



## Memorial Sloan-Kettering Cancer Center IRB Protocol

**IRB#: 07-029A(6)**

### A Pilot study of Topical Imiquimod Therapy for the Treatment of Recurrent Extramammary Paget's Disease

#### MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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### 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Population	Patients with Recurrent Extramammary Paget's Disease (EMPD)
Study Design	Pilot, prospective cohort study
Therapy	Imiquimod 5% Cream applied T.I.W.
Duration of Therapy	12 weeks
Assessment of Response	a. Clinical assessment of before and after photographs by an independent reviewer b. Non-blinded histologic assessment of baseline biopsies and post therapy excisional biopsies 4 weeks after end of treatment
Number of evaluable subjects required	20
Target sample size	Assuming a 15% dropout rate, target sample size is 17

This is a pilot study of the use of a topical immunomodulatory agent, imiquimod, for the treatment of recurrent Extramammary Paget's disease (EMPD). In this protocol we will assess the clinical and histologic effects of topical imiquimod on recurrent EMPD.

Imiquimod 5% cream (Aldara, 3M Pharmaceuticals, St Paul, Minnesota) is an FDA approved safe and effective treatment of anogenital warts, superficial basal cell carcinoma, and actinic keratoses.<sup>i</sup>

Imiquimod has been demonstrated to induce cytokines that promote a T<sub>H</sub>1 immune response following both systemic and topical administration.<sup>ii</sup> The induced cytokines include alpha interferon, gamma interferon, and interleukin 12. The specific mechanism of action by which imiquimod eliminates warts, basal cell carcinoma, and actinic skin cancers is unknown.

Several published case reports suggest the potential efficacy of topical 5% imiquimod cream in the treatment of EMPD after median treatment duration of 7.5 weeks (range 6-16).<sup>iii, iv, v, vi</sup> In addition, a recent abstract presented at the annual Society of Gynecologic Oncology meeting reported complete response of recurrent EMPD in five of six (83%) patients treated with imiquimod for a median duration of 12 weeks (range 6-48).<sup>xxi</sup> In this study we will recruit individuals with biopsy-proven recurrent EMPD. Imiquimod 5% cream will be applied by the patient 3 times per week for 12 weeks. The patient will be seen in clinic every six weeks during treatment for examination, teaching, and to assess compliance. Punch biopsy and photography will be performed at the baseline and 12 week time points. Biopsies will be performed using the 3mm punch biopsy instrument. The location will be at the periphery of the lesion as determined by the physician with an attempt made to incorporate some normal tissue. Biopsy or biopsies will be obtained of the most suspicious area. If the lesion is still present after 12 weeks of therapy, the treating physician will recommend excision of the lesion four weeks after completion of therapy (week 16). The patient will have a follow-up exam 6 weeks after excision and then every 3 months for at least 2 years. If no

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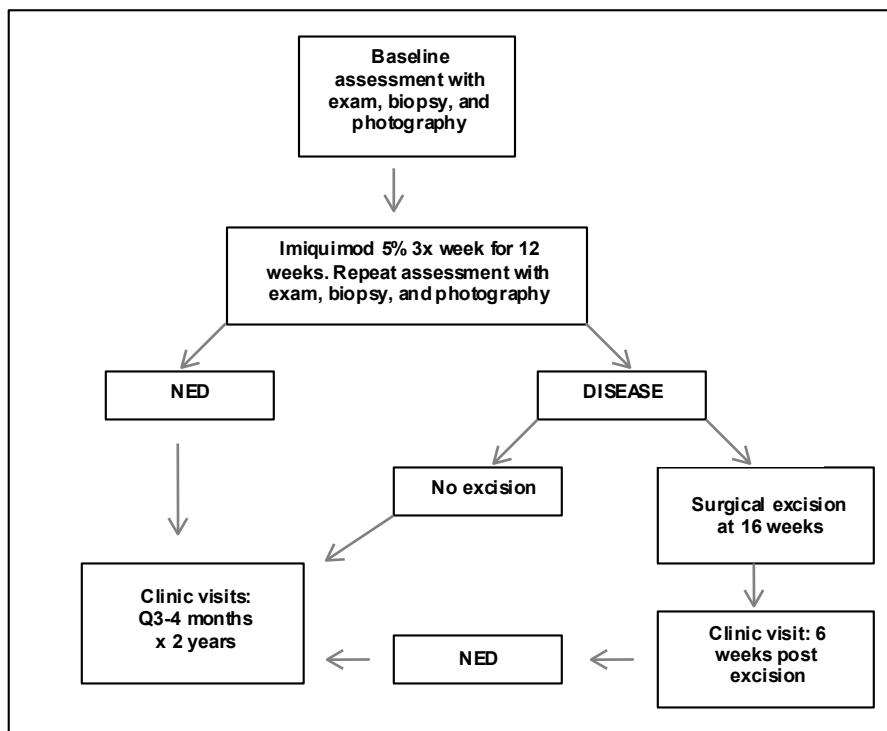
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lesion is present or the patient refuses surgical excision at week 16, the patient will return for follow-up exams every 3 months for at least 2 years. The treating physician will continue to offer surgical excision at any later point during follow-up if the lesion is still present.

