Effect of topical imiquimod as primary treatment for lentigo maligna

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Conflicts of interest:

None

Bulleted statements required for the following questions (max 70 words)

What's already known about this topic?

Imiquimod can cause clinical regression of lentigo maligna (LM).

What does this study add?

The pathological complete regression (pCR) rate is estimated for topical treatment with imquimod for LM.

The accuracy of clinical complete regression with targeted biopsies after imiquimod in predicting pCR at subsequent resection of the treated site is investigated.

The pCR rate dermatologists regard as sufficient to justify the use of imiquimod for LM, adverse events, the acceptability of treatment to patients, and patients' preferences for imiquimod versus surgery are documented.

Summary

Background

Topical imiquimod is sometimes used for lentigo maligna (LM) in-situ melanoma instead of surgery, but frequency of cure is uncertain. Pathological complete regression (pCR) is a logical surrogate marker for cure after imiquimod, although residual LM and atypical melanocytic hyperplasia may not be reliably distinguished. A trial comparing imiquimod versus surgery might be justified by a high imiquimod pCR rate.

Objectives

Primary: to estimate pCR rate for LM following imiquimod. Secondary: to assess accuracy of prediction of pCR, using clinical complete regression (cCR) plus negative post-treatment biopsies, tolerability, resource use, patients' preferences; and induced melanoma immunity.

Methods

This was a single arm phase II trial of 60 imiquimod applications over12 weeks for LM then radical resection. A pCR rate ≥25/33 would reliably discriminate between pCR rates <60% and ≥85%. Clinical response was assessed and biopsies taken after imiquimod. Patients recorded adverse events in diaries. Patient preference was measured after surgery using a standard gamble tool.

Results

The pCR rate was 10/27 (37%, 95% CI 19%, 58%). The rate of cCR plus negative biopsies was 12/28 of whom 7/11 had pCR on subsequent surgery. Median dose intensity was 86.7%. Of surveyed patients, 8/16 preferred primary imiquimod over surgery if the cure rate for imiquimod was 80% and 4/16 if it was ≤50%.

Conclusions

The pCR rate was insufficient to justify phase III investigation of imiquimod versus surgery. Clinical complete response and negative targeted biopsies left uncertainty regarding pathological clearance. Some patients would trade less aggressive treatment of LM against efficacy.

Trial registration: clinicaltrials.gov identifier: NCT01161888

Key words: Lentigo maligna; lentigo maligna melanoma; imiquimod; surgery; pathological complete response;

Introduction

Lentigo maligna (LM) in-situ melanoma characteristically presents as a slowly developing brown or dark brown macule on chronically sun-exposed skin in people over 50 years. In UK guidelines, complete surgical resection is recommended with curative intent[1]. Five percent of patients with typical LM may actually have early invasive melanoma, and the risk of progression to invasive lentigo maligna melanoma (LMM) is poorly quantified[2]. Reported outcomes following surgery vary, including a 30% probability of recurrence at 66-98 months and 1.5% probability of transformation to LMM for 81 patients[3], a crude failure rate (recurrence plus incomplete excision) of 8/102 following resection excision with 2mm margins [4], and crude recurrence rates of 16/269 (5.9%) following wide local excision and 3/154 (1.5%) following Mohs micrographic surgery [5]. LM occurs most frequently on the head and neck so surgery can cause significant functional and cosmetic disability and, in some cases, might not be feasible.

In 2001, a UK survey showed that the most widely used treatments for LM were surgery, cryotherapy, radiotherapy and observation respectively, with non-surgical approaches possibly associated with higher recurrence rates and used more for patients >70 years [6]. Radiotherapy may have a place in LM management, with the aim of trading less invasive intervention and better function and cosmesis, against a possibly higher risk of reccurrence or progression to melanoma[7-10]. No trials have been undertaken comparing the outcomes of surgery and radiotherapy or other non-surgical treatments [11].

