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DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: Pilot Trial of Leflunomide in Patients with CD30+ Lymphoproliferative Disorders

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Clinical Trial Protocol

Pilot Trial of Leflunomide in Patients with Cutaneous CD30+ Lymphoproliferative Disorders

Version Date:	07/08/2021
Protocol Version:	01
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Participating Sites:	City of Hope (Duarte)
Short Title	Leflunomide Pilot for CD30+ LYPD

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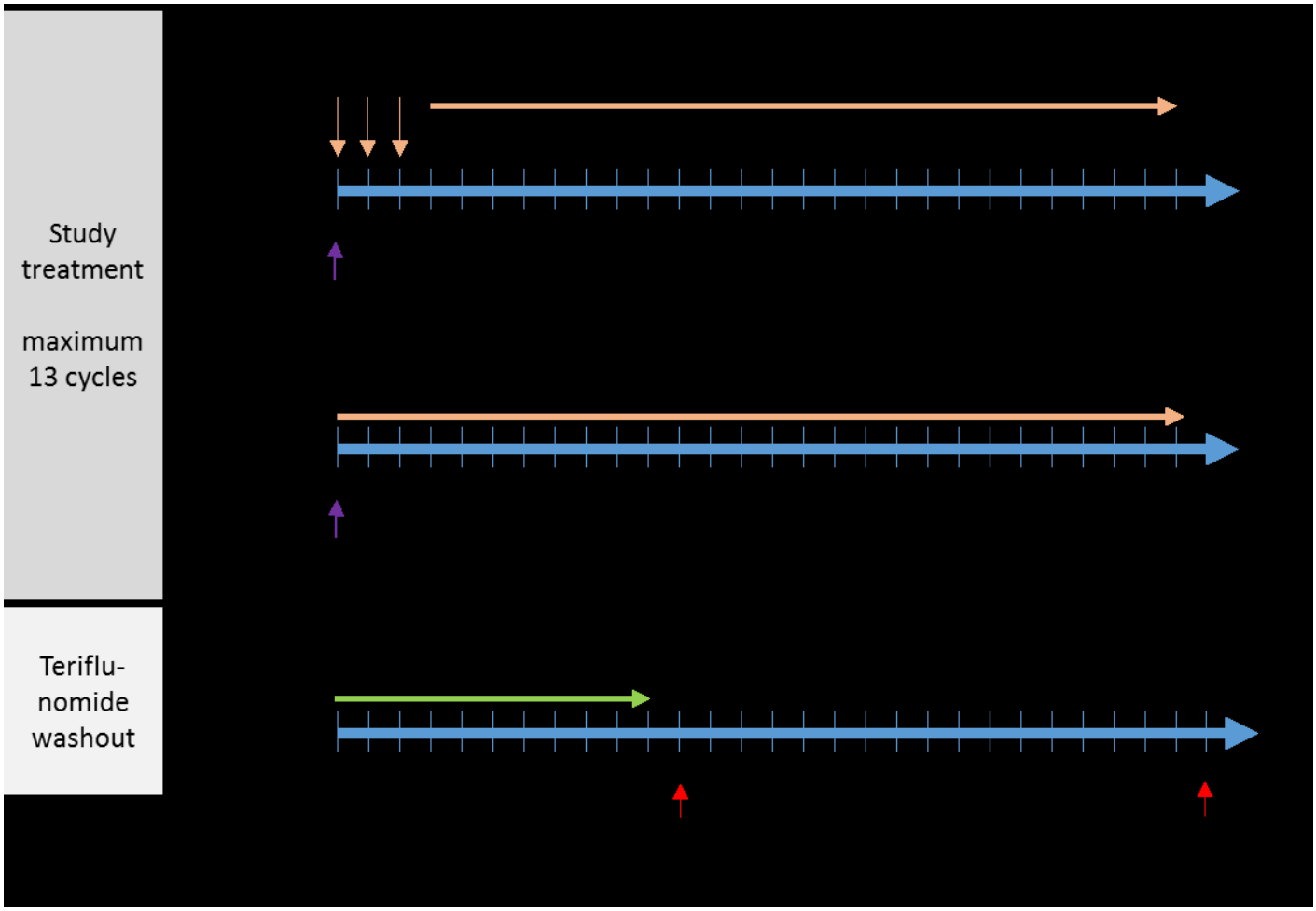
STUDY SCHEMA



*Initial biopsy prior to first dose of leflunomide on C1D1

†On C2D1, C5D1, and end of therapy if lesions are present, and at disease progression.

PROTOCOL SYNOPSIS

Protocol Title

Pilot Trial of Leflunomide in Patients with Cutaneous CD30+ Lymphoproliferative Disorders

Study Detail

Population/Indication(s):	Patients with cutaneous CD30+ lymphoproliferative disorders
Phase:	Pilot study
Sample Size:	Expected: 12, Maximum: 14
Estimated Accrual Duration:	3 years
Estimated Study Duration	Up to 5 years
Participant Duration:	Up to 24 months (12 months of treatment + 12 months of follow-up).
Participating Sites:	• City of Hope Duarte, CA
Study Agents:	Leflunomide, commercially available ...
Sponsor:	City of Hope
Industry Partner:	PendingPendingPendingPendingPendingPendingPending

Rationale for this Study

Cutaneous CD30 lymphoproliferative disorders include lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. Systemic therapies for widespread cutaneous disease include methotrexate, radiation therapy, and brentuximab vedotin, all of which have poor side effect profiles for a group of diseases that have a relatively indolent course. Leflunomide is a commercially available oral immunosuppressive agent that has been FDA approved since 1998 for the treatment of rheumatoid arthritis (RA). The primary mechanism of action of leflunomide is inhibition of de novo pyrimidine synthesis by targeting dihydroorotate dehydrogenase (DHODH), resulting in anti-proliferative effects in B- and T-lymphocytes. Leflunomide has been investigated for its anti-neoplastic potential in a variety of pre-clinical tumor models. Recent pre-clinical studies have demonstrated significant anti-neoplastic activity in CD30+ lymphoproliferative disorders. In addition, limited clinical experience is suggestive of a beneficial response when leflunomide is used to treat CD30+ lymphoproliferative disorders (CD30+LYPD). Considering the favorable toxicity profile and extensive clinical experience with leflunomide in rheumatoid arthritis, this drug represents a potential new candidate for therapy CD30 LYPDs.

Treatment Description

Leflunomide will be administered orally at a dose of 20 mg/day following a loading dose of 100 mg/day for the first three days of administration. Patients will be treated in planned 28-day treatment cycles. Patients may continue to receive cycles of treatment on study (maximum 13 cycles) until disease progression or unacceptable toxicity, or other criteria for removal from study treatment are satisfied. While on active treatment patients will undergo evaluation for response after every cycle. At the time of terminating leflunomide, all participants will receive 11 days of oral cholestyramine treatment (8 g three times daily) to reduce the plasma leflunomide levels. Patient will be followed for 1 year after terminating leflunomide treatment, or until disease progression, whichever is earlier.

Objectives

Primary Objective

- To evaluate overall response rate of leflunomide treatment

Secondary Objectives

- To assess complete response rate and duration of response of leflunomide treatment
- To assess toxicities of leflunomide treatment
- To assess disease status by the CAILS (composite assesment of index lesion severity)

Exploratory Ex-vivo and Molecular Objectives

- To generate a preliminary RNA signature associated with response of CD30+LYPD to leflunomide

Study Design

This study will be conducted as a single center, single agent pilot study.

Evaluation Criteria and Endpoints

Primary Endpoint(s):

- The primary endpoint is overall response (CR + PR). Response will be categorized by mSWAT. The response categories and criteria are summarized in Table 11.2 of the protocol.

Statistical Considerations

Sample size: This study will accrue 12 response evaluable patients, with a maximum accrual of 14 patients. Because this is a rare disease that has not been systematically studied in a prospective clinical trial, there is a lack of historical data on the response rate (and by modified severity weighted assessment tool [mSWAT]) in this patient population. The sample size for this pilot study was chosen based on feasibility considerations, and not based on any definitive statistical criterion.

With 12 patients, the 95% exact binomial confidence interval for the overall response rate will have a width of 55% (33% response rate, with 4 responders), 57% (42% response rate, with 5 responders), 58% (50% response rate, with 6 responders), 57% (58% response rate, with 7 responders), 55% (67% response rate, with 8 responders), 52% (75% response rate, with 9 responders), and 46% (83% response rate, 10 responders) respectively. For any AE with a true incidence of 15% or higher, with 12 patients there is at least an 86% chance of observing 1+ patients with such AE.

We project to accrue approximately one patient every 3 months. The projected study accrual duration is therefore 3 years.

Analysis: Observed toxicities will be summarized in terms of type (organ affected or laboratory determination), severity, attribution, time of onset, duration, serum concentration of the active leflunomide metabolite, probable association with the study treatment and reversibility or outcome. Baseline information (e.g. the extent/type of prior therapy) and demographic information will be presented as well to describe the patients treated in this study.

Rates and 95% Clopper Pearson binomial confidence interval (CI) will be calculated for overall response rate (patients that have confirmed CR or PR) and clinical benefit rate (patients that have confirmed CR/PR/MR or SD). In addition, sub-analyses will be performed where participants will be considered evaluable for response if they are confirmed eligible, receive at least 75% of leflunomide during the first cycle of therapy and have their disease re-evaluated. Response rates will also be explored based on number/type of prior therapy(ies) and serum concentration of the leflunomide metabolite (µg/mL). Time to response and survival will be estimated using the product-limit method of Kaplan and Meier.

Preliminary molecular profiles for mRNA will be derived from skin biopsies. These profiles will be used to identify molecular correlates of therapeutic response using pathway identification and supervised principal components analysis.

Abbreviated Eligibility Criteria

Main Inclusion Criteria

- Adult patients with a diagnosis of CD30+LYPD with life expectancy of > 3 months
- ECOG ≤2
- Relapsed or refractory to at least 1 prior line of therapy
- Platelet count ≥ 50,000/µL, ANC ≥ 1000/mm^3, AST and ALT < 2.0 x ULN, total bilirubin < 1.5 x ULN

Main Exclusion Criteria

- Prior treatment with lenflunomide
- Prior diagnosis of rheumatoid arthritis
- Prior allogeneic transplant
- Acute active infection, known HIV, HBV, HCV infection
- Preexisting liver disease

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to leflunomide or cholestyramine.
- Non-hematologic malignancy within the past 3 years aside from the following exceptions:
    - adequately treated basal cell or squamous cell skin cancer
    - carcinoma in situ of the cervix
    - prostate cancer < Gleason Grade 6 with a stable PSA
    - successfully treated in situ carcinoma of the breast

Investigational Product Dosage and Administration

Leflunomide will be administered orally at a dose of 20 mg/day following a loading dose of 100 mg/day for the first three days of administration.