We will evaluate the clinical and histologic response of recurrent EMPD to treatment. Clinical response will be assessed by a pathologist (non-blinded) and an independent reviewer who will compare clinical photographs obtained at study completion to those obtained at baseline. Lesions will be evaluated based on size as having undergone complete response, partial response, no change, or progression. Histologic evaluation will entail quantifying the number of residual Paget cells following treatment. Side effects and toxicities of therapy will be monitored and recorded.

Presented below is the treatment schema for this prospective cohort.



### 2.0 OBJECTIVES AND SCIENTIFIC AIMS

To assess the clinical and histologic effects of topical imiquimod therapy on recurrent extramammary Paget's disease (EMPD).

### 3.0 BACKGROUND AND RATIONALE

#### 3.1 Topical chemotherapy for the treatment of recurrent EMPD

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EMPD represents 1% to 5% of all vulvar neoplasia. The diagnosis is confirmed by the histological identification of unique intraepithelial neoplastic cells showing glandular differentiation.<sup>vii</sup> Surgery is accepted to be the standard modality of treatment; however, this is associated with significant disfigurement and high local recurrence rate with many patients requiring multiple excisions. In a review of 100 patients treated surgically for vulvar Paget's disease, there was a recurrence rate of 34% after a median follow-up of 3 years (range, 0.6-15 years).<sup>viii</sup> Topical chemotherapeutic agents including 5-fluorouracil (5-FU), bleomycin and imiquimod have been used to treat EMPD. Unfortunately, 5-FU and Bleomycin were associated with poor response rates and toxic side effects.<sup>ix, x</sup> Case reports of imiquimod therapy in 5 patients with EMPD demonstrate a complete clinical response after a median follow-up of 6 months (range, 0.5-14 months).<sup>iii, iv, v, vi</sup> There are no prospective clinical trials evaluating EMPD and imiquimod therapy. Although the incidence of EMPD is small, MSKCC treats approximately 5 patients a year and therefore has a unique opportunity to perform a pilot study evaluating the effects of imiquimod on recurrent EMPD.

### 3.2 The therapeutic agent

Imiquimod is an immune response modifier that has been demonstrated to induce cytokines that promote a T<sub>H</sub>1 response following both systemic and topical administration. The cytokines induced include alpha and gamma interferon and interleukin 12. In humans, imiquimod 5% cream (Aldara, 3M Pharmaceuticals, St Paul, MN) is an FDA approved safe and effective treatment of anogenital warts, actinic keratosis, and superficial basal cell carcinoma. As noted above, isolated cases have been reported of the eradication of EMPD with topical 5% imiquimod therapy.

## 4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

### 4.1 Design

This is a pilot study of the use of a topical immunomodulatory agent, imiquimod, for the treatment of recurrent Extramammary Paget's disease (EMPD). In this protocol, we will assess the clinical and histologic effects of topical imiquimod on recurrent EMPD.

Imiquimod 5% cream is an FDA approved safe and effective treatment of anogenital warts, superficial basal cell carcinoma, and actinic keratoses.<sup>xi</sup>

Imiquimod has been demonstrated to induce cytokines that promote a T<sub>H</sub>1 immune response following both systemic and topical administration.<sup>xii</sup> The induced cytokines include alpha interferon, gamma interferon, and interleukin 12. The specific mechanism of action by which imiquimod eliminates warts, basal cell carcinoma, and actinic skin cancers is unknown.

