.1.6 Adequate bone marrow function: WBC> 2000/uL; platelet count> 75,000/mm3; ANC> 1000

3.1.7 Required wash out period for prior therapies (Note: patients with progressive disease may be treated earlier than required washout period per Investigator’s decision)
  - Topical therapy: 2 weeks
  - Systemic biologic, monoclonal antibody or chemotherapy: 4 weeks
  - Radiotherapy (excluding TSEBT) or phototherapy: 4 weeks
  - Other investigational therapy: 4 weeks

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

3.2 Exclusion Criteria

3.2.1 Prior courses of TSEBT (Note: localized skin-directed radiotherapy is allowed if administered at least 4 weeks prior to initiation on study)

3.2.2 Underlying medical condition including unstable cardiac disease, or other serious illness that would impair the ability of patient to undergo treatment

3.2.3 Prior malignancy (active within 5 years of screening) except completely excited non-invasive basal cell or squamous cell carcinoma of the skin, or in situ squamous cell carcinoma of the cervix

3.2.4 Pregnant or lactating

3.2.5 Initiation or change in dosage of topical corticosteroids within 3 weeks of study treatment (Note: topical steroid use within 3 weeks is allowed provided the strength and use has been stable for at least 1 month; “prescription strength” topical corticosteroids cannot be started during the study)

3.2.6 Any other medical history, including laboratory results, deemed by the Investigator to be likely to interfere with patient participation in the study
3.3 **Informed Consent Process**

Patients who may be eligible for the trial will be approached by the Investigatory and offered participation in the trial. The Investigator or co-Investigator will explain the study to the potential subject verbally, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation, etc.), and will allow the potential subject ample opportunity to ask questions. Following this verbal explanation, the potential subject will be provided with the IRB approved informed consent form and will be afforded sufficient time to consider whether or not to participate in the study. After allowing the potential subject time to read the consent form, the investigator or approved designee (study coordinator) will answer any additional questions the potential subject may have and will obtain the subject’s signature on the consent form. The investigator or designee will also sign the consent form. A signed copy of the consent form will be given to the patient, scanned into the medical record per Stanford Cancer Clinical Trials office Standard Operating Procedures. Before any protocol-specified procedures are conducted, each prospective participant must provide informed consent.

4. **TREATMENT PLAN**

4.1 **Investigational Agent or Device Administration**

4.1.1 **Screening Period:**

Screening will take place up to four weeks prior to initiation of TSEBT course. Studies to evaluate the extent of tumor burden may be performed up to 6 weeks prior to TSEBT initiation.

Patients will undergo the following procedures during the screening period:

- Written informed consent
- Medical history and physical exam, including vital signs, weight, ECOG status, and medication history
- Physical exam to assess baseline skin disease according to the modified Severity Weighted Assessment Tool (mSWAT)
- Simulation/set-up for TSEBT in the Department of Radiation Oncology
- Hematology: CBC with differential
- If clinically indicated, determination of peripheral blood Sezary burden with Sezary cell screen and Sezary flow cytometry. This may be performed within 6 weeks of initiation of treatment
- Urine pregnancy test (for females of childbearing potential)
- If clinically indicated, determination of extent of disease with CT or any other imaging procedures determined appropriate by the investigator to
evaluate all areas of known or suspected disease. This may be performed within 6 weeks of initiation of treatment.

4.1.2 Treatment Period:

Total skin electron beam therapy will be administered in the Department of Radiation Oncology according to the Stanford six-field technique previously described [21]. Patients will receive a planned total skin dose of 12 Gy fractionated at 2 Gy/cycle (each cycle requiring 2 days of treatment) 4 days each week, for 3 weeks. Supplements will routinely be applied to the perineum and soles as well as any other “shadowed” sites involved by disease, such as the inframammary regions (1-2 Gy fractions to a total dose of 12 Gy). Discrete tumors may receive additional “boost” treatment not to exceed 12 Gy.

During the course of TSEBT patients will be evaluated weekly in the Department of Radiation Oncology for determination of adverse events and toxicity grading according the NCI Common Toxicity Criteria (CTC).

On the day of first treatment a baseline evaluation will take place at which time the following procedures will be performed:

- Physical exam, including vital signs, weight, ECOG status
- Physical exam to assess baseline skin disease according to the modified Severity Weighted Assessment Tool (mSWAT)
- Baseline standardized photography
- Concomitant medications

4.1.3 Follow-up Period:

Following the completion of TSEBT, patients will be followed monthly for 6 months, and then every 2 months for a total of 12 months, or until there is disease progression or relapse. Patients who withdraw during the treatment period due to intolerance to radiotherapy will be followed weekly until toxicities have reverted to Grade ≤ 2 or have stabilized in the opinion of the Investigator, at which point a final visit will be scheduled. A final visit should be attempted for all patients who are lost to follow-up.