Clinical Observations and Tests to be Performed

- Clinical observations will include tolerance as well as response to treatment.
- Baseline studies will include: history and physical, skin biopsies (the skin biopsy will be used for clinical assessment and leftover samples will be used for correlative laboratory studies), as well as a laboratory evaluation to include CBC with differential, comprehensive chemistry panel (to include LDH, magnesium, phosphorus and uric acid).
- Clinical observation of response will take place on day 1 of each 28-day cycle. Subjects will be evaluated through clinic visits and physical exams as well as laboratory tests to include CBC with differential, comprehensive chemistry panel. Blood tests will be performed at a minimum of every 28 days but may be done more frequently as clinically indicated.
- Skin biopsy will be performed at the baseline, after 1 month, 4 months of Leflunomide therapy and at end of therapy (if lesions are present), and at disease progression.
- Patients will undergo toxicity assessment every two weeks for the first three cycles following initiation with leflunomide and will undergo, at a minimum, monthly toxicity assessments thereafter.

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ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRC	Clinical Research Coordinator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLCO	Carbon Monoxide Diffusing Capacity
DLT	Dose Limiting Toxicity
DHODH	Dihydroorotate Dehydrogenase
DSMC	Data Safety Monitoring Committee
EOT	End of Treatment
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICG	Integrated Genomics Core
IDS	Investigational Drug Service
IND	Investigational New Drug
IRB	Institutional Review Board
LYPDs	Lymphoproliferative Disorders
MNC	Mononuclear Cells
MR	Minimal Response
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
RP2D	Recommended Phase II Dose
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
sCR	Stringent Complete Response
SD	Stable Disease

1.0 OBJECTIVES

In patients with CD30+ Lymphoproliferative Disorders (CD30+LYPDs)

1.1 Primary Objective

- To evaluate overall response rate of leflunomide treatment

1.2 Secondary Objectives

- To assess complete response rate and duration of response of leflunomide treatment
- To assess toxicities of leflunomide treatment
- To assess disease status by the CAILS (composite assessment of index lesion severity).

1.3 Exploratory Objectives

- To generate a preliminary RNA signature associated with response of CD30+LYPDs cells to leflunomide.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

The term "CD30+ T-cell lymphoproliferative disorders" (CD30+LYPDs) describes a group of diverse diseases of the skin.[1] Primary cutaneous CD30+ T cell lymphoproliferative disorders (pcCD30+ T cell LPDs) are the second most common type of cutaneous T cell lymphomas (CTCL), after mycosis fungoides (MF), accounting for 30% of all primary cutaneous lymphomas [2, 3]. CD30+LYPD includes primary cutaneous anaplastic large cell lymphoma (pCALCL) and lymphomatoid papulosis (LyP). Their diagnostic hallmark is CD30 expression by the atypical lymphocytes, in the same typical membranous and golgi pattern observed in systemic anaplastic large cell lymphoma (sALCL) [4]. The treatment and prognosis of cutaneous CD30+ T cell LPDs differ significantly from those of systemic lymphomas, emphasizing the importance of a clinical pathological correlation and thorough workup to ensure an accurate diagnosis [5].

For both LyP and pcALCL, treatments are determined by the extent of disease. In LyP, topical treatments such as corticosteroids and nitrogen mustard are not effective in changing the overall course of disease. Current therapies treat only current existing lesions and associated symptoms, such as pruritus [6, 7]. Patients with diffuse disease are treated with phototherapy or methotrexate [8]. Both therapies cannot be continued indefinitely due to the risk of long term side effects. Once these therapies are discontinued, lesions usually recur with the same intensity. In pcALCL, for single or localized lesions the main effective treatments are surgical excision or radiotherapy. For multifocal or recurrent pcALCL, systemic therapies are used such as methotrexate, bexarotene or Brentuximab Vedotin [9]. Treatment decision making is particularly challenging, given the toxic nature of available agents for a relatively indolent lymphoma.

2.2 Leflunomide

Leflunomide is a commercially available oral immunosuppressive agent that has been FDA approved since 1998 for the treatment of rheumatoid arthritis (RA) as a single agent or in combination with methotrexate. It has been used in over 300,000 patients worldwide for RA treatment. Leflunomide is generally well-tolerated and may be taken over a long period of time.

The in vitro and in vivo mechanisms of leflunomide are not completely defined. The primary clinical mechanism of action is inhibiting de novo pyrimidine synthesis by targeting dihydroorotate dehydrogenase (DHODH), and thus achieving anti-proliferative effect in B- and T-lymphocytes. A secondary mechanism of action is inhibition of cytokine and growth factor receptor associated tyrosine kinase activity [10].

Leflunomide (the pro-drug) is rapidly converted to its active primary metabolite teriflunomide (A77 1726), which mediates leflunomide's pharmacologic activity. Teriflunomide serum concentrations show wide inter-patient variability; in one study, the mean serum teriflunomide concentration in patients receiving 20 mg/ daily was 42 mg/l with a range from 3-150 mg/l and a standard deviation of 35 mg/l [11]. Of note, the serum concentration of this metabolite was shown to predict RA response [11].

The FDA approved dose in adults for the treatment of RA is a loading dose of 100 mg orally (PO) once daily for 3 days, followed by a maintenance dose of 10-20 mg PO once daily. Leflunomide has been used at up to 40 mg/day in patients with Wegner's granulomatosis with a safety profile similar to the 20mg/day dose used in RA [12, 13]. Doses up to 60 mg/day have been safely used for the treatment of allograft polyoma BK virus in renal allograft patients to achieve a targeted blood level of teriflunomide (A77 1726) of 50-100 micrograms/mL [14]; the targeted blood level was frequently achieved with a dose of 40mg/ day with no increase in toxicity reported [14].

In addition to studies that demonstrate the serum concentration of the metabolite may predict response, recent work demonstrates that polymorphisms in the gene encoding DHODH may be associated with leflunomide treatment outcome in RA patients[15, 16].

The long half-life of the metabolite (about 2 weeks) affects management of patients taking leflunomide. A loading dose of 100 mg for 3 days is used to facilitate rapid attainment of steady state levels of M1. Without a loading dose, it is estimated that attainment of steady state concentrations would require nearly two months of dosing [17]. To eliminate the metabolite, a drug elimination procedure using cholestyramine is recommended. Cholestyramine, a bile acid sequestrant, fixes the metabolite, preventing reabsorption and expediting drug elimination. Without the drug elimination procedure, it may take up to 2 years to reach non-detectable plasma levels after stopping treatment with leflunomide [17]

2.3 Preclinical Studies of Leflunomide as an antineoplastic agent

Leflunomide has been investigated for its anti-neoplastic potential in a variety of pre-clinical tumor models. The first reports of anti-tumor activity in mouse xenograft models of glioma indicate that inhibition of pyrimidine synthesis is not sufficient for anti-tumor activity and concomitant inhibition of tyrosine phosphorylation may also play a role[18]. In chronic lymphocytic leukemia (CLL), leflunomide has been shown to inhibit the cell cycle progression in primary leukemic cells in vitro [19]. Dietrich et al showed that teriflunomide (A77 1726) affects proliferation of CLL by blocking DHODH at very low concentration (3-5 μg/ml) and by additionally inhibiting JAK/STAT pathway at intermediate concentrations (>10 μg/ml)[20]. The metabolite is also effective in fludarabine-refractory cells [20]. In addition, pre-clinical anti-tumor activity of leflunomide has been reported for melanoma [21] and prostate cancer [22].

Recent pre-clinical studies of teriflunomide (A77 1726) have demonstrated significant antineoplastic activity in myeloma [23]. Teriflunomide inhibits cell growth and induces apoptosis in common myeloma cell lines at clinically achievable concentrations (50-200 μmol/L) in a time- and dose-dependent manner. The stimulatory effect of conditioned medium of HS-5 bone marrow stromal cells on multiple myeloma cell growth is completely abrogated by teriflunomide. In addition, studies revealed additive effects when teriflunomide was combined with the genotoxic agents melphalan and doxorubicin and synergistic effects when combined with bortezomib and treosulfan[23]. Finally, the Rosen laboratory has found leflunomide to be active in both glucocorticoid sensitive and resistant myeloma cell lines (Steven Rosen, personal communication).

With respect to cutaneous lymphoma, the Querfeld laboratory has found the active metabolite teriflunomide to be effective at 48-72 hours in inducing apoptosis in mycosis fungoides, sezary syndrome, and CD30+LYPD cell lines. In particular, the apoptosis was achievable at the 50-200umol/L concentration.

2.4 Background for Correlative Studies

Leflunomide is rapidly converted to its active primary metabolite teriflunomide (A77 1726), which mediates leflunomide's pharmacologic activity. Previous population-based PK studies in patients with RA have demonstrated a high degree of intersubject variability in measured steady-state total (free + albumin-bound) teriflunomide serum concentrations, resulting in coefficients of variation in CL/F estimates of >50% [29, 30]. Teriflunomide is >99% bound to serum albumin and free drug concentrations have also been reported to be highly variable, with a median of 55.8 µg/l and a range of 27.9-148.4 µg/l [31]. Moreover, measured total and free teriflunomide levels have been shown to predict response and toxicity in RA patients, leading some investigators to suggest a role for therapeutic drug monitoring and dose optimization of leflunomide [16]. It has also been reported that genetic polymorphisms in CYP1A2 and CYP2C19, the hepatic enzymes responsible for leflunomide metabolism, and DHODH, a key enzyme in the de novo synthesis of pyrimidines and the main target of teriflunomide, can all influence the risk of leflunomide-associated toxicity in RA patients [32-34].