Imiquimod is a synthetic imidazoquinolin nucleoside analogue available as a 5% strength topical formulation with low systemic availability. Skin application induces local inflammation with intensity related to frequency of application. The use of topical imiquimod as a non-surgical treatment for LM has increased following an initial case report in 2000 of disease control for 9 months after treatment for 7 months[12]. Treatment duration is not defined, but 12 weeks is widely used[13]; any benefit of longer treatment is unclear. An effect against LM has been confirmed in subsequent case reports and small uncontrolled trials, and in a systematic review[14], with response rates of 77-90%. These studies lacked long term follow up to substantiate disease control and post treatment histology: the majority of cases involved biopsy only, with the possibility of sampling error[15-22]. One small study used complete surgical excision following imiquimod treatment, and reported complete responses in 4 out of 6 patients recruited[23]. A recent retrospective series reported recurrence of LM following imiquimod alone in 6/22 patients versus 2/36 having surgery plus imiquimod with mean follow up around 40 months[13].

The routine use of imiquimod as primary therapy for LM requires proof of efficacy in a large trial compared to the outcomes of surgical excision. We reasoned that, to justify this investment, imiquimod treatment should be shown to have a high probability of achieving pathological complete

response (pCR). Patients and clinicians might take into account the probability of cure with imiquimod and avoiding surgery for a pre-malignant condition, assuming progression is susceptible to surveillance. We surveyed UK dermatologists' opinion regarding what threshold of pCR rate would justify routine use of imquimod instead of surgery. We then designed a single arm trial to justify progression to a larger randomised trial. We sought opinion from trial participants regarding what threshold of efficacy they would trade against avoiding surgery, using a structured questionnaire.

Patients and Methods

Participants

This study was coordinated through the Nottingham Clinical Trials Unit (NCTU), approved by Nottingham Research Ethics Committee 2 and eight hospitals recruited between October 2010 and August 2011

To be eligible, patients had to give informed written consent, have a clinical diagnosis of primary untreated LM (acquired pigmented macule present >12 months, no change in skin surface texture or contour, no palpability, diameter >10 mm, sited on the head or neck) and histologically confirmed LM without invasive melanoma in one or more 4mm punch biopsies(s) from the darkest area, reported by a pathologist member of a recognised NHS skin cancer Multi-Disciplinary Team. The LM had to be suitable for complete surgical excision using a 5mm lateral margin, and to be easily definable visually around its entire circumference. Patients had to be aged >45 years age, fit and willing for surgery, without co-existing or adjacent melanoma or non-melanoma skin cancer that might compromise study treatment; neither pregnant nor breastfeeding, without hypersensitivity to imiquimod or excipients, not taking immunosuppressive medication or participating in another intervention study.

Treatment and follow-up

Trial interventions and investigations are detailed in figure 1. The pre-treatment lesion was photographed, tattooed at 360, 90, 180 and 270 degrees, outlined in ink and traced on a transparency. Training in mapping and tattooing was provided. Patients applied imiquimod (Aldara®; MEDA Pharmaceuticals) 5 days per week to the visible lesion plus a 2cm margin of normal surrounding skin for approximately 8 hours (overnight) and washed off with soap and water as defined in the Patient Information Leaflet. After 12 weeks' treatment, lesions were remapped, biopsied and excised with central pathological reporting. The User Opinion Questionnaire Patient was undertaken 12 weeks post-surgery by the first 16 patients.

Outcome Measures

The primary outcome measure was pCR, i.e. absence of LM in both post treatment biopsies and resected LM. Imiquimod is an experimental treatment in which post-treatment biopsies would be part of assessment of clearance. Resection is standard of care and, in this trial, permits assessment of LM clearance in the whole lesion. Other pathological outcomes were partial regression (pPR – atypical melanocytes present in the epidermis with abnormal distribution and number, but insufficient features to define LM), no change (pNC – presence of LM) or progressive disease (pPD – invasive melanoma).

Clinical outcomes were complete regression (cCR – complete disappearance of abnormal pigmentation), partial regression (cPR – reduction in size of pigmented area or obvious reduction in its intensity), no change (cNC – appearance identical to that pre-treatment) and progressive disease (cPD – increased size or intensity of pigmentation or development of a papule or nodule within LM). Targeted biopsies were scored as for the resection specimen, above. For each individual, the prediction of pCR using clinical examination of the mapped regions (weeks 22-24) plus targeted pre-surgical biopsies was compared with the pathological response in the whole post-treatment resected lesion, including any LM outside the clinically mapped margins of disease.