Several case reports suggest the potential efficacy of topical 5% imiquimod cream in the treatment of EMPD after median treatment duration of 7.5 weeks (range 6-16).<sup>xiii, xiv, xv, xvi</sup> In this study, we will recruit a total of 20 individuals with biopsy-proven recurrent EMPD. Imiquimod

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5% cream will be applied by the patient 3 times per week for 12 weeks. The patient will be seen in clinic every six weeks during treatment for examination, teaching, and to assess compliance. Compliance with therapy will be monitored with a patient diary (see Appendix) with quantification of residual medication at study completion. Punch biopsy and photography will be performed at the baseline and 12 week time points. If the lesion is still present after 12 weeks of therapy, the treating physician will recommend excision of the lesion four weeks after completion of therapy (week 16). The patient will have a follow-up exam 6 weeks after excision and then every 3 months for at least 2 years. If no lesion is present or the patient refuses surgical excision at week 16, the patient will return for follow-up exams every 3 months for at least 2 years. The treating physician will continue to offer surgical excision at any later point during follow-up if the lesion is still present.

### 4.2 Intervention

The patient will be seen in clinic every six weeks during treatment for examination. Imiquimod cream is to be applied 3 times per week for 12 weeks. Several case reports suggest the potential efficacy of topical 5% imiquimod cream in the treatment of EMPD after median treatment duration of 7.5 weeks (range 6-16). The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of imiquimod therapy. It should be applied prior to normal sleeping hours, and left on the skin for 6-10 hours. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of imiquimod therapy. Handwashing is recommended before and after applying imiquimod 5% cream.

Punch biopsy and photography will be performed at the baseline and 12 week time points. If the lesion is still present after 12 weeks of therapy, the treating physician will recommend excision of the lesion four weeks after completion of therapy (week 16). The patient will have a follow-up exam 6 weeks after excision and then every 3 months for at least 2 years. If no lesion is present or the patient refuses surgical excision at week 16, the patient will return for follow-up exams every 3 months for at least 2 years. The treating physician will continue to offer surgical excision at any later point during follow-up if the lesion is still present.

### 5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Aldara™ (imiquimod) Cream, 5% is the brand name for imiquimod which is an immune response modifier.<sup>xvii</sup> Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isosteric acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben. Chemically, imiquimod is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of C14H16N4 and a molecular weight of 240.3.<sup>xviii</sup>

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### Pharmacodynamics

The mechanism of action of imiquimod in treating genital/perianal warts, superficial basal cell carcinoma, and actinic keratoses is unknown. Imiquimod has no direct antiviral activity in cell culture. Mouse skin studies suggest that imiquimod induces cytokines including interferon- $\alpha$ . However, the clinical relevance of these findings is unknown.<sup>xviii</sup>

### Pharmacokinetics

Percutaneous absorption of [14C] imiquimod was minimal in a study involving 6 healthy subjects treated with a single topical application (5 mg) of [14C] imiquimod cream formulation. No radioactivity was detected in the serum (lower limit of quantitation: 1 ng/mL) and <0.9% of the radiolabelled dose was excreted in the urine and feces following topical application.<sup>xviii</sup>

### Administration of topical imiquimod

Imiquimod cream is to be applied 3 times per week, prior to normal sleeping hours, and left on the skin for 6-10 hours. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. Local skin reactions (erythema) at the treatment site are common. Local anesthetic cream or non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions. Treatment may resume once the reaction subsides. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of imiquimod therapy. Handwashing before and after cream application is recommended. Imiquimod 5% cream is packaged in single-use packets which contain sufficient cream to cover an area of up to 20 cm<sup>2</sup>; use of excessive amounts of cream should be avoided. A thin layer is applied to the skin and rubbed in until the cream is no longer visible. The application site is not to be occluded.

Aldara (imiquimod, 5%), is supplied in single-use packets which contain 250 mg of the cream. Available as: box of 12 packets NDC 0089-0610-12. Store below 25°C (77°F). Avoid freezing.<sup>13</sup>

## 6.0 CRITERIA FOR SUBJECT ELIGIBILITY

### 6.1 Subject Inclusion Criteria

All patients presenting to the Gynecology outpatient service at a participating institution who meet eligibility requirements may be included in this clinical trial. The eligibility requirements are as follows:

1. Age  $\geq$ 18.
2. Ability to give informed consent.
3. Patients must have biopsy proven recurrent extramammary Paget's disease confirmed at the participating site.

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### 6.2 Subject Exclusion Criteria

1. Patients with known hypersensitivity to imiquimod.
2. Pregnant and nursing women are not eligible
3. Patients with underlying adenocarcinoma on biopsy of lesion confirmed at the participating site.