Transcriptomic diversity exists within the clonal tumor cells that comprise cutaneous lymphomas as noted by recent work in mycosis fungoides and Sézary Syndrome [24, 25]. This correlates with the clinical experience of many experts that monotherapy alone is unable to produce response rates higher than 30-40% or meaningful durations of response in these patients as well. In addition, it is not only the tumor heterogeneity but also the response to the tumor in the microenvironment in the form of T-cell exhaustion that contributes to a lack of higher response rates [26]. For these reasons, it is important to assess the heterogeneity of gene expression of tumor cells and the cells of the microenvironment that likely exists within CD30+LYPDs. Single-cell RNA analysis provides a view of all involved cellular components simultaneously and their individual gene expression states. Utilizing single cell mRNA sequencing will not only allow us to note the multiple mutations and the molecular signature of this group of diseases for the first time by assessing the baseline biopsies, but also will help us to explore the mechanism by which the leflunomide suppresses the growth of the CD30+LYPDs as noted in work conducted on CTCL lines by the Querfeld group. In addition, this will contribute to determining what future combination therapies can be utilized for better clinical and durable response as well as for tailoring patient-specific treatment.

The parallel assessment of immunohistochemistry will allow us to correlate the new single cell data with what is seen/noted pathologically. Tumor cells in CD30+LYPD will be characterized utilizing a standard immunohistochemistry panel which includes CD3, CD4, CD8, CD30, BF1, Gamma, TRAF1, MUM1, perforin, granzyme, TIA-1 [27]. Current work in this area has noted that the predominant cells in the tumor microenvironment of CD30+LYPDs include a large percentage of CD163+ macrophages (M2) (44.7% in LyP vs. 35% in pcALCL). However, there are a number of tumor infiltrating CD8+ lymphocytes, FOXP3+ T-regulatory cells (Tregs) and only a few programmed cell death (PD1) lymphocytes [28]. We would like to examine the effect leflunomide has on the changing microenvironment as well.

2.5 Overview and Rationale of Study Design

Teriflunomide, the active metabolite of leflunomide, is approved for treatment of multiple sclerosis [15]. The "on target" effect of leflunomide and teriflunomide, which occurs at low doses, is mediated through inhibition of the cellular dihydroorotate dehydrogenase (DHODH) enzyme [16]. DHODH is required for *de novo* pyrimidine synthesis (but not for pyrimidine synthesis mediated by the salvage pathway), and "on target" effects of the leflunomide/teriflunomideare is reversed *in vitro* by supplementing the media with uridine, which restores *de novo* pyrimidine synthesis. Lymphocytes are particularly dependent upon *de novo*pyrimidine synthesis for their proliferation [17], and the major "on target" immunosuppressive effect of leflunomide/teriflunomide is thought to be due to decreased T cell proliferation. In addition to decreasing the amount of pyrimidine-based nucleotides available for DNA/RNA synthesis, drugs that inhibit DHODH activity globally decrease the level of O-linked GlcNAcylate-modified proteins through an "on-target" effect [18]. Diffuse large B-cell lymphoma (DLBCL) cell lines and primary DLBCL tumor cells have higher levels of nuclear O-GlcNAcylate-modified proteins than do normal B-cells, and the levels of these proteins correlate with DLBCL cell growth and survival [19]. With respect to cutaneous lymphoma the Querfeld laboratory has found the active metabolite teriflunomide to be effective at 48-72 hours

in inducing apoptosis in mycosis fungoides, Sézary cell, and CD30+LYPD cell lines. In particular, the apoptosis was achievable at the 50-200umol/L concentration.

These pre-clinical data, and the relatively low toxicity profile seen with prolonged administration in the rheumatoid arthritis population as well as the multiple myeloma population, in total provide evidence to support the investigation of leflunomide as an anti-CD30+ agent.

While the standard dose of leflunomide (20mg daily), following a loading dose of 100mg daily for 3 days, is FDA approved for continuous treatment of rheumatoid arthritis, leflunomide has been administered without an increase in the type, frequency or severity of adverse events at doses up to 40 mg/day in patients with Wegner's granulomatosis, and up to 60mg/day in a subset of patients with polyoma BK neuropathy to achieve targeted therapeutic levels [12, 13].

Because the current dosing guideline for patients with rheumatoid arthritis do not to exceed 20 mg daily maintenance doses [17], the 20mg/day dose is selected as the safe starting dose. In addition, in personal communications, Miles Prince has used leflunomide at doses of 10-20mg daily for 6 weeks in patients who have failed methotrexate with report of minimal side effects.

Patients will be treated in planned 28-day treatment cycles. Patients may continue to receive cycles of treatment on study until disease progression or unacceptable toxicity, or other criteria for removal from study treatment are satisfied. While on active treatment patients will undergo monthly evaluation for response by mSWAT and the CAILs (composite assessment of index lesion severity) [29, 30]. Following the decision to end leflunomide treatment, all patients will undergo 11 days of treatment with cholestyramine, which fixes the metabolite, preventing re-absorption and effectively lowering drug levels. Cholestyramine has been shown to decrease plasma levels of teriflunomide (A77 1726) in healthy volunteers by approximately 40% in 24 hours and by 49-65% in 48 hours [17].

In addition, molecular correlates and *ex vivo* responses will be evaluated using skin specimens, which will be collected from patients before treatment, after one cycle, four cycles of leflunomide treatment, end of therapy (if lesions are still present), and at disease progression. Molecular correlate analysis of leflunomide response will include single cell RNA sequencing. Specimens derived from before and after leflunomide treatment (after 1 month and at progression or complete response, if possible) will be analyzed, as well as pre-treatment specimens exposed to teriflunomide *ex vivo*.

3.0 ELIGIBILITY CRITERIA

Patient MRN (COH Only)	Patient Initials (F, M, L):

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent

__1. Documented informed consent of the participant and/or legally authorized representative.

- Assent, when appropriate, will be obtained per institutional guidelines

Age Criteria, Performance status

__2. Age:≥ 18 years

__3. Patients must have a life expectancy of > 3 months

__4. ECOG ≤ 2

Nature of Illness and Illness Related Criteria

__5. Patients must have a diagnosis of cutaneous CD30+LYPD

__6. Patients must be relapsed or are refractory to at least 1 prior line of therapy

__7. At least 2 weeks from prior therapy to time of start of treatment. Prior therapy includes steroids (except prednisone or equivalent – up to 10 mg/day is allowed).

Clinical Laboratory and Organ Function Criteria (To be performed within 21 days prior to Day 1 of protocol therapy unless otherwise stated [see Section 10.0])

__8. ANC ≥ 1000/mm^3 **NOTE:** Growth factor is not permitted within 14 days of ANC assessment unless cytopenia is secondary to disease involvement.	ANC:	Date:
__9. Platelets ≥ 50,000/mm^3 **NOTE:** Platelet transfusions are not permitted within 14 days of platelet assessment unless cytopenia is secondary to disease involvement.	Plts:	Date:
__10. __10. Total bilirubin ≤ 1.5 X ULN (unless has Gilbert's disease)	ULN: Bil:	Date:
__11. AST ≤ 2.0 x ULN	ULN: AST:	Date:
__12. ALT ≤ 2.0 x ULN	ULN: ALT:	Date:
__13. Creatinine clearance of ≥ 30 mL/min per 24 hour urine test or the Cockcroft-Gault formula or $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ (x 0.85 for females) **Or** $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}}$ (x 0.85 for females)	Serum Cr: Cr Clearance:	Date:

__14. Seronegative for HIV Ag/Ab combo, HCV*, active HBV (Surface Antigen Negative) *If positive, Hepatitis C RNA quantitation must be performed. __15. Meets other institutional and federal requirements for infectious disease titer requirements **Note** Infectious disease testing to be performed within 28 days prior to Day 1 of protocol therapy.	HIV: HCV: HBV: Syphilis:		Date:
__16. Negative for tuberculosis antigen (e.g. T-Spot test).			Date:
__17. **Women of childbearing potential (WOCBP)**: negative urine or serum pregnancy test If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	Urine:	Serum:	Date:

Contraception

__18. Agreement by females **and** males of childbearing potential* to use an effective method of birth control (hormonal or barrier method of birth control or abstinence) or abstain from heterosexual activity for the course of the study through at least three months after the last dose of protocol therapy. The effects of study treatment on a developing fetus have the potential for teratogenic or abortifacient effects. Should a woman become pregnant or suspect that she is pregnant while participating on the trial, she should inform her treating physician immediately.

* Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 2 years (women only).

3.2 Exclusion Criteria

Prospective participants who meet any of the following criteria will not be eligible for admission into the study:

Concomitant medications

__1. Current or planned use of other investigational agents, or concurrent biological, chemotherapy, or radiation therapy during the study treatment period. (See inclusion criterion #7 for washout times).

__2. Current or planned growth factor or transfusion support. If growth factor or transfusion support is provided between screening and start of treatment, the participant will no longer be eligible.

Other illnesses or conditions

__3. Prior Allogeneic transplant.

__4. Acute active infection requiring systemic therapy within 2 weeks prior to enrollment.

__5. Known history of hepatitis B or hepatitis C infection

__6. Known HIV infection.

__7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to leflunomide or cholestyramine.

__8. Non-hematologic malignancy within the past 3 years aside from the following exceptions:

- adequately treated basal cell or squamous cell skin cancer
- carcinoma in situ of the cervix
- prostate cancer < Gleason Grade 6 with a stable PSA
- successfully treated in situ carcinoma of the breast

__9. Clinically significant medical disease or condition that, in the investigator's opinion, may interfere with protocol adherence or the patient's ability to give informed consent.

__10. Pregnant women and women who are lactating. Leflunomide has potential for teratogenic or abortifacient effects. Because there is a potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued if the mother is enrolled on this study.

__11. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.

Noncompliance

__12. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

3.3 Inclusion of Women and Minorities

The study is open anyone regardless of gender or race/ethnicity. Efforts will be made to extend the accrual to a representative population. However, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

4.0 PARTICIPANT ENROLLMENT

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see Section 17.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0 (Study Calendar).

4.2 Participant Enrollment

4.2.1 COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

- Phone: (626) 218-7904
- E-mail: DCC@coh.org

4.2.2 Slot verification and reservation

Designated study staff should call or email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials). Slots can only be held for a limited time.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.3 Registration Process

To register a participant the subsequent procedure is to be followed:

1. The study team (data manager/coordinator/research nurse) should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The data manager/coordinator/research nurse will email a copy of the following documents to the DCC:
    - Completed eligibility checklist (printed from Section 3.0 of the protocol)
    - Source documentation to support eligibility criteria**
    - Signed Informed Consent
    - Signed subject's bill of Rights
    - Signed HIPAA authorization form (if separate from informed consent)

    ** It is **NOT** acceptable to submit emails as source documentation
3. After having received all transferred documentation, the DCC will complete the review of the documents to verify eligibility, working with the study team as needed to resolve any missing required source elements. A participant failing to meet all protocol eligibility requirements will not be registered.
4. Once eligibility is confirmed, DCC staff will send a Confirmation of Registration Form and signed Eligibility Checklist within 24 hours, including the participant study number and cohort assignment (dose level or expansion cohort) to:
    - The study team: Principal Investigator, treating physician, protocol statistician, protocol nurse, CRC and COH IDS Pharmacy.
    - the COH sponsor team designees, including Study PI

5. Upon receipt of the Confirmation of Registration email from the DCC, COH study team will register the patient in OnCore.