Patients kept weekly diaries through 12 week's treatment of adverse reactions, numbers of treatments, treatment acceptability on a visual analogue scale and reasons for treatment withdrawal. The number of consultations was recorded.

Following surgery, the participants completed a questionnaire selecting between "I want to have imiquimod as first treatment" versus "I want to have surgery now" for 15 hypothetical trial results ranging from "imiquimod cures 100% of people; surgery cures 95% of people" to "imiquimod cures 10% of people; surgery cures 95% of people". The explanation included that imiquimod treatment included surveillance and deferred surgery in the event of progression.

Whole blood samples, 40ml, were harvested before and after imiquimod treatment and sent by first class post to the Human Biomaterials Resource Centre, Birmingham where peripheral blood mononuclear cells (PBMC) were isolated by differential centrifugation and cryopreserved in the vapour phase of nitrogen. Circulating T lymphocyte responses against melanocyte differentiation antigens melan A, gp100, tyrosinase and against cancer testis antigens MAGE A1, MAGE A3 and NYESO were measured using an ex vivo ELIspot assay [24], using overlapping peptides covering the whole of each antigen.

Statistical Design and Analysis

In 2009 all consultant members of the British Association of Dermatologists were asked to mark on a visual analogue scale the pCR rate for imiquimod below which "I do not think that imiquimod has any potential at all to be used for primary treatment for lentigo maligna" and the pCR rate above which "I would be persuaded that imiquimod definitely should be used in the primary treatment of lentigo maligna".

This was a single arm phase II trial with a sample size of 33, requiring pCR in 25 participants to justify progression to phase III (A'Hern's method p0=60%, p1=85%, α=5%, 1-β=95%)[25]. The bounds (p0 and p1) were derived from the upper quartile of pCR thresholds for dermatologists responding to the two questions above. The recruitment target was 40 participants to account for attrition.

The primary intent-to-treat (ITT) analysis included patients who discontinued imiquimod treatment early but proceeded to surgery as per protocol requirements. The pCR rate for patients undergoing surgery after imiquimod was estimated with 95% confidence intervals.

The accuracy of clinical assessment was reported as proportion of cases where cCR plus negative biopsies correctly predicted pCR in the subsequent surgical resection specimen.

Imiquimod dose intensity was calculated from patient diary returns, assuming 60 applications (i.e. 5 days/week for 12 weeks) to be 100%.

Patients' opinions are presented descriptively as the proportion of patients preferring imiquimod over surgery in relation to a range of hypothetical cure rates for imiquimod compared to a cure rate for surgery of 95%.

Analyses were performed using Stata v12.

Results

Responses from 174 UK consultant dermatologists each identified a lower pCR rate below which they considered imiquimod to have no potential to treat LM (median 40%; interquartile range (IQR) 30-60%), and an upper pCR rate above which they could definitely be persuaded of the potential of imiquimod to treat LM (median 80%; IQR 60-85%). This was interpreted as indicating only 25% of clinicians would reject further investigation of imiquimod as a treatment for LM even if the pCR rate was ≥ 60%, and only 25% of clinicians would demand a pCR rate ≥ 85% to justify further investigation of imiquimod. We determined that an observed pCR threshold rate of ≥25/33 would reliably exclude a true pCR rate <60% and be powered not to miss a true pCR rate ≥85% (see statistical design).

Twenty-nine patients consented; one withdrew consent and 28 were evaluable. Median age was 72 years (IQR 65, 79), 18 male, median size of LM 14mm (IQR 12, 22; range 10-70mm), located on the cheek (11), ear (4), forehead (4), nape of neck (1), nose (7) and scalp (2). The median dose intensity over 12 weeks was 86.7%, including three patients stopping treatment early after 4, 8 and 11 weeks, and 27 underwent surgical excision post imiquimod (see figure 1).

Twenty-seven patients were evaluable for the primary outcome. Ten achieved complete pathological regression i.e. pCR (37%, 95% CI 19, 58). None showed LM at the surgical margins. The patients with pCR had achieved imiquimod dose intensity below (7) and above (3) the median of 86.7%.