### 7.0 RECRUITMENT PLAN (WITH LIMITED WAIVER OF AUTHORIZATION)

As a multi-center trial, participants will be recruited from MSKCC as well as the participating site OSUMC. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or the research team at each respective institution. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes. If the woman agrees to study participation, a consenting individual (listed below in section 15.1) will obtain informed consent from the patient until a goal of 20 eligible patients are entered into the study.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (*partial*) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

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### 8.0 PRETREATMENT EVALUATION

The pre-therapy evaluation will include:

- Histologic confirmation of recurrent EMPD
- A history and physical examination as per standard clinical work-up for a vulvar lesion at the participating site
- Photography of lesion

### 9.0 TREATMENT/INTERVENTION PLAN

The patient will be seen in clinic every six weeks during treatment for examination, teaching, and to assess compliance. Imiquimod cream is to be applied 3 times per week for 12 weeks. It should be applied prior to normal sleeping hours, and left on the skin for 6-10 hours. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of imiquimod therapy. Handwashing is recommended before and after applying imiquimod 5% cream.

Punch biopsy and photography will be performed at the baseline and 12 week time points. If the lesion is still present after 12 weeks of therapy, the treating physician will recommend excision of the lesion four weeks after completion of therapy (week 16). If no lesion is present or the patient refuses surgical excision at week 16, the patient will return for follow-up exams every 3 months for at least 2 years. The treating physician will continue to offer surgical excision at any later point during follow-up if the lesion is still present.

### 10.0 EVALUATION DURING TREATMENT/INTERVENTION

The patient will be seen in clinic at approximately six week intervals during treatment for examination (e.g. week 6 visit will be completed between 35-49 days, week 12 visit between 77-91 days, and week 16 visit between 105-119 days after baseline). Punch biopsy and photography will be performed at the baseline and 12 week visit. The lesion will be assessed after the initial 12 weeks of therapy by visual inspection by the treating physician. Photodocumentation of the area will also be performed at this time. If the lesion is still present, repeat punch biopsy with histologic assessment will be performed (week 12). If the lesion is still present after the initial 12 weeks of therapy, the treating physician will recommend excision of the lesion four weeks following completion of therapy (week 16) to permit resolution of treatment associated inflammation. During this four week time period, the patient will not use imiquimod 5% cream. Any lesion progressing to a clinical appearance suspicious for evolving adenocarcinoma will be excised prior to study completion. The patient will have a follow-up exam 6 weeks after excision and then every 3 months for at least 2 years. If no lesion is present or the patient refuses surgical excision at week 16, the patient will return for follow-up exams every 3 months for at least 2 years. The treating physician will continue to offer surgical excision at any later point during follow-up if the lesion is still present.

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	Baseline	Week 6	Week 12	Week 16	Week 22 (if lesion was excised)	Every 3 months for 2 years
Clinical Assessment	✓	✓	✓	✓	✓	✓
Photography	✓		✓			
Biopsy	Punch biopsy of lesion		Repeat Punch biopsy of lesion	Excision of lesion if still present (recommended)		

### 11.0 TOXICITIES/SIDE EFFECTS

Topical imiquimod therapy has been generally well tolerated although both local and systemic side effects have been observed. Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common. Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with imiquimod cream can be resumed after the skin reaction has subsided. Overall, in reported studies of patients treated with imiquimod™ three times weekly, 1.2% (4/327) of the patients discontinued due to local skin/application site reactions.<sup>xix</sup> The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.<sup>xix</sup>

#### 3X/WEEK APPLICATION

##### FEMALES

Imiquimod      Vehicle  
(n=117)      (n=103)

##### MALES

Imiquimod      Vehicle  
(n=156)      (n=158)

#### APPLICATION SITE REACTIONS

Itching	32%	20%	22%	10%
Burning	26%	12%	9%	5%
Pain	8%	2%	2%	1%
Soreness	3%	0%	0%	1%

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FUNGAL INFECTION*	11%	3%	2%	1%
<u>SYSTEMIC REACTIONS:</u>				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%

\*Incidences reported without regard to causality with imiquimod

Remote site skin reactions were also reported in patients treated three times weekly with imiquimod 5% cream. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%).

Adverse events judged to be possibly or probably related to imiquimod and reported by more than 1% of patients include: Application Site Disorders: Burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness; Remote Site Reactions (bleeding, burning, itching, pain, tenderness, tinea cruris); Body as a Whole: fatigue, fever, influenza-like symptoms; Central and Peripheral Nervous System Disorders: headache; Gastro-Intestinal System Disorders: diarrhea; Musculo-Skeletal System Disorders: myalgia.