4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Notify the DCC if the participant screen fails after registration or if the participant does not start treatment.

Issues that would cause treatment delays should be discussed with the Principal Investigator.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

Treatment on study will be in the outpatient setting and will consist of daily treatment with leflunomide; patients will be treated in planned 28-day treatment cycles for up to 13 cycles (approximately 1 year) until meeting any off-protocol treatment criteria (Section 5.6). After the decision to end study treatment has been made, participants will receive treatment with cholestyramine (Section 5.5) to eliminate leflunomide. Participants who end study treatment for reasons other than disease progression will undergo active follow-up (Section 5.7) until disease progression or 12 months of active follow-up, whichever is earlier. For a detailed tabular view of the treatment, monitoring, and follow-up schedule, see the Study Calendar in Section 10.0.

5.2 Cycle Definition

The planned cycle length is 28 days. Leflunomide will be taken orally once daily. Missed or held doses will not be made up. The day count continues despite a hold in agent administration. Day 1 safety assessments must be reviewed prior to the initiation of the cycle. **For a cycle to commence, the participant must be actively taking study agent.** Windows for procedures are detailed in Section 10.0.

5.3 Agent Administration

5.3.1 Leflunomide

Participants will be instructed to take each dose of leflunomide orally, once a day, at approximately the same time each day. They may take it with or without food. If a patient forgets or misses a dose for whatever reason, it should not be replaced or made up. Participants will be given a study calendar (pill diary, see Appendix D) to document each dose of leflunomide that is taken or missed.

Leflunomide is administered with a loading dose of 100 mg/day for the first three doses (first three days) in Cycle 1. Starting day 4 in Cycle 1 and for all later cycles, it will be administered at 20 mg/day (or 10 mg/day if dose reduced due to toxicities).

There will be no intra-patient dose escalation; patients will undergo dose modification due to toxicity per Section 7.2.

5.3.2 Cholestyramine

Cholestyramine is not a study agent but is required for the elimination of the study agent leflunomide. See Section 5.5 for cholestyramine administration details.

5.4 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see Section 10.0.

5.5 End of Treatment Evaluations and Leflunomide Detoxification

All participants will be followed until resolution or stabilization of any serious adverse events occurring during treatment and completion of the Day 30 End of Treatment assessments. See Section 10 for a list of all assessments and windows.

Because of the ability of leflunomide to be reabsorbed through the colon, resulting in a very long half-life, all participants will be treated with cholestyramine to prevent re-absorption of leflunomide after the decision to end study treatment has been made.

Participants removed from study treatment will undergo oral administration of cholestyramine 8 grams oral suspension three times daily for 11 days. It will not be a deviation if an administration of cholestyramine is delayed or if the 11 days are not consecutive. Cholestyramine administration may be adjusted per the discretion of the treating investigator. After the treatment with cholestyramine, clinical laboratory testing will be performed to verify plasma levels less than 0.02 mg/L or 0.02µg/mL by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L or 0.02µg/mL, additional cholestyramine treatment will be considered. See Section 10 for a tabular view of cholestyramine administration and metabolite testing windows and days of administration.

Note: Cholestyramine can affect the absorption of other oral medications. Such medications should be taken 1 hour before administration of cholestyramine on any day or per other guidance in the package insert. Watch for bleeding abnormalities due to vitamin K deficiency for which intravenous vitamin K may be administered.

5.6 Duration of Therapy and Criteria for Removal from Protocol Therapy

Patients will receive study treatment for a maximum of 13 cycles until disease progression, unacceptable toxicity or other criteria for removal from study treatment are satisfied. Participants may be removed from treatment for any of the following reasons:

- Evidence of disease progression per mSWAT (see Appendix C)
- Participant receives 13 cycles (~ 12 months of protocol therapy)
- Patient is deemed intolerant to study treatment because of toxicity, despite dose modification/delay
- Participant withdraws from the treatment phase of the study
- General or specific changes in the participant's condition, including non-compliance, which renders the participant unacceptable for further treatment in the opinion of the treating investigator.

Documentation of the reason for discontinuing therapy and the date effective should be made in the medical record and appropriate eCRF. The participant should then proceed to off-treatment procedures for safety monitoring, leflunomide elimination and follow-up procedures. The participant’s status is to be modified in the OnCore system once the off-treatment period is completed. Alternative care options will be discussed with the participant.

5.7 Active Follow-Up

Participants who do not progress while on treatment (regardless of whether the patient finished 13 cycles or terminated treatment early) will be in *Active Follow Up*, for 12 months after the end of the protocol treatment, where they will continue to undergo response assessment every 3 months, until disease progression or otherwise meeting an criteria for removal from study participation as detailed in Section 5.8.

The schedule and windows for assessments and data collection points are further detailed in Table 10.

Assessment time points and windows are detailed in Section 10.0.

5.8 Duration of Study Participation

Participants may be removed from the study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuing study participation should be documented and may include:

- Completion of 12 months of active follow up after the end of protocol treatment
- Disease progression per mSWAT, after completing the End of Treatment assessments
- Disease progression per mSWAT during active follow-up
- Withdrawal of consent
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF

5.9 Prohibited and Concomitant Therapies/Medications

5.9.1 Allowed concomitant medications

Concomitant medications and treatments that are permitted while on study treatment include allopurinol, anti-emetics, anti-diarrheals, FDA-approved bisphosphonates, erythropoietin, transfusions (as necessary), and palliative radiation.

Concurrent treatment with any other anti-neoplastic therapies will not be permitted while on study treatment. Concurrent administration of live vaccines will not be permitted while on study treatment.

During cycle 1 only: Transfusions are not permitted unless platelets <25,000/mm^3 or platelets < 50,000/ mm^3 accompanied by bleeding. Growth factors are not permitted unless ANC <500/ mm^3.

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded in the eCRF and documented in the Electronic Health Record/medical record.

5.9.2 Prohibited medications

- Exposure to any new immunosuppressive medication in the 4 weeks prior to enrollment.
- Patients may not be receiving any other parenteral investigational agents. Oral chemotherapeutic agents or biologics –for example ruxolitinib, rituxan, ibrutinib therapy (either past or current exposure) - is allowed.
- The use of medication that are CYP1A2 inducers and CYP2C8 inhibitors and vitamin K antagonists are prohibited.

5.10 Supportive care

With the exception of prohibited therapies, participants should receive prophylactic or supportive as clinically indicated per institutional policies.

6.0 ANTICIPATED ADVERSE EVENT LIST

6.1 Leflunomide

Per the package insert for leflunomide, the expected toxicities for leflunomide follow, where the asterisk (*) signifies a common event (10%-30% of patients), unmarked items are infrequent events (1-3% of patients), a double asterisk (**) signifies a rare but possibly serious event, and a triple asterisk (***) signifies an event that may become serious and occurs in up to 10% of patients:

Blood and lymphatic system	anemia (including iron deficiency anemia), ecchymosis, pancytopenia**, agranulocytosis**, neutropenia**, thrombocytopenia**, leukopenia**
Cardiac	angina pectoris, migraine, palpitation, tachycardia, vasodilatation

Endocrine	diabetes mellitus, hyperthyroidism
Eye	blurred vision, cataract, conjunctivitis, eye disorder
Gastrointestinal	diarrhea*, abdominal pain, dyspepsia, nausea, vomiting, oral ulceration, anorexia, pancreatitis**, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder
Hepatobillary	cirrhosis**, hepatitis**, hepatic failure**, acute hepatic necrosis**, cholelithiasis**, cholestasis**, elevated hepatic enzymes (primarily ALT and AST)
Immune system	allergic reactions, anaphylactoid reactions**
Infections	respiratory infection*, infections (including bronchitis, rhinitis, sinusitis, pharyngitis, pneumonia, and urinary tract infections, oral or vaginal candidiasis, herpes simplex, herpes zoster, and fungal dermatitis), opportunistic and/or severe infections** including sepsis, that may be fatal (especially Pneumocystis jiroveci pneumonia, tuberculosis, aspergillosis)
Metabolism and nutrition	hyperglycemia, creatine phosphokinase increased, hyperlipidemia
Musculoskeletal and connective tissue	arthrosis, bone necrosis, bone pain, bursitis, muscle cramps, myalgia, tendon rupture
Neoplasms	secondary malignancy**, cyst
Nervous system	headache*, peripheral neuropathy* (including peripheral numbness, tingling, burning, severe pain, cold sensation in the distal extremities, or extremity weakness), paresthesias, taste perversion (dysgeusia), anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweating increased, vertigo, migraine
Renal and urinary	albuminuria, cystitis, dysuria, hematuria, hypophosphaturia, hyperuricemia, increased urinary frequency
Reproductive	menstrual irregularity/disorder, menstrual disorder, vaginal moniliasis vaginal moniliasis, prostate disorder
Respiratory	interstitial lung disease** (sometimes fatal), interstitial pneumonitis**, pulmonary fibrosis**, asthma, dyspnea, epistaxis, lung disorder
Skin and subcutaneous tissue	maculopapular rash*, dry skin*, alopecia*, hair discoloration*, Stevens-Johnson syndrome**, toxic epidermal necrolysis**, erythema multiforme**, cutaneous lupus erythematosus**, acne, contact dermatitis, fungal dermatitis, hematoma, nail disorder, skin discoloration, skin disorder, skin nodule, subcutaneous nodule, skin ulcer
Vascular	varicose veins, hypertension***, vasculitis, cutaneous necrotizing vasculitis**
Miscellaneous	weight loss*, leg cramps*, jaundice**, allergy related angioedema**, fever, peripheral edema, hernia, neck pain, pelvic pain, pain, abscess, malaise

6.2 Cholestyramine

Per the package insert for cholestyramine, the expected toxicities for cholestyramine follow, where the double asterisk (**) signifies a common event, and a single asterisk (*) signifies a less common event, and remaining unmarked items are less likely:

Blood and lymphatic system	anemia, ecchymosis, prolonged prothrombin time, hypoprothrombinemia
Ear and labyrinth	tinnitus, vertigo
Eye	uveitis
Gastrointestinal	constipation**, abdominal pain*, anorexia*, nausea*, vomiting*, diarrhea*, flatulence*, diarrhea*, eructation,* steatorrhea,* diverticulitis, bleeding from known duodenal ulcer, dysphagia, gastrointestinal hemorrhage, hemorrhoidal bleeding, hiccups, intestinal obstruction (rare), melena, pancreatitis, rectal pain, tongue irritation, tooth enamel damage (dental erosion), dental bleeding, dental caries, dental discoloration

Hepatobillary	abnormal hepatic function tests, biliary colic, gallbladder calcification
Immune system	hypersensitivity reaction
Infections	
Metabolism and nutrition	hyperchloremic metabolic acidosis
Musculoskeletal and connective tissue	arthralgia, arthritis, backache, myalgia, osteoporosis associated with vitamin D deficiency
Nervous system	anxiety, dizziness, drowsiness, dysgeusia, fatigue, headache, neuralgia, paresthesia, syncope
Renal and urinary	hematuria, dysuria, burnt odor to urine, diuresis
Respiratory	asthma dyspnea and wheezing associated with hypersensitivity reaction
Skin and subcutaneous tissue	perianal skin irritation, skin irritation, skin rash, urticaria
Miscellaneous	adenopathy, increased libido, edema, bleeding tendencies due to vitamin K deficiency, vitamin deficiency (A, D, E, K), weight loss, weight gain, hematoma, hemorrhage, femoral nerve pain

7.0 DOSE DELAY/MODIFICATION GUIDELINES

7.1 Dose Modifications for Leflunomide

7.1.1 General Information

a. The study will use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to grade toxicities. A copy of the version 5.0 can be downloaded from:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

b. Rules for dose modification are found in Table 7.1.1.

c. Baseline values are from the last values obtained prior to treatment.

d. **For holds due to toxicities related to study agent, if the participant does not meet criteria to resume treatment within 14 days, the participant must permanently discontinue study treatment.**

7.1.2 Dose Modifications

The tables below detail the specific dose modifications for toxicities on single agent leflunomide (Table 7.1.1) and are to be used in agreement with the information in Section 7.1.1.

Table 7.1.1 Dose Modifications for Leflunomide Treatment

Adverse Event	Treatment modification
Hematological Toxicities:	
Febrile Neutropenia Grade 3 (ANC: <1.0 x10^9/L with a single temperature of >38.3 ˚C or a sustained temperature ≥ 38.0˚C for more than one hour.	At 20 mg: ○ Hold study agent. ○ If resolves to ANC ≥ 1.0 x 10^9/L and temperature < 38.0◦C within 14 days, resume study agent at 10 mg. ○ If does not resolve within 14 days, permanently discontinue study agent. At 10 mg: Permanently discontinue study agent
Febrile Neutropenia Grade 4 Life threatening consequences; urgent intervention needed.	Permanently discontinue study agent.
Neutropenia (ANC) Grade 1 (1.5x 10^9/L -<LLN)	Maintain study agent.

Neutropenia (ANC) Grade 2 (1.0 –<1.5x 10^9/L)	Maintain study agent.
Neutropenia (ANC) Grade 3 (0.5 –< 1.0x 10^9/L)	Maintain study agent. Growth factor recommended after cycle 1.
Neutropenia (ANC) Grade 4 (<0.5x 10^9/L)	At 20 mg: o Hold study agent and provide supportive care. o If ANC does not resolve to ≤ grade 3 (ANC ≥ 0.5 x 109/L) in 5 days, permanently discontinue study agent. Otherwise proceed as follows: o If resolves to ≤ grade 2 (ANC ≥ 1.0 x 109/L) in ≤ 14 days, resume study agent at 10 mg. o If ANC does not resolve to ≤ grade 2 (ANC ≥ 1.0 x 109/L) by 14 days, permanently discontinue study agent. At 10 mg: Permanently discontinue study agent.
Thrombocytopenia Grade 1 (75 x 10^9/L -<LLN)	Maintain study agent
Thrombocytopenia Grade 2 (50 – <75 x 10^9/L)	Maintain study agent
Thrombocytopenia Grade 3 without bleeding (25 – <50 x 10^9/L)	Maintain study agent.
Thrombocytopenia Grade 3 with bleeding (25 – <50 x 10^9/L)	At 20 mg: o Hold study agent and provide supportive care. o If bleeding does not resolve in 5 days, permanently discontinue study agent. Otherwise proceed as follows: o If bleeding resolves within 5 days and platelets resolve to ≤ grade 2 (platelets ≥ 50 x 109/L) in ≤ 14 days, resume study agent 10 mg. o If bleeding resolves within 5 days but thrombocytopenia does not resolve to ≤ grade 2 (platelets ≥ 50 x 109/L) by 14 days, permanently discontinue study agent. At 10 mg: Permanently discontinue study agent.
Thrombocytopenia Grade 4 (<25 x 10^9/L)	At 20 mg: o Hold study agent and provide supportive care. o If platelets do not resolve to ≤ grade 3 (platelets ≥ 25 x 109/L) in 5 days, permanently discontinue study agent. Otherwise proceed as follows: o If resolves to ≤ grade 2 (platelets ≥ 50 x 109/L) in ≤ 14 days, resume study agent 10 mg. o If thrombocytopenia does not resolve to ≤ grade 2 (platelets ≥ 50 x 109/L) by 14 days, permanently discontinue study agent. At 10 mg: permanently discontinue study agent.
Gastrointestinal	
Diarrhea Grade 1 (2-3 stools/day >baseline)	Maintain treatment.
Diarrhea Grade 2 (4-6 stools/day > baseline)	Maintain study agent.
Diarrhea Grade 3 (7-9 stools/day > baseline)	At 20 mg: Hold study agent and provide optimal anti-diarrheal therapy. *First Occurrence:* If resolves to ≤ grade 1 in ≤ 7 days, resume at 20 mg. If resolves to ≤ grade 1 in 8-14 days, resume study agent at 10 mg. If does not resolve within 14 days, permanently discontinue study agent. *Recurrence:* If resolves to ≤ grade 1 in ≤ 14 days, resume at 10 mg. If does not resolve within 14 days, permanently discontinue study agent. At 10 mg: Permanently discontinue study agent.

Diarrhea Grade 4 (≥10 stools/day > baseline)	At 20 mg: Hold study agent and provide optimal anti-diarrheal therapy. If does not resolve to Grade 3 within 48 hours, permanently discontinue study agent. If resolves to Grade 3 within 48 hours, then: *First Occurrence:* Hold until resolution to ≤ grade 1. If resolved in ≤ 7 days, resume at pre-hold dose. If resolved in 8-14 days, resume study agent at 10 mg. If not resolved within 14 days, permanently discontinue study agent. *Recurrence:* Hold until resolution to ≤ grade 1. If resolved in ≤ 14 days, resume study agent at 10 mg. If not resolved within 14 days, permanently discontinue study agent. At 10 mg: Permanently discontinue study agent.
Vomiting or Nausea Grade 1	Maintain study agent.
Vomiting or Nausea Grade 2	Maintain study agent.
Vomiting or Nausea Grade 3	At 20 mg: Hold study agent and provide optimal supportive care/therapy. *First Occurrence:* If resolves to ≤ grade 1 in ≤ 7 days, resume at pre-hold dose. If resolves to ≤ grade 1 in 8-14 days, resume study agent at 10 mg. If does not resolve within 14 days, permanently discontinue study agent. *Recurrence:* If resolves to ≤ grade 1 in ≤ 14 days, resume at 10 mg. If does not resolve within 14 days, permanently discontinue study agent. At 10 mg: Permanently discontinue study agent.
Vomiting Grade 4	At 20 mg: Hold study agent and provide optimal supportive care/therapy. If does not resolve to Grade 3 within 48 hours, permanently discontinue study agent. If resolves to Grade 3 within 48 hours, then: *First Occurrence:* Hold until resolution to ≤ grade 1. If resolved in ≤ 7 days, resume at pre-hold dose. If resolved in 8-14 days, resume study agent at 10 mg. If not resolved within 14 days, permanently discontinue study agent. *Recurrence:* Hold until resolution to ≤ grade 1. If resolved in ≤ 14 days, resume study agent at 10 mg. If not resolved within 14 days, permanently discontinue study agent. At 10 mg: Permanently discontinue study agent.
Hepatic investigations	
ALT (SGPT) or AST (SGOT) ≤ 3.0 x ULN or TBili ≤ 1.5 x ULN	Maintain study agent.
ALT (SGPT) or AST (SGOT) >3.0 - 5.0 x ULN or TBili >1.5 - ≥ 3.0 x ULN	*First Occurrence:* Hold until resolution to < 3.0 x ULN for ALT or AST or < 1.5 for TBili. Resume at pre-hold dose if resolved within 14 days. If does not resolve within 14 days, permanently discontinue study agent. *Recurrence:* Hold until resolution to < 3.0 x ULN for ALT or AST or <1.5 for TBili. Resume at 10 mg if resolved within 14 days. If does not resolve within 14 days, permanently discontinue study agent.

ALT (SGPT) or AST (SGOT) > 5.0 x ULN or TBili > 3.0 x ULN	Permanently discontinue study agent.
Electrolyte/metabolic toxicity	
Electrolyte/metabolic Grade 3	Provide support care. Maintain study agent per investigator discretion. If alteration persists despite aggressive replacement therapy, then dose reduce or permanently discontinue (per investigator discretion with PI consultation).
Electrolyte/metabolic Grade 4	Provide support care. Maintain study agent per investigator discretion. If resolves to Grade 1 or baseline within 48: for first event, maintain at pre-hold dose; for recurrent event, dose reduce or permanently discontinue (per investigator discretion with PI consultation). If does not resolve to Grade 1 or baseline within 48 hours, permanently discontinue study agent.
Other unspecified Non-Hem toxicities considered related to leflunomide	
Grade 1	Maintain study agent.
Grade 2	Maintain study agent.
Grade 3	*First Occurrence:* Hold until resolution to ≤ Grade 2. Resume at pre-hold dose if resolved within 7 days. If does not resolve within 7 days, permanently discontinue study agent. *Recurrence:* Hold until resolution to ≤ Grade 1. Resume at 10 mg if resolved within 14 days. If does not resolve within 14 days, permanently discontinue study agent.
Grade 4	Permanently discontinue study agent.
Other unspecified Non-Hem Toxicities considered UNRELATED to study agent	
Other unspecified events of any grade considered unlikely to be related or not related to study agents.	Maintain treatment with study agents. Interruption of study agent or dose de-escalation is permitted if the investigator consults with the Principal Investigator to determine that this is in the best interest of the participant.