The following procedures will be performed during each Follow-up Visit and the Final Visit:

- Physical exam including vital signs, weight, and ECOG status
- Recording of concomitant medications
- Physical exam to assess clinical response to treatment according to the mSWAT
- Standardized photography
• Elicitation of adverse events and toxicity grading according to the NCI CTC

4.2 General Concomitant Medication and Supportive Care Guidelines

During the course of TSEBT, patients with facial or scalp disease will use internal lead eye shields with an inner coating of paraffin or dental acrylic. These shields are placed under the lids after the eyes have been anesthetized topically. In absence of scalp or facial disease external lead eye shields are taped over the closed eyes. Additional individualized shielding may be utilized as clinical circumstances warrant, as described previously [7].

All participating patients will be encouraged to apply emollients daily to alleviate radiation-induced generalized erythema and xerosis. Aggressive emolliation should be continued following completion of the TSETB course until resolution of erythema and xerosis.

4.3 Duration of Therapy

Patients will receive a planned total skin dose of 12 Gy fractionated at 2 Gy/cycle (each cycle requiring 2 days of treatment) 4 days each week, for 3 weeks

4.4 Duration of Follow Up

Following completion of TSEBT, patients will be followed 1 week, monthly for 6 months, and then every 2 months for a total of 12 months or until there is relapse or disease progression. Patients who withdraw during the Treatment Period due to intolerance to radiotherapy should be followed weekly until toxicities have reverted to Grade ≤ 2 or have stabilized in the opinion of the Investigator, at which point a final visit will be scheduled. All patients who withdraw during the Treatment Period for any reason other including progressive disease will be seen within 4 weeks of withdrawal for a final visit.

4.5 Criteria for Removal from Study

Patients may withdraw from the study at any time and possible reasons for withdrawal include:

• Progressive disease
• Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
• Patient withdraws consent to continue participation
• An adverse event which in the opinion of the Investigator precludes further participation in the trial
• The Investigator removes the patient from the trial in the best interests of the patient
- Study termination
- The Investigator removes the patient from the trial due to non-compliance
- The patient is lost to follow-up
- Female patients who become pregnant during this study

4.6 Alternatives

Alternative therapies for this patient population will be discussed with each patient and would include standard topical therapies, systemic biologic and chemotherapeutic regimens, phototherapy, monoclonal antibodies, radiotherapy, other investigational treatments (if available), or watchful waiting.

4.7 Compensation

Patients will not receive compensation for participation in this study.

5. INVESTIGATIONAL DEVICE/PROCEDURE INFORMATION

Total skin electron beam therapy will be administered in the Department of Radiation Oncology. Degraded 9 MeV electrons produced by a conventional medical linear accelerator will be utilized to administer treatment according to the Stanford six-dual field technique, described previously [7]. Patients will receive a planned total skin dose of 12 Gy fractionated at 2 Gy/cycle (each cycle requiring 2 days of treatment) 4 days per week, for 3 weeks. Patients with discrete number of cutaneous tumors may receive local boost treatments to these lesions concurrent with the TSEBT in order to reduce their thickness and permit better penetration by the electron beam. Underdosed or "shadowed" regions including the scalp, soles of feet, perineum, inframammary folds, and under the panniculus of obese individuals may receive supplemental electron irradiation.

6. DOSING DELAYS/DOSE MODIFICATIONS

Since the proposed TSEBT dose is less than is currently considered standard, significant toxicity requiring treatment modification is not anticipated. However, patients will be monitored weekly to assess for toxicity. The only short term toxicity of this treatment is in the skin. Treatment will be interrupted (or discontinued entirely) if grade 2 skin toxicity develops during the course of therapy.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

Common acute complications of TSEB therapy are erythema and dry desquamation which are likely to be minimal with this low dose regimen. Intermediate term complications may include alopecia which is likely to be incomplete and only
temporary since the scalp dose will be less than 25 Gy [7]. Other complications typically seen after conventional dose TSEBT include temporary loss of nails, temporary inability for proper sweating and chronically xerotic skin. Rarely patients will have scattered telangiectasias.

Secondary skin cancers such as squamous cell and basal cell carcinomas are increased in incidence after the use of TSEBT but usually become problematic only in patients who receive repeated treatments with multiple therapies, including phototherapy. Hematologic toxicity is not observed with conventional dose therapy and is not anticipated with an even lower dose, since there is only a limited depth of penetration of the electrons.