### Carcinogenicity, Mutagenesis, and Impairment of Fertility

In a 52 week dermal photo-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing (3X/week; 40 weeks of treatment followed by 12 weeks of observation) with concurrent exposure to UV radiation (5 days per week) with imiquimod Cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, imiquimod, to the vehicle cream.

Imiquimod was without effect in a series of eight different mutagenicity assays including Ames, mouse lymphoma, CHO chromosome aberration, human lymphocyte chromosome aberration, SHE cell transformation, rat and hamster bone marrow cytogenetics, and mouse dominant lethal test. Daily oral administration of imiquimod to rats, at doses up to 8 times the recommended human dose on a mg/m<sup>2</sup> basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.

While there is no data to suggest the carcinogenicity of topical imiquimod in the setting in which it is being employed in this study, the possibility of progression of EMPD to invasive carcinoma cannot be ruled out.

### Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Imiquimod should only be used during pregnancy only if the potential benefit justifies the

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potential risk to the fetus. Systemic embryofetal development studies were conducted on rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day [8X Maximum recommended human dose] included increased resorptions, decreased fetal body weights, delay in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day.

### Nursing Mothers

It is not known whether topically applied imiquimod is excreted in breast milk.

### Postmarketing experience

Individuals who used Imiquimod Cream after it was approved by the Food and Drug Administration have reported the following adverse reactions. It is not possible to reliably estimate their frequency or to establish a causal relationship to drug exposure. These events include the following:

- Angioedema - swelling, similar to hives, but the swelling is beneath the skin rather than on the surface
- Capillary leak syndrome - is a rare medical condition where the number and size of the pores in the capillaries are increased which leads to a leakage of fluid from them
- Cardiac Failure - the inability of the heart to fill with or eject blood due to any structural or functional cardiac conditions.
- Cardiomyopathy - serious disease in which the heart muscle becomes inflamed and doesn't work as well as it should.
- Arrhythmias - disorder of the heart rate (pulse) or heart rhythm, such as beating too fast (tachycardia), too slow (bradycardia), or irregularly.
- Chest pain - discomfort or pain in the chest that may be a key warning symptom of a heart attack
- Ischemia - a condition in which the blood flow (and thus oxygen) is restricted to a part of the body
- Myocardial infarction - commonly known as a heart attack, is the interruption of blood supply to a part of the heart
- Syncope - temporary loss of consciousness and posture, described as "fainting" or "passing out."
- Thyroiditis - inflammation of the thyroid gland
- Decrease in white blood count
- Decrease in red blood count
- Decrease in platelet count
- Abnormal liver function
- Agitation - Emotional state of excitement or restlessness
- Cerebrovascular accident – this is also known as a “stroke,” which is the loss of brain function(s) due to disturbance in the blood supply to the brain
- Convulsions - when a person's body shakes rapidly and uncontrollably

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- Depression - mental disorder characterized by an low mood accompanied by low self-esteem, and by loss of interest or pleasure in normally enjoyable activities
- Insomnia – when a person is unable to fall asleep or remain asleep for an adequate length of time
- Multiple Sclerosis aggravation – worsening of the symptoms of Multiple Sclerosis
- Paresis - partial loss of movement, or impaired movement
- Suicide - the act of a human being intentionally causing his or her own death
- Dyspnea - difficulty in breathing
- Proteinuria - the presence of an excess of proteins in the urine
- Exfoliative dermatitis - widespread scaling of the skin, often with itching, skin redness, and hair loss

### 12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The biopsied lesion will be the focus of the histologic assessment. All biopsies will be routinely sectioned and stained (H&E). Photographs will be obtained by the treating physician. Standardized 1:1 fixed distance photography will be performed with a contact camera with a built in light source to ensure standardized images. Millimeter scales will be included in each image to ensure spacial standardization.

Clinical response will be assessed by comparison of pairs of clinical photographs obtained at study completion and baseline. Pairs of photographs will be graded as:

- Complete response = reversion to clinically normal appearing skin.
- Partial response = 50% or greater reduction in diameter of affected skin.
- Progression = 50% or greater increase in diameter of affected skin.