7.2 Dose Modifications of Cholestyramine

Cholestyramine will be administered and dose modified per the discretion of the treating investigator in agreement with standard administration practices.

8.0 AGENT INFORMATION

8.1 Leflunomide

Leflunomide is an FDA approved agent for the treatment of rheumatoid arthritis. Please refer to the Package Insert for additional details not provided in this section.

8.1.1 Description and classification

The chemical name for leflunomide is N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide. It has a molecular formula C H F N O, a molecular weight of 270.2. Leflunomide is a pyrimidine synthesis inhibitor.

8.1.2 Mode of action

Leflunomide is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity. Several in vivo and in vitro experimental models have demonstrated an anti-inflammatory effect.

8.1.3 Toxicology

See Section 6.1

8.1.4 Pharmacology

Following oral administration, leflunomide is metabolized to an active metabolite teriflunomide (A77 1726) which is responsible for essentially all of its activity *in vivo*. Following oral administration, peak levels of the active metabolite occurred between 6 to 12 hours after dosing. Due to the very long half-life of teriflunomide (~2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of teriflunomide. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. Biliary recycling is a major contributor to the long elimination half-life of teriflunomide. The active metabolite of leflunomide is eliminated slowly from the plasma. Use of a drug elimination procedure (cholestyramine or activated charcoal) is used to reduce the drug concentration more rapidly after stopping leflunomide therapy.

8.1.5 Storage and stability

Leflunomide tablets should be stored at 25°C (77°F); excursions are permitted to 15–30°C (59–86°F). Protect from light.

8.1.6 Preparation

Leflunomide is commercially available for oral administration as tablets containing 10, 20, or 100 mg of active drug.

8.1.7 Agent administration

Leflunomide is administered orally. Participants will be given a study calendar to track all doses taken or missed. There will be an initial loading dose of 100 mg/day for the first 3 days of doses. Participants will then receive leflunomide at the assigned dose level. See Section 5.3.1 for administration details.

8.1.8 Availability and supply

Tablets in 10 and 20 mg strengths are packaged in bottles of 30 pills per bottle. Leflunomide will be provided to patients by the study as an investigational agent. A commercial supply will be purchased and distributed as an investigational agent by the Investigational Drug Pharmacy at City of Hope.

8.2 Cholestyramine

Cholestyramine is not the study agent being evaluated for efficacy, but is required for the elimination of the study agent leflunomide. Cholestyramine is FDA approved for hypercholesterolemia. **Cholestyramine use is indicated in the leflunomide package insert to eliminate the leflunomide metabolite.**

8.2.1 Description

Cholestyramine is a strong anion exchange resin comprised of a quaternary ammonium group attached to an inert styrene-divinylbenzene copolymer. Cholestyramine removes bile acids from the body by forming insoluble complexes with bile acids in the intestine, which are then excreted in the feces.

8.2.2 Other names

Questran®, Questran Light, Cholybar, Olestyr

8.2.3 Mode of action

Cholestyramine resin adsorbs and combines with the bile acids in the intestine to form an insoluble complex which is excreted in the feces. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption.

8.2.4 Toxicology

See Section 6.2.

8.2.5 Storage and stability

Store between 20º-25ºC (68º-77ºF). [See USP Controlled Room Temperature]. Excursions permitted to 15º-30ºC (59º-86ºF).

8.2.6 Agent administration

Cholestyramine should be administered orally after being prepared per package insert (powder diluted in fluid). See Section 5.3.2 for study administration details.

8.2.7 Availability and supply

Cholestyramine will be provided to participants by the study. A commercial supply will be purchased and distributed by the pharmacy at City of Hope.

9.0 CORRELATIVE/ SPECIAL STUDIES

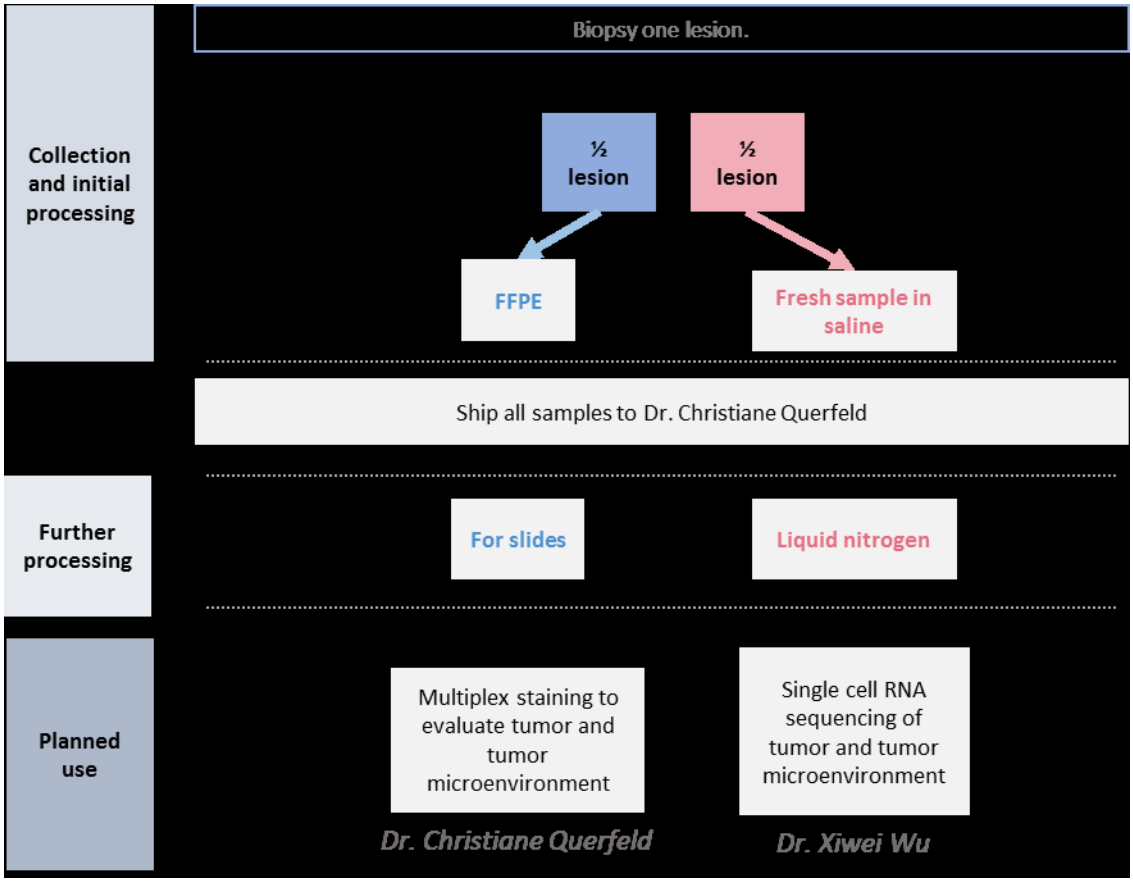
9.1 Central Pathology Review

A slide from a baseline skin biopsy of the participant taken in the preceding 6 months must be sent to City of Hope for diagnostic review.

9.2 Skin Biopsies

The diagram below diagram provides an overview for the skin biopsy samples.

Figure 9.1 Overview of collection and analysis for CD30+LYPD tissue samples



9.2.1 Collection details

A single skin lesion will be sampled from participants at baseline and subsequent timepoints.

Samples will be a ~1x1 cm punch biopsy for all timepoints

9.2.2 Timepoints of collection

Lesion samples will be taken at the following timepoints:

- Pre-dose Cycle 1 Day 1 (baseline samples may be collected anytime post-informed consent and prior to the Cycle 1 Day 1 dose)
- Cycle 2 Day 1, and Cycle 5 Day 1 if lesions are present
- At end of protocol therapy (13 or fewer cycles) if lesions are present.
- At disease progression

9.2.3 Processing details

The collected samples will be processed as follows:

- ½ of each lesion will be formalin fixed (FFPE).
- ½ of each lesion will be collected in saline.

9.2.4 Labeling of samples

Samples will labeled with the study number, subject ID, type of biopsy (shave or punch), date and timepoint of collection (as stated in Section 9.2.1), and if applicable patient initials.

9.2.5 Sample shipment

Samples collected at the above indicated timepoints will be taken to Dr. Querfeld's laboratory (Kaplan Rm#1024) for processing as stated in Figure 9.1.

9.2.6 Single Cell RNA Sequencing

The samples at baseline and beginning of cycle 2 for each patient will be analyzed together to identify changes in both CD30 tumor cells and other immune cell populations. Cells with mitochondrial read rate > 10% and < 200 detectable genes are considered as low-quality and filtered out. Unwanted sources of variation will be regressed out of the data by constructing linear models to predict gene expression based on the number of UMIs per cell as well as the percentage of mitochondrial gene content. Normalized and scaled data will be clustered using the top significant principal components of the highly variable genes. The t-distributed stochastic neighbor embedding (t-SNE) algorithm will be used to visualize the resulting clusters. Cluster specific markers will be identified to generate heatmap and identify cell types in each cell cluster. T cell subtype markers, such as T reg, memory T cells, effector T cells, exhausted T cells etc. will be used to identify different T cell populations. Chromium's V(D)J-Loupe will be used for analysis of TCR clonotypes and for visualization. Over-represented TCR clone in each patient will be identified and considered as indication of malignant cells. Genes will be compared between malignant and non-malignant cells using Bioconductor package "Limma" on log transformed and normalized scRNA-seq data. Gene Set Enrichment analysis (GSEA) v3 will be performed to evaluate the significance activation of the Hallmark and KEGG gene sets in MSigDb. This analysis will help us understand what specific pathways are activated in tumor cells and how the pathways are changing after treatment. Single cell trajectory analysis will be conducted with diffusion pseudotime method using Bioconductor package "destiny", which will capture the dynamic changes of tumor cells before and after treatment.

9.2.7 Immunohistochemistry

In addition, immunohistochemistry will be performed on all specimens to better examine the effect leflunomide has on the changing tumor and tumor microenvironment as well as correlate these findings with those from scRNA-seq. Current work in this area has noted that the predominant cells in the tumor microenvironment of CD30+LYPDs include CD163+ M2, tumor infiltrating CD8+ lymphocytes, FOXP3+ Tregs and programmed cell death (PD-1) lymphocytes.