7.2 **Adverse Event Reporting**

An *adverse event* is any untoward medical occurrence in a patient treated on this protocol during treatment and follow-up regardless of causality assessment. This includes adverse clinical or laboratory findings, intercurrent illness or an exacerbation or progression of a disease/condition present at the time the study was initiated. The study will collect adverse event information during the 3-week treatment period and for 3 months following completion of TSEBT (this applies to patients who withdraw from the study). An adverse event is considered serious if it fulfills one of the following criteria:

- Results in death
- Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

All serious adverse events will be reported to the IRB in the required time frame following first knowledge of the event’s occurrence. A “Serious Adverse Event Report” will also be completed and submitted according to the Adverse Event SOP.
Study patients will be instructed to report any adverse events to investigators and patients will be evaluated for adverse events at every clinic visit. All adverse events will be documented by investigators, which will contain the following information:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date and time of onset of the event
- The date and time of resolution of the event and whether the event is serious or not
- Intensity of the event using the NCI Common Toxicity Criteria Version 2.0, found in Appendices.
- Seriousness of the event
- Frequency of the event
- Intervention
- Outcome
- The probability of an association between the event and study drug

### 8. STUDY CALENDAR

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10. MEASUREMENT OF EFFECT

10.1 Anti-tumor Effect

Patients will be evaluated one week after completing therapy (i.e. Week 4), monthly for 6 months (i.e. Week 7 through 27) and every 2 months thereafter until progression of disease or initiation of another MF-directed treatment for assessment of response. Clinical response will be assessed according to changes in the modified Severity-Weighted Assessment Tool (mSWAT) [Appendix C] and documented as stable disease (SD), partial response (PR), complete clinical response (CCR), or progressive disease (PD) as defined below.

10.1.1 Response Criteria

- **Complete clinical response (CCR):** no evidence of cutaneous disease on exam. This will need to be confirmed at the 4 week time point
- **Partial response (PR):** ≥ 50% decrease of the modified SWAT score compared to the baseline score. This will need to be confirmed at the 4 week time point
- **Stable disease (SD):** Neither CR, PR, or PD, i.e. change from baseline is less than 50% decrease, but also less than a 25% increase in the mSWAT score compared to the nadir score
- **Progressive disease (PD):** ≥ 25% increase in the modified SWAT score compared with the nadir score.

10.1.2 Time to Response

The duration of time from initiation of TSEBT to first documentation of CCR or PR.

10.1.3 Duration of Response (DOR)

Duration of time from first documentation of CCR or PR to first documentation of progressive disease (PD).

10.1.4 Time to Progression (TTP)

Duration of time from initiation of TSEBT to confirmed progressive disease (PD) or death related to mycosis fungoides.

10.1.5 Response Review
Patient clinical response will be independently verified by a dermatologist or oncologist who is not a co-investigator on this study.

10.2 Other Response Parameters

*Patient’s Assessment of Pruritus: The severity of pruritus will be assessed using a 5-point scale as outlined below. A reduction of at least one grade from baseline lasting at least 4 weeks is judged to be clinically significant.*

0 = No itch  
1 = Minimal: intermittent, transient itch  
2 = Moderate: Frequent itch, multiple times per day with reflex scratching  
3 = Severe: Interrupts daily activities and always associated with scratching  
4 = Very severe: Unrelieved itch, prevents routine activities, awakens patient from sleep

11. DATA REPORTING / REGULATORY CONSIDERATIONS

The Stanford Cancer Center Data and Safety Monitoring Committee (DSMC) will be the monitoring board for this study.

11.1 Monitoring plan

The research team will meet on a monthly basis to review adverse events, patient response, accrual and other study-related issues. Stopping rules may be implemented at this time or earlier as criteria for their implementation is met.

11.2 Stopping rules (for the individual patient and for the study as a whole)

Patients will be discontinued from study treatment for any of the following reasons:

- They experience grade ≥ 3 toxicities, intolerance to radiotherapy or SAE  
- Development of PD  
- Patient’s initiation of an anti-MF treatment including topical therapies, phototherapy, or systemic chemo/biological therapy  
- Protocol violations  
- Non-compliance with the treatment schedule  
- Development of an AE, intercurrent illness, condition, or procedural complication that may interfere with patient participation  
- Withdrawal of consent  
- Death of patient  
- Investigator decision

The study will be terminated for any of the following reasons:

- If more than 1/3 of all enrolled patients experience grade ≥ 3 toxicities.
• If at time of interim analysis the number of patients who achieve an
  objective response is 5 or fewer out of the 12 enrolled
• A request to discontinue the trial from a regulatory authority
• Investigator decision
• Poor patient enrollment

11.3 Data management

All data required by the trial will be entered onto case report forms. Any corrections
to data required into the paper case report forms must be made in such a way that the
original entry is not obscured. Only designated study staff will enter the data for each
study patients after each study visit. Case report forms will be checked for
correctness against source document data by study staff.