Primary histologic evaluation will entail quantification of the number of involved areas /mm<sup>2</sup> that have Paget's cells. Histologic response will be graded as:

- Complete response = No evidence of Paget's cells
- Partial response = ratio of involved areas/mm<sup>2</sup> in post-treatment biopsy specimen/ pre-treatment biopsy specimen < 50%
- Progression = ratio of involved areas/mm<sup>2</sup> in post-treatment biopsy specimen/ pre-treatment biopsy specimen > 150%

We recognize the subjective nature of determining "significant" changes in appearance of the skin lesion. This problem, common to many dermatology studies, has defied a standardized technologic solution to date. We will use the method that is similar to that employed by a recently published study evaluating the effects of imiquimod on dysplastic nevi.<sup>xx</sup> In this study, Junctional lesional cells were counted in multiple high power fields and reported as lesional cells/mm<sup>2</sup> and lesional cell



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counts were compared between treated and untreated nevi. Complete response was defined as reversion to clinically normal appearing skin. Partial response was defined as a 50% or greater reduction in diameter and progression was defined as a 50% or greater increase in diameter.

### 13.0 CRITERIA FOR REMOVAL FROM STUDY

In the event that the treated lesion changes in a clinically worrisome fashion with correlating histology demonstrating invasive carcinoma during the study, the patient will be removed from the study. Patients who have unacceptable toxicities will be removed from the study. Unacceptable toxicities consist of headache, influenza-like symptoms, and myalgia,

If, at any time, the patient withdraws consent to participate in the study, he/she will be removed from the study. In such event the investigator will carefully consider whether the patient's withdrawal of consent is due to an adverse event, and if so, record the adverse event as the reason for withdrawal.

### 14.0 BIOSTATISTICS

The purpose of this pilot study is to assess the clinical and histologic effects of a topical immunomodulatory agent, imiquimod, on extramammary Paget's disease (EMPD). This is a multicenter study in which the patient and the pathologist will not be blinded to treatment status. Photographs obtained before and after treatment will be evaluated by an independent reviewer. The institutions involved in this study include: Memorial Sloan-Kettering Cancer Center in New York City, NY (MSKCC), and Ohio State University College of Medicine (OSUMC) in Columbus, Ohio.

Twenty patients will be accrued onto this study. It is unknown how patients will respond to this topical treatment and 20 patients is the maximum number of patients that can be accrued in a reasonable time period. Assuming a drop out rate of 15% our target sample size is 17. At the end of this study, we hope to estimate a response rate with a 95% confidence interval  $\pm$  24 % based on 17 patients. Approximately 7 patients are diagnosed a year with EMPD at MSKCC and approximately 1-2 patients a year from OSU. From this we expect to accrue 5-8 patients per year until 20 patients are accrued on study (approximately 3 years). At the end of the study, descriptive statistics will be performed to evaluate the effectiveness of imiquimod therapy on extramammary Paget's disease patients.

### 15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

#### 15.1 Research Participant Registration

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

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

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

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

### **15.2 For Participating Sites:**

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

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to fax registration/eligibility documents to the **Department of Surgery, Gynecology Service** at MSKCC at **212.557.2434**.

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

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

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review to confirm all documents are received to complete registration.

If the participant meets all criteria, all source documentation is received, the participating site local IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSK RSA will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

### **15.3 Protocol Participant Number at Participating sites**

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC clinical research database (CRDB) number (protocol participant

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number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

### **16.0 DATA MANAGEMENT REQUIREMENTS FOR PARTICIPATING SITES**

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

#### **16.1.0 Data and Source Documentation**

##### **Data**

Standardized Case Report Forms (CRFs), directions for use and sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

##### **Source Documentation**

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

- MD office visit notes
- Pathology reports
- Photographs
- Clinical assessment forms
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports

#### **16.1.1 Data and Source Documentation Submission**

Participating sites should fax the CRFs to MSKCC to the contact provided below. Submissions should include a cover page listing all CRFs enclosed per participant.

**FAX: 212.557.2434 to the attention of Protocol 07-029 RSA**

#### **16.1.2 Data and Source Documentation Submission Timelines**

- CRFs and source documentation to support data in the CRFs should be submitted according to chart below.

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

### 16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:

<http://cancertrials.nci.nih.gov/researchers/dsm/index.html>

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://mskweb2.mskcc.org/irb/index.htm>

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

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

### 16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC IRB/PB. Prior to implementing this protocol at the participating centers, approval must be obtained from the participating center's Local IRB of Record.

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

- Participating site IRB of approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating site IRB approved consent form
- Participating site IRB's membership list
- Participating site IRB's of Record's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional

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- Documentation of Human Subject Research Certification and HIPAA training for investigators and key staff members

### 16.3.1 Amendments

Each change to the protocol must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. After approval at the lead institution, MSKCC will distribute the non-expedited amendments to the participating centers, for approval by their local IRBs.