The multiplex immunohistochemistry of the tumor microenvironment will distinguish the CD30+ T cells (tumor cells) from other cells (M2, Tregs, tumor infiltrating T cells) and whether or not PD1 co-expression is noted. The findings will be correlated to clinical response.

10.0 STUDY CALENDAR

Table 10 describes required procedures. All procedures may increase in frequency if clinically indicated or oriented following toxicity. Adjustments to the treatment cycle due to a hold in study agent are detailed in Section 5.2.

Table 10.0 Study Activity Calendar

	Screen-ing [a]	Cycle 1, 2, 3		Cycle 4+	End of Treatment [e]				Active Follow-Up [j]
		Day 1[b]	Day 14[c]	Day 1[d]	Day 0 [f]	Days 1-11[g]	Day 14[h]	Day 30 [i]	
Informed Consent [k]	X [s]								
Inclusion/Exclusion Criteria [l]	X								
Registration [m]	X [n]								
Medical history [n]	X								
Physical exam	X	X		X				X	
Vital signs [o]	X	X		X				X	
Adverse events assessment [p]		X	X	X	X			X	
Concomitant meds review	X	X		X	X			X	
ECOG status (Appendix A)[l]	X	X		X				X	
Pregnancy test [q]	X								
TB antigen test [r]	X								
Hepatitis A, B, C testing	X [s]								
Skin photographs [t]	X	X		X	X			X	X
mSWAT [u]	X	X		X	X			X	X
Skin biopsy [v]		X [w]		X [w]				X [w]	
CBC with differential [x]	X	X	X	X				X	X
Chemistry panel [y]	X	X	X	X				X	X
Response assessment [z]		X		X	X			X	X
Teriflunomide clinical testing [aa]					X		X [dd]	X [dd]	
Leflunomide administration [bb]		Daily							
Cholestyramine [g]						X [g]			

a. All screening procedures to be performed within 21 days of start of study agent except informed consent, acute hepatitis panel, skeletal survey which may occur within 30 days of start of treatment (footnote u) and except for registration which must occur within 7 days from start of treatment (footnote n).

b. Day 1 assessments to be performed within 5 days (120 hours) prior to Day 1 drug (except footnote u for C1 only). Day 1 safety assessments must be resulted and reviewed prior to administration of agent for the cycle that is initiating. Screening assessments, if performed within this aforementioned time frame, may serve as C1D1 assessments. Note: items with footnote "aa" are not performed for C1D1; the windows for screening assessments still apply.

c. Day 14 evaluations have +/- 3 day window.

d. Day 1 assessments to be performed within 5 days (120 hours) prior to Day 1 drug. Day 1 safety assessments must be resulted and reviewed prior to administration of agent for the cycle that is initiating.

e. Reasons to end study treatment include disease progression and unacceptable toxicity. See Section 5.8 for all criteria.

f. End of Treatment (EOT) Day 0 is defined as the day the determination to end treatment is made. EOT Day 0 assessments to be performed as soon as feasible, especially in the event of off treatment due to unacceptable toxicity and no later than 7 days after decision to end treatment; assessments performed after last dose of study agent(s) and within 7 days of the decision to end treatment may serve as EOT Day 0 assessments.

g. EOT Day 1 is defined as the day cholestyramine administration begins; it will usually follow immediately after EOT Day 0, although it will not be deviation if this does not occur. If it does not follow immediately after EOT Day 0, the rest of calendar will follow per the actual EOT Day 1 (not EOT Day 0). Cholestyramine (8 grams three times daily for 11 days) will be administered according to Section 5.5.

h. EOT Day 14 assessments must occur after completion of cholestyramine, and may occur on Day 14 +/- 3 day window. If the cholestyramine administration period is extended beyond 11 consecutive days, the EOT Day 14 assessments may occur outside of this defined window.

i. EOT Day 30 visit has a +/- 2 day window, however this window may be adjusted without deviation to ensure that it corresponds to the final teriflunomide clinical test (see footnote ee). All participants will be followed until resolution or stabilization of any serious adverse events occurring during treatment or starting within 30 days of last study drug administration or within the time to complete the EOT Day 30 assessments, which every occurs later.

j. Active follow-up will occur for participants who have completed EOT procedures and yet to demonstrate disease progression. Disease response will be assessed every 3 months. Active follow-up will continue for 12 months or until disease progression, whichever is earlier.

k. Informed consent process to be fully documented: e.g. prospective participant had sufficient time for deliberation, all questions were answered, treatment options provided by MD, full study reviewed including risks, and a copy of signed consent given to participant.

l. Inclusion/exclusion criteria are detailed in .Section 3.

m. See Section 4.3 for slot reservation and registration process. Treatment must begin within 7 days of registration. Documentation providing Investigator's confirmation that all eligibility criteria are met must be available prior to registration.

n. Medical history to include review treatment history for CD30+LYPD medical history pertaining to eligibility, and demographic information.

o. Vital signs: Weight, heart rate, blood pressure, respiration rate, temp. Height required only at baseline.

p. Adverse event (AE) reporting begins for events that occur after start of study agent. AE recording and reporting will continue until the completion of the EOT Day 30 visit or until resolution or stabilization of any serious AE occurring before the completion the EOT Day 30 assessments, which every occurs later.

q. Serum or urine pregnancy test for women of child bearing potential only.

r. T-Spot or other TB antigen test.

s. Consent, acute hepatitis panel, to be completed within 30 days prior to registration.

t. Skin photographs: for subjects with skin lesions, up to five designated index lesions, representative of the subject's extent of disease, will be selected at baseline and measured and photographed using a digital camera. Photos should be taken against a blue backdrop. The photos will be taken on Day 1, prior to the first dose and then Cycle 2 Day 1 (-7 days) then every Cycle. In addition, half-body global photos (waist to feet, waist to top of head and sides) will also be obtained. Photos must be labeled with patient's protocol number and initials.

u. Modified Severity Weighted Assessment Tool (mSWAT)[30] (Appendix C)

v. skin biopsies for research will not be taken at baseline if patients have a recent biopsy taken containing needed information.

w. skin biopsies for research at baseline, at C2D1, C5D1, and EOT (if lesions are present), and at disease progression (Section 9.2).

x. CBC with differential: erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus absolute differential counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

y. Serum chemistry panel: Comprehensive metabolic panel (sodium, potassium, chloride, carbon dioxide, creatinine, urea nitrogen, calcium, glucose, albumin, total bilirubin, alkaline phosphatase, total protein, ALT/SGPT, AST/SGOT) LDH, magnesium, phosphorus, and uric acid.

z. See Section 11.2 for response assessment criteria.

aa. Teriflunomide clinical blood assay to be ordered as “leflunomide metabolite” miscellaneous clinical test.

bb. Clinical testing must demonstrate teriflunomide plasma levels less than 0.02 mg/L or 0.02 µg/ml by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L or 0.02 µg/mL, additional cholestyramine treatment will be considered.

cc. Participants will receive leflunomide orally on a daily basis which will be recorded on the pill diary (Appendix D). The first 3 loading doses will be given at a dose of 100 mg, after which treatment will continue at a dose of 20 or 10 mg daily. See administration details in Section 5.3.

11.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

11.1 Safety Endpoints

Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events version 5.0.

11.2 Efficacy Endpoints

Response on this study will be assessed by mSWAT (see Appendix C). In addition to mSWAT, individual lesions will also assessed by the Composite Assessment of Index Lesion Severity (CAILS) tool (see Appendix E).

Overall Response Rate:

- Defined as the proportion of patients with a documented response (CR or PR) any time during study treatment.

Complete Response Rate:

- Defined as the proportion of patients with a documented CR any time during study treatment.

Duration of response:

- Defined as the time interval from the date of first documented response (CR or PR) to the first documented disease progression or death, whichever occurs first. Patients without a documented CR or PR will be excluded. Patients who do not achieve CR or PR are excluded from this analysis.

11.3 Exploratory Endpoints

Endpoints for the exploratory objective on RNA signature are the RNA expression levels.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This study will be conducted as a single center pilot study to obtain some preliminary data on leflunomide treatment for patients with cutaneous LYPD. Patients will receive up to 13 cycles of leflunomide until any criterion for off-treatment is met. Patients without progressive disease at the time of off-treatment will be followed for up to 1 year after off-treatment as active follow-up. Response will be assessed after every cycle per mSWAT while on treatment and every 3 months while in active follow-up. The primary endpoint is overall response rate. Secondary endpoints include complete response rate, duration of response, and toxicities.

12.2 Sample Size and Accrual Rate

This study will accrue 12 response evaluable patients, with a maximum accrual of 14 patients. Because this is a rare disease that has not been systematically studied in a prospective clinical trial, there is a lack of historical data on the response rate (and by mSWAT) in this patient population. The sample size for this pilot study was chosen based on feasibility considerations, and not based on any definitive statistical criterion.With 12 patients, the 95% exact binomial confidence interval for the overall response rate will have a width of 55% (33% response rate, with 4 responders), 57% (42% response rate, with 5 responders),

58% (50% response rate, with 6 responders), 57% (58% response rate, with 7 responders), 55% (67% response rate, with 8 responders), 52% (75% response rate, with 9 responders), and 46% (83% response rate, 10 responders) respectively. For any AE with a true incidence of 15% or higher, with 12 patients there is at least an 86% chance of observing 1+ patients with such AE.

We project to accrue approximately one patient every 3 months. The projected study accrual duration is therefore 3 years.

12.3 Evaluable Participants and Participant Replacement

All participants who received at least 1 dose of study drug will be evaluable for toxicity. All participants who received at least 1 dose of protocol leflunomide and had at least 1 post-baseline response assessment will be evaluable for response; patients inevaluable for response (for example patients who did not receive any protocol treatment, or patients who had no response assessment on study due to withdrawal of consent during cycle 1) will be replaced.

12.4 Statistical Analysis Plan

Patient demographic and baseline characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median, and range will be provided. For categorical variables, patient counts and percentages will be provided.

Observed toxicities will be summarized, in terms of type, grade, time of onset, duration, and attribution to the study treatment. The overall response rate and complete response rate will be calculated along with the Clopper Pearson binomial 95% exact confidence intervals. Duration of response will be calculated using Kaplan-Meier product limit estimator; median duration of response will also be estimated when possible.