Central review of a single pre-treatment section did not confirm diagnosis of LM in three patients: reporting epidermal hyperpigmentation without melanocyte atypia; compound melanocytic naevus; and pigmentation and elongated rete ridges without melanocyte atypia. The pCR rate was 8/24 (33%, 95% CI 16, 55) if these patients are excluded. However, priority was given to the fuller clinicopathological diagnosis made by the multidisciplinary team at the site.

Post-treatment resection specimens from a further 9 patients were scored as pPR (i.e. abnormal features falling short of defining persistent LM – see methods), 7 had definite residual LM in the resection specimen and one had evidence of LMM.

Clinical evaluation showed that 13/28 patients had complete disappearance of the LM after imiquimod, i.e. cCR (46%, 95% CI 28, 66). Of these, on the post-treatment biopsies, 12 were negative for LM and one showed probable residual LM. Thus clinical and targeted pathological evaluation yielded a response rate of 12/28 (43%, 95% CI 24, 63). Of the 12, one declined resection, and 7/11 (64%, 95% CI 31, 89) had pCR on the resection specimen. Three of 15 who did not achieve cCR were observed nonetheless to have pCR (figure 2). Regarding the 3 with pathological evidence falling short of LM on central review of a single diagnostic slide, the outcomes were cCR+pCR, cCR+pPR and cPR+pCR.

Eleven of 29 (38%) patients had a severe local site reaction over the study period; 10 (35%) a moderate reaction; 8 (27%) had mild or no reaction. This peaked at week 4, when 24%, 48%, and 14% had mild, moderate or severe reactions respectively. By week 12, 11% and 15% respectively still had moderate or severe reactions. Nine of 19 (47%) patients having a moderate or severe local site reaction had a pCR, whereas 1/8 (13%) patients with mild or no reaction had a pCR. Scores for acceptability of imiquimod through 12-weeks treatment were reported by 24/29 patients. Dose reductions occurred in 5/12 reporting consistently good tolerance and 8/12 reporting variably poor tolerance.

There were 143 adverse events of which 84 (59%) were definitely related to treatment. Medication was provided for 117 (82%) of adverse events, and 140 (98%) resolved. There was no additional health service use for 18/29 (62%), 1 unscheduled visit for 8 (28%) and >1 unscheduled visit for 3 patients (10%).

Sixteen patients completed the treatment preference survey having experienced both treatments (figure 3). One expressed a strong preference for immediate surgery even with a hypothetical cure rate of 100% for imiquimod and 4 strongly preferred imiquimod, tolerating hypothetical cure rates for imiquimod ≤ 40% as against 95% for surgery. Half of patients stated they would opt for surgery if the cure rate for imiquimod was ≤85%.

Imiquimod might work by inducing immune responses against proteins characteristic of melanoma cells. We tested blood samples from 16 patients for such responses of whom 11 had paired samples analysed about three months apart. Target proteins were a number of proteins characteristic of melanoma (melan A, gp100, tyrosinase, NYESO1, MAGE A1 and MAGE A3) and, to confirm the patients' cells were working, proteins made by common infections (termed CEPT). Positive recognition of target proteins was defined conventionally as a number of reacting immune cells against target proteins that was more than double background immune reactivity. Twenty seven samples from 16 patients were tested and of these 18 from 12 patients made a clear positive recognition of the CEPT control. Of the 18 samples with a positive CEPT response, 3 samples from 2 patients exhibited recognition of a melanoma antigen – both MAGE A1. Only 6 patients had paired samples with positive CEPT recognition on both samples – and of these, 1/6 (who had pPR and cPR) showed an amplified response over time, defined as the later recognition value being double that on the earlier reading.

Discussion

It is reasonable to try to spare patients surgery for LM; it can impair function, be disfiguring, and may not be feasible. Non-surgical approaches need not equal surgery in efficacy, provided treatment failure could be recognised and surgery undertaken before progression to invasive melanoma.