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

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

- Participating site IRB approval
- Participating site IRB approved, revised documents including the protocol, informed consent form and HIPAA authorization

### 16.3.2 Additional IRB Correspondence

#### **Annual re-approval or Continuing Review Approval**

Annual re-approval from the participating center's Local IRB of Record and the most current approved version of the consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval will result in suspension of accrual privileges.

#### **Deviations and Violations**

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

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

Participating sites should report deviations and violations to the Local IRB of Record as soon

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as possible per local guidelines. Approvals/acknowledgments from the Local IRB of Record for protocol deviations and violations should be submitted to MSKCC as received.

### Other correspondence

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

#### 16.3.3 Document maintenance

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

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

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

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

### 16.4 Quality Assurance

Study personnel will generate monthly registration reports to monitor patient accrual and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Data quality and protocol compliance audits will be conducted by the study team on a regular basis throughout the study period.

#### 16.4.1 Quality Assurance for Participating sites

Each site participating in the accrual of participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected participant records can be audited on-site at participating sites or (2) source documents for selected participants will be sent to MSKCC for audit. Audits will usually be determined by participant

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accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of MSKCC PI.

Audits will be conducted at least once shortly after initiation of participant recruitment at a site, during the study (if the trial lasts 3 or more years) and at the end or closeout of the trial at a site. At a minimum, audits will be conducted once a year or more frequently, if indicated. The number of participants audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Informed Consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Required specimen submission
- Pharmacy review, if applicable
- Case Report Form submissions to MSKCC: timing and accuracy

A wrap-up session will be conducted at the outside site and preliminary findings will be discussed with the outside site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating institution within 30 days of the audit. The report will include a summary of findings, participant by participant case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating institution must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the outside site must be sent to the MSKCC IRB, CRQA and maintained in the department's protocol regulatory binder.

### 16.4.2 Response Review

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

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obtained from the outside sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC within sixty days of request to the site.

### 16.5 Noncompliance

If a participating site is noncompliant with the data and regulatory requirements set forth in protocol document, accrual privileges may be suspended and/or contract payments maybe withheld (if applicable), until the outstanding issues have been resolved.

## 17.0 PROTECTION OF HUMAN SUBJECTS

**Risks:** It is unlikely that significant risks will be associated with the limited topical use of imiquimod planned in this study.

**Benefits:** Patients with a good clinical response to imiquimod may benefit from future broader application of this therapy.

**Possible Toxicities and Side Effects:** Local application site reactions can be anticipated. Previously reported toxicities/side effects of topical imiquimod are elaborated in section 11.0 of this protocol. While there is no data to suggest the carcinogenicity of topical imiquimod in this setting, the possibility of progression of a lesion to cancer cannot be ruled out.

**Consent Process:** Participation in this protocol is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC IRB guidelines.

**Costs:** Patients will not be charged for protocol related costs.

**Alternatives:** There are no proven nonsurgical treatments for EMPD. All study patients will be offered surgical treatment for EMPD.

### 17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

### 17.2 Serious Adverse Event (SAE) Reporting

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

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)

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- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

### Data needing to be entered:

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

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

### **17.2.1 Serious Adverse Event (SAE) Reporting for Participating Sites**

#### Responsibility of participating sites:

- Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within 3 calendar days of learning of the event.
- Participating sites should notify the MSKCC PI of any grade 5 events immediately.
- Participating sites should use the SAE Report Template (*appendix #2*) to report SAEs to MSKCC.

#### **SAE contact information for the Coordinating Center is listed below:**

Dennis Chi, M.D., Principal Investigator  
Department of Surgery, Division of Gynecologic Oncology  
Memorial Sloan-Kettering Cancer Center  
New York, NY 10021  
(212) 639-5016

*Gina Gualtieri, RSA*  
Department of Surgery, Division of Gynecology Oncology  
Memorial Sloan-Kettering Cancer Center  
New York, NY 10021  
(646) 227-2232

#### Responsibility of MSKCC

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- The MSKCC RSA is responsible for submitting all SAEs to the MSKCC IRB as specified in 17.2.
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

### 17.3 Safety Reports

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

## 18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

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

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

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

### 18.1 For Participating Centers

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

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

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

### 19.0 reference(s)

<sup>i</sup> Beutner, KR, Geisse, JK, Helman D, Fox TL, Ginkel A, Owens ML. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. *J Am Acad Dermatol* 41:1002-7, 1999