The miRNA/mRNA expression profile data will be summarized by descriptive statistics. The data will also be used to explore the miRNA/mRNA that show significant differences between responders and non-responders after leflunomide treatment. For miRNA/RNA profiling, fold changes >3 with an FDR <0.05 will be considered significant.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms/Data Submission Schedule

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	Within 10 calendar days of AE assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (concomitant medications)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study
Follow up/Survival Forms	Within 14 calendar days of the follow up activity

13.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

14.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite –** The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

14.2 Routine AE Collection and Reporting Guidelines

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (e.g., reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

Routing AEs recorded in the CRF will include:

During protocol treatment through EOT, all grade 2 or higher adverse events

All SAEs

14.3 Expedited Reporting

The table below indicates what events to report to expeditiously (Table 14.3).

Table 14.3 Expedited Reporting Guidelines

Time point	What to report
From signing of the consent to study completion	• All UPs and AEs that meet the definition of a UP
For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier	• All SAEs regardless of relationship to protocol therapy • All AESIs, overdose • AESIs (Section 14.2)- irAEs, overdose

All reportable events will require follow up until stabilization or resolution per the agreement of the Study PI.	
From Day 1 of protocol therapy up to 90 days post-last leflunomide dose	• Pregnancies and lactation
Post Safety follow-up to removal from study	• All SAEs that are at least possibly related to leflunomide.
NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or determined to be irreversible by the investigator.	

14.3.1 Expedited reporting guidelines

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. This includes all SAEs and UPs that meet COH DSMC/IRB expedited reporting criteria that occurred at COH and non-COH sites. For non-COH sites, the DCC will be responsible for reporting (see section 14.5.2).

14.4 Adverse Events of Special Interest (AESI) Requiring Expedited Reporting

14.4.1 Definition of Overdose

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of lenalidomide assigned to a given patient, regardless of any associated adverse events or sequelae.

PO any amount over 60 mg leflunomide

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported.

14.4.2 Second Malignancies

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

The investigator must immediately notify the Study PI/ DCC via an expedited report.

15.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the Clinical Research Protocol Deviation policy.

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

16.2 Study PI Responsibilities

The Study PI is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The PMT minimally consisting of the Study PI, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

16.4 Auditing & Quality Assurance

Clinical site auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. This trial will be audited by the City of Hope Office Office for Safety and Data Quality. Details of clinical site auditing are documented in the City of Hope Institutional Data and Safety Monitoring Plan (DSMP).

16.5 Risk Determination

This is a moderate risk study, as defined in the City of Hope Institutional DSMP. This determination was made because the study is an investigator-initiated Phase 2 study that is IND exempt.

16.6 City of Hope Data and Safety Monitoring Committee (DSMC)

The COH DSMC will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for

the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable, NIH policies and procedures
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or

future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the study drugs have been determined to be embryolethal and teratogenic in animal testing.

17.6.2 Pediatric Population

Pediatric participants (< 18 years of age) are excluded from this study since safety and effectiveness of protocol therapy has not yet been defined for the study population. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult study population.

The incidence of CTCL is rare in the pediatric population.

17.6.3 HIV Positive Individuals

Participants with HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

17.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens with a limited data set will be provided to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved CTCL biorepository (COH#15185) with some clinical information and potentially PHI attached or (b) discarded.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

The drugs, leflunomide and cholestyramine, will be provided free of charge by City of Hope.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov. Results will be reported on ClinicalTrials.gov generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

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APPENDIX A: ECOG PERFORMANCE STATUS SCALE

ECOG Performance Scale [32]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: ISCL/EORTC TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS

T: skin
T1: solitary skin involvement
T1a: solitary lesion <5 cm diameter
T1b: solitary lesion >5 cm diameter
T2: regional skin involvement : multiple lesions limited to 1 body region or 2 contiguous body regions*
T2a: all-disease-encompassing in a <15 cm diameter circular area
T2b: all-disease-encompassing in a >15 cm and <30 cm diameter circular area
T2c: all-disease-encompassing in a >30 cm diameter circular area
T3: generalized skin involvement
T3a: multiple lesions involving 2 noncontiguous body regions
T3b: multiple lesions involving ≥3 body regions
N: node
N0: no clinical or pathologic lymph node involvement
N1: involvement of 1 peripheral lymph node region† that drains an area of current or prior skin involvement
N2: involvement of ≥2 peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3: involvement of central lymph nodes
M: visceral
M0: no evidence of extracutaneous non-lymph node disease
M1: extracutaneous non-lymph node disease present

*Definitions of body regions: Head and neck: inferior border, superior border of clavicles, T1 spinous process. Chest: superior border, superior border of clavicles; inferior border, inferior margin of rib cage; lateral borders, midaxillary lines, glenohumeral joints (inclusive of axillae). Abdomen/genital: superior border, inferior margin of rib cage; inferior border, inguinal folds, anterior perineum; lateral borders, midaxillary lines. Upper back: superior border, T1 spinous process; inferior border, inferior margin of rib

cage; lateral borders, midaxillary lines. Lower back/buttocks: superior border, inferior margin of rib cage,; inferior border, inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders, midaxillary lines. Each upper arm: superior borders, glenohumeral joints (exclusive of axillae); inferior borders, ulnar/radial-humeral (elbow) joint. Each lower arm/hand: superior borders, ulnar /radial-humeral (elbow) joint. Each upper leg (thigh): superior borders, inguinal folds, inferior gluteal folds; inferior borders, midpatellae, midpopliteal fossae. Each lower leg/foot: superior borders, midpatellae, midpopliteal fossae.

†Definition of lymph node regions is consistent with the Ann Arbor system. Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal –femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraortic, iliac.

APPENDIX C: MODIFIED SEVERITY WEIGHTED ASSESSMENT TOOL (MSWAT)

The mSWAT scoring tool [30] will be used to assess disease severity. Assessments will be performed at the time points indicated in Section 10.0. To eliminate inter-observer variability for a given patient, the mSWAT should preferably be performed by the same qualified individual at all time points.

Region	% TBSA for the region	% TBSA Patch (or flat erythema)	% TBSA Plaque (or elevated/indurated erythema)	% TBSA Tumor/Ulceration (or erythema w/ fissuring, ulceration)
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper Arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower Leg	14			
Feet	7			
% BSA by category	100			
Severity Weighting Factor		×1	×2	×4
Skin Score Subtotal				

NOTE: mSWAT score equals summation of each column line.
Abbreviations: TBSA- total body surface area

APPENDIX D-1: LEFLUNOMIDE MEDICATION DIARY INSTRUCTIONS

Remember to bring this diary, all pill bottles, and any unused pills to each clinic visit.
Call your study doctor or nurse immediately if you are having any new or worsening side effects.

Study drug Instructions – When and How:

Take leflunomide **once a day** by mouth
Take the pills with a large glass of water (~250ml) at approximately the same times each day
Swallow pills; do not chew them or crush them
Do not skip any doses unless your doctor tells you to.

When to stop taking leflunomide

Do not stop taking leflunomide unless your doctor tells you to.

What if I miss a scheduled dose?

If **less than 3 hours** have passed from the scheduled time, then **take the missed dose** as soon as you remember.
If more than 3 hours have passed from the scheduled time, then skip the missed dose. Wait for your next scheduled dose. Do not take extra medicine to make up the missed dose.

What if I vomit after taking leflunomide?

If you vomit your pills, write this down in your pill diary.
Wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Additional Instructions:

Bring this diary, all pill bottles, and any unused pills to each clinic visit.
Keep your study drug in the original container until you take it.
Do NOT throw away empty pill bottles or unused pills.
Your dose may be adjusted based on your side effects

Contact Information		
Study Doctor **Phone:** **Name:**	**Study Nurse** **Phone:** **Name:**	**Backup Study Nurse** **Phone:** **Name:**

APPENDIX D-2: MEDICATION DIARY

Study Name: Pilot Trial of Leflunomide in Patients with CD30+ Lymphoproliferative Disorders

Subject ID#:	DPatient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:

Day	Week Day	Date	Time	Dose (mg)	# tablets taken	If dose missed, please provide reason:
1			__:__AM/PM			
2			__:__AM/PM			
3			__:__AM/PM			
4			__:__AM/PM			
5			__:__AM/PM			
6			__:__AM/PM			
7			__:__AM/PM			
8			__:__AM/PM			
9			__:__AM/PM			
10			__:__AM/PM			
11			__:__AM/PM			
12			__:__AM/PM			
13			__:__AM/PM			
14			__:__AM/PM			
15			__:__AM/PM			

Participant/Caregiver signature (please sign when submitting your diary): _____ Date ___/____/____

Study Name: Pilot Trial of Leflunomide in Patients with CD30+ Lymphoproliferative Disorders

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:

Day	Week Day	Date	Time	Dose	# tablets taken	If dose missed, please provide reason:
16			__:__AM/PM			
17			__:__AM/PM			
18			__:__AM/PM			
19			__:__AM/PM			
20			__:__AM/PM			
21			__:__AM/PM			
22			__:__AM/PM			
23			__:__AM/PM			
24			__:__AM/PM			
25			__:__AM/PM			
26			__:__AM/PM			
27			__:__AM/PM			
28			__:__AM/PM			

Participant/Caregiver signature (please sign when submitting your diary): _____ Date ___/____/____

APPENDIX E: COMPOSITE ASSESSMENT OF INDEX LESION SEVERITY (CAILS)

	Index Lesion				
Clinical Sign and Degree of Size (scale of 0-8)	1	2	3	4	5
Erythema					
Scaling					
Plaque Elevation					
Hypo- or hyperpigmentation					
Lesion size*					
Total (sum of subtotals)					

NOTE. Cannot be used as skin assessment in global response score. Suggestions for improvement include using actual size of lesion versus categorical score for size and eliminating pigmentation as a clinical parameter.

*Lesion size (cm^2): 0: no measurable area; 1: > 0 to ≤ 4; 2: > 4 to ≤ 10; 3: > 10 to ≤ 16; 4: > 16 to ≤ 25; 5: >25 to ≤ 35; 6: > 35 to ≤ 45; 7: > 45 to ≤ 55; 8: > 55 to ≤ 70; 9: > 70 to ≤ 90; 10: > 90 to ≤ 110; 11: > 110 to ≤ 130; 12: > 130 to ≤ 155; 13: > 155 to ≤ 180; 14: > 180 to ≤ 210; 15: > 210 to ≤ 240; 16: > 240 to ≤ 270; 17: > 270 to ≤ 300; 18: > 300.