Imiquimod promotes an inflammatory state through the activation of macrophages and antigen-presenting cells via Toll-like receptor 7 signalling, and this localised inflammation can result in regression of neoplastic cells[26]. We undertook a single arm phase II trial to determine whether investment is justified in a phase III trial comparing imiquimod with surgery. Clinical regression following imiquimod treatment can be followed by relapse[3]. Therefore, pCR, measured by detailed histological examination of LM resected after imiquimod therapy, was selected as surrogate outcome measure for possible long term disease control.

The pCR rate of LM to imiquimod was estimated as 37% (10/27) with confidence intervals indicating a true pCR rate >60% was unlikely and >85% very unlikely. Even had accrual continued to target, the highest possible observed pCR rate would have been 16/33, falling short of the pre-planned efficacy threshold of 25/33.

It is improbable that we missed a true effect. Firstly, 27/29 patients completed the study and were available for analyses. Second, 21 of 29 patients had moderate or severe skin inflammation, similar to imiquimod toxicity described in case reports of apparently successful imiquimod treatment. Third, median dose intensity was 87% and reduced dose intensity across 12 weeks did not obviously associate with lower probability of achieving pCR. Our pCR rate by detailed pathological examination is lower than the >75% regression rate judged by clinical inspection and biopsies in a systemic review of predominantly retrospective series and cases. Note that these case reports and series lacked consistent definition and were susceptible to selection and publication bias[14]. Recently, another trial observed a pCR rate of 20/38 assessable patients with LM treated with imiquimod for 12 weeks[19]. A further study compared topical imiquimod with topical imiquimod plus topical tazarotene, followed by Mohs excision of the treatment site, with pCR rates of 57 versus 66% respectively [18].

Can we rationally offer imiquimod as first line treatment for LM, reserving surgery for treatment failure? Persistent or progressive clinical abnormality after imiquimod might reasonably be taken to indicate proceeding to surgery because only 3/15 such patients had pCR on the resected specimen. Conversely, apparent cCR and negative biopsy was an unreliable predictor of pCR, with only 7/11 cases with cCR plus negative biopsies confirmed as pCR on examination of the excision specimen. We recognise that pPR as defined in this study is indistinguishable from actinic melanocytic hyperplasia, likely to be present in chronically sub damaged skin[27]. Thus there is uncertainty whether

pPR induced by imiquimod might also be a marker for long term clinical remission, which was not addressed in our study.

The efficacy threshold to justify phase III evaluation had been selected to exclude, at the 5% probability level, proceeding to phase III despite a true pCR rate of <60% and rejecting further investigation despite a true pCR rate >85%. These thresholds were based on a survey of a large group of UK dermatologists. However, reported opinions were diverse. Only half would definitely reject imiquimod treatment even if the true pCR rate was <40% and a quarter would have settled for a true pCR rate <60% to definitely proceed to phase III. Offering imiquimod treatment for a pre-malignant condition, with surgery reserved for progression, is a credible strategy for some clinicians despite a low pCR rate. How might patients view this issue? We surveyed the opinion of the first sixteen consecutive patients after each had experienced both imiquimod and surgery and again observed diversity of opinion including 4/16 who would still have opted for imiquimod even with the probability of cure ≤40%. However, we had not expected the very high early attrition on accrual in which only a fifth of identified patients enrolled for the trial. This might cause bias favouring imiquimod because this attrition itself may reflect patients' preference for surgery.

Destroyed cells in a pro-inflammatory milieu might act as an autologous vaccination against melanoma, resulting in systemic immunity. However, we observed our participants generally had a frequency of circulating activated T cells recognising melanoma differentiation or cancer germline antigens below the limit of detection with the ex vivo ELIspot assay (~$50/10^6$ PBMC) even after imiquimod treatment. A larger sample would be needed to confidently estimate the immune response rate and this would also require assays able to detect and measure lower abundance immune reactivities.

In summary, imiquimod causes local skin adverse reactions which are variably tolerated by patients and can be managed by adjusting the frequency of applications. We estimated the pCR rate of LM to imiquimod to be 37%. This fell short of our pre-defined endpoint that would justify progression to randomised comparison versus surgery, assuming that pCR is a prerequisite for term disease control. The uncertainty over the interpretation of pPR and the possibility that imiquimod given for a longer duration might convert pPR to pCR might still justify such a trial. We observed that clearance of LM clinically and on targeted biopsies missed patients in whom LM was either pathologically persistent or in whom pathological persistence was, at best, uncertain. Based on this, without a larger long term trial, the use of imiquimod cannot be recommended as standard first line treatment for LM outside exceptional circumstances.

Contributors

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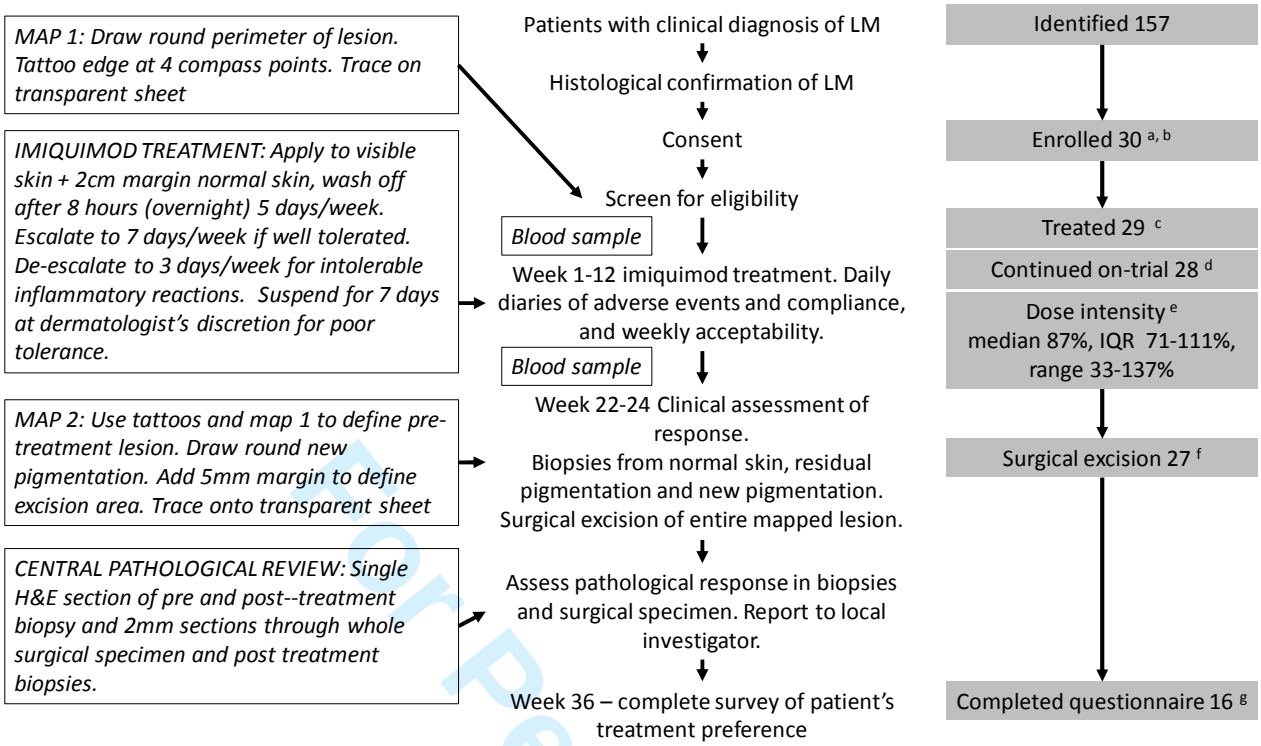

Figure 1. Trial design and recruitment.

The sample size was constituted 28 patients evaluated on an intention to treat basis and 27 treated patients with post-treatment surgical specimens: (a) 75 patients were ineligible, most commonly because LM size <10mm, invasive or recurrent disease, not on head or neck, LM histology not conclusive, steroid treatment, ill-defined lesion, inadequate surgical clearance, LM present <12 months; (b) 52 patients declined trial entry: the most common reasons were burden of travelling (10) or time involved (15), delay in surgery (13), and concerns over side effects (3) or lack of efficacy (2) of imiquimod; (c) one patient withdrew consent before starting imiquimod; (d) one patient withdrew consent after 5.3 weeks treatment; (e) dose intensity was number of imiquimod applications as a proportion of expected 60 applications over 12 weeks (f) one treated patient declined surgery post imiquimod; (g) the questionnaire was completed by the first 16 patients on trial.

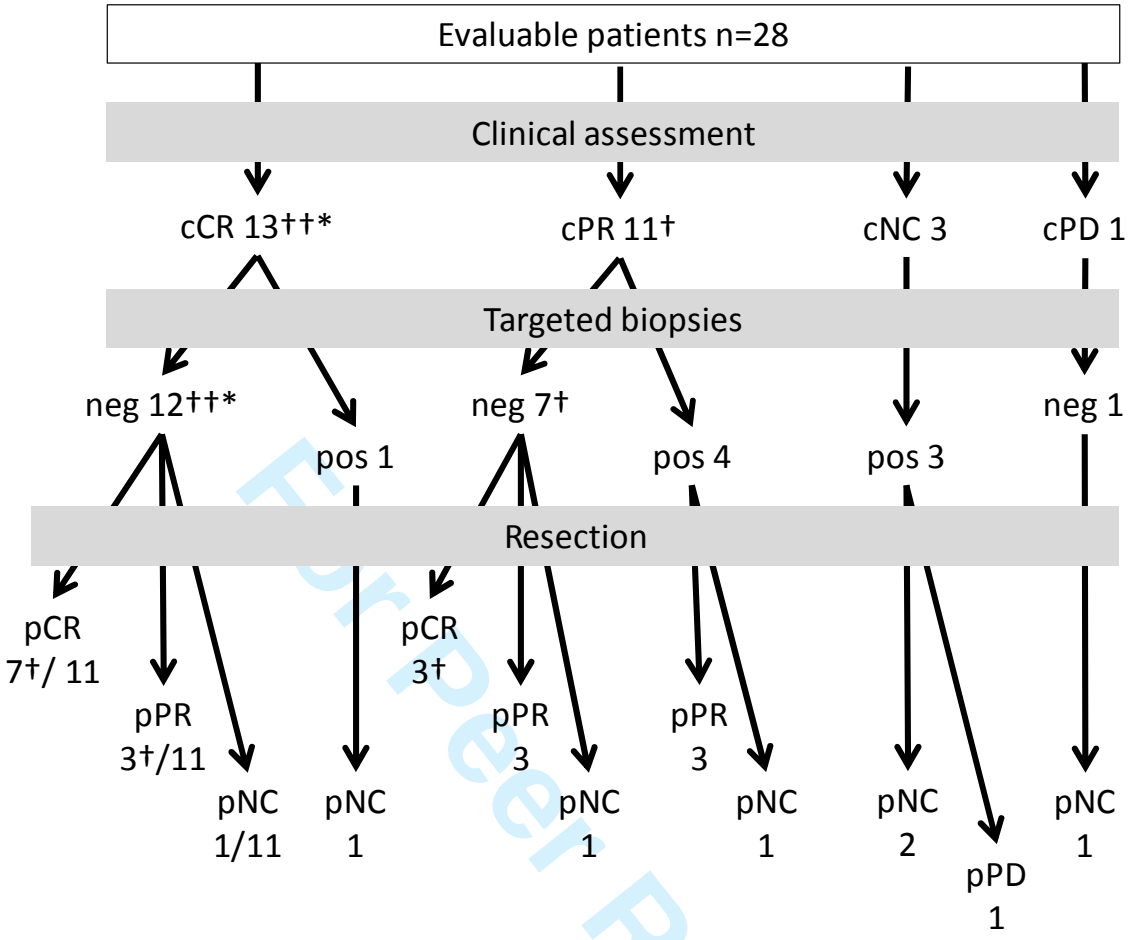

Figure 2. Clinical and pathological responses to treatment

cCR = clinical complete response; cPR = clinical partial response i.e. clinical evidence of improvement in the LM falling short of complete regression; cNC = clinical no change; cPD = clinical progressive disease; pCR = pathological complete response; pPR = pathological partial response; pNC = pathological no change i.e. continuing evidence of LM in specimen; pPD = development of LMM.

† marks a patient whose local diagnosis of LM was not confirmed on central review of the pre-treatment biopsy; * marks a patient who declined resection of LM post imiquimod.