<sup>ii</sup> Testerman TL, Gerster JF, Imbertson LM et al. Cytokine induction by the immunomodulators imiquimod and S-27609. *J Leukocyte Biol* 58:365-372, 1995

<sup>iii</sup> Zampogna JC, Flowers FP, Roth WI, Hassenein, A. Treatment of primary limited cutaneous extramammary Paget's disease with topical imiquimod monotherapy. Two case reports. *J Am Acad Dermatol* 47:229-35, 2002

<sup>iv</sup> Wang LC, Blanchard A, Judge DE, Lorincz AA, Medenica MM, Busbey S. Successful treatment of recurrent extramammary Paget's disease of the vulva with topical imiquimod 5% cream. *J Am Acad Dermatol* 49(4):769-72, 2003

<sup>v</sup> Qian Z, Zeitoun N, Shieh S et al. Successful treatment of extramammary Paget's Disease with Imiquimod. *J Drugs Dermatol* 2:73-76, 2003

<sup>vi</sup> Berman B, Spencer J et al. Successful treatment of extramammary Paget's disease of the scrotum with Imiquimod 5% cream. At: the European Academy of Dermatology Meeting, Oct 2002, Prague, Czech Republic

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<sup>vii</sup> Jones RE, Austin C, Ackerman AB, Extramammary Paget's Disease: A critical reexamination. *Am J. Dermatopathol* 1:101-102, 1979

<sup>viii</sup> Fanning J, Lamber L et al. Paget's disease of the vulva: Prevalence of associated underlying adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. *Am J Obstet Gynecol* 180:24-7, 1999

<sup>ix</sup> Bewley AP, Bracka A et al. Extramammary Paget's disease of the scrotum: treatment with topical 5-fluorouracil and plastic surgery. *Br J Dermatol* 131:445-46, 1994

<sup>x</sup> Watring WG, Roberts JA et al. Treatment of recurrent Paget's disease of the vulva with topical Bleomycin. *Cancer* 41:10-11, 1978

<sup>xi</sup> Beutner, KR, Geisse, JK, Helman D, Fox TL, Ginkel A, Owens ML. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. *J Am Acad Dermatol* 41:1002-7, 1999

<sup>xii</sup> Testerman TL, Gerster JF, Imbertson LM et al. Cytokine induction by the immunomodulators imiquimod and S-27609. *J Leukocyte Biol* 58:365-372, 1995

<sup>xiii</sup> Zampogna JC, Flowers FP, Roth WI, Hassenein, A. Treatment of primary limited cutaneous extramammary Paget's disease with topical imiquimod monotherapy. Two case reports. *J Am Acad Dermatol* 47:229-35, 2002

<sup>xiv</sup> Wang LC, Blanchard A, Judge DE, Lorincz AA, Medenica MM, Busbey S. Successful treatment of recurrent extramammary Paget's disease of the vulva with topical imiquimod 5% cream. *J Am Acad Dermatol* 49(4):769-72, 2003

<sup>xv</sup> Qian Z, Zeitoun N, Shieh S et al. Successful treatment of extramammary Paget's Disease with Imiquimod. *J Drugs Dermatol* 2:73-76, 2003

<sup>xvi</sup> Berman B, Spencer J et al. Successful treatment of extramammary Paget's disease of the scrotum with Imiquimod 5% cream. At: the European Academy of Dermatology Meeting, Oct 2002, Prague, Czech Republic

<sup>xviii</sup> Product Information: Imiquimod(R), imiquimod 5% cream. 3M Pharmaceuticals, St. Paul, MN, 2004.

<sup>xix</sup> Beutner K, Spruance S, Douglas J et al. Double-blind, vehicle controlled, randomized, multicenter trial of 5% imiquimod cream for the treatment of genital and perianal warts (abstract). *Second Int Cong Papillomavirus Human Pathol* 93, 1994

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<sup>xx</sup> Dusza S, Delgado R, Busam K, Marghoob A, Halpern A. Treatment of Dysplastic Nevi with 5% Imiquimod Cream, A Pilot Study. *J Drugs Dermatol* 5:56-62, 2006

<sup>xxi</sup> Denehy T, MsWweeney D, Taylor R, Gregori C, Breen JL. Successful immune modulation therapy with topical imiquimod 5% cream in the management of recurrent extramammary Paget's disease (EMPD) of the vulva. *Proc Soc Gynecol Oncol* 2006. Poster session 3/23/06.

### 20.0 APPENDICES

Appendix 1. Patient calendar