11.4 Confidentiality

Patient records will be kept in a secure location at Stanford University Medical Center
accessible only to research authorized personnel. The patient identity will be kept as
confidential as possible as required by law. Except as required by law, the patient will not
be identified by name, social security number, address, telephone number, or any other
direct personal identifier. Study patients will be assigned an ID code that will consist of a
three digit number. Information about the code will be kept in a secure location and
access limited to research study personnel. The results of this research study may be
presented at scientific or medical meetings or published in scientific journals. However,
the patient identity will not be disclosed. The patient's personal data which may be
included in the investigator’s database shall be treated in compliance with all applicable
laws and regulations.

12. STATISTICAL CONSIDERATIONS

12.1 Endpoints

12.1.1 Primary endpoint

Objective response rate defined as the proportion of patients achieving CCR
and PR (i.e. overall response (OR)) as assessed by the modified Severity-
Weighted Assessment Tool (mSWAT) [Appendix C] during the follow-up
period.

12.1.2 Secondary endpoints

• Time to response
• Duration of response
• Time to progression
• Patient’s assessment of pruritis
• Frequency and severity of adverse events
12.2 Plan of Analysis

Descriptive statistics will be used, including proportions and exact 95% confidence intervals. Time to event data will be summarized by Kaplan-Meier curves.

12.3 Sample Size

12.3.1 Accrual estimates

A planned 36 patients will be enrolled over an estimated period of 3 years.

12.3.2 Sample size justification

Thirty six patients will be enrolled. This sample size together with the interim analysis specified below gives 80% power to reject an overall ORR of 40%, when the true ORR is 65%. The probability of stopping early is 66% under the null hypothesis (ORR=40%) and 8% under the alternative (ORR=65%)

12.4 Interim analyses

An interim analysis will be carried out when 12 patients have been observed for at least 2 months and are evaluable for ORR. If the number of patients who achieve an objective response is 5 or fewer, no further patients will be accrued. Otherwise the trial will continue to accrue 24 additional patients to a total of 36; the trial will be considered a success if at least 20 of the 36 patients respond.

REFERENCES


APPENDICIES

A. Informed Consent Form

Attached Separately

B. Participant Eligibility Checklist

Study Institution #_______________
Participant #________

PARTICIPANT ELIGIBILITY CHECKLIST

1. Does the patient have a histologically proven diagnosis of mycosis fungoides? (Y)
2. Does the patient have stage IB to IIIA disease? (Y)
3. Has the patient failed or been intolerant to at least one prior systemic or topical therapy? (Y)
4. Is the patient at least 18 years of age? (Y)
5. Does the patient have a life-expectancy greater than 6 months? (Y)
6. Does the patient have an ECOG score ≤ 2 (Y)
7. Were the following lab parameters confirmed within 4 weeks prior to study entry?
   - WBC ≥ 2,000/mm³
   - Absolute neutrophil count (ANC) ≥ 1,000 cells/mm³
   - Platelets ≥ 100,000 cells/mm³ (Y/NA)
8. For women of childbearing potential, was a pregnancy test completed within 2 weeks of registration? (N)
9. Is the patient pregnant or lactating? (Y)
10. Has the patient completed a wash-out period of at least 2 weeks from topical therapies and 4 weeks from systemic/biologic, phototherapy, or radiotherapy? (N)
11. Has there a history of prior invasive malignancy (other than completely excised non-melanomatous skin cancer or in situ SCC of the cervix)? If yes, has the patient been disease free for greater than 5 years? (N)
12. Has the patient received prior course of TSEBT? (N)
13. Does the patient have an underlying medical condition or serious illness that would impair his ability to undergo treatment? (N)
14. Has there been a change in dose or frequency of patient’s topical corticosteroid use in the past 3 weeks? (N)

Signed

Print Name

Dated

22 of 16
## C: Modified Severity-Weighted Assessment Tool (m SWAT)

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<th>Region</th>
<th>% TBSA for the region</th>
<th>% TBSA Patch</th>
<th>% TBSA Plaque</th>
<th>% TBSA Ulceration/Tumor</th>
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TBSA: Total Body Surface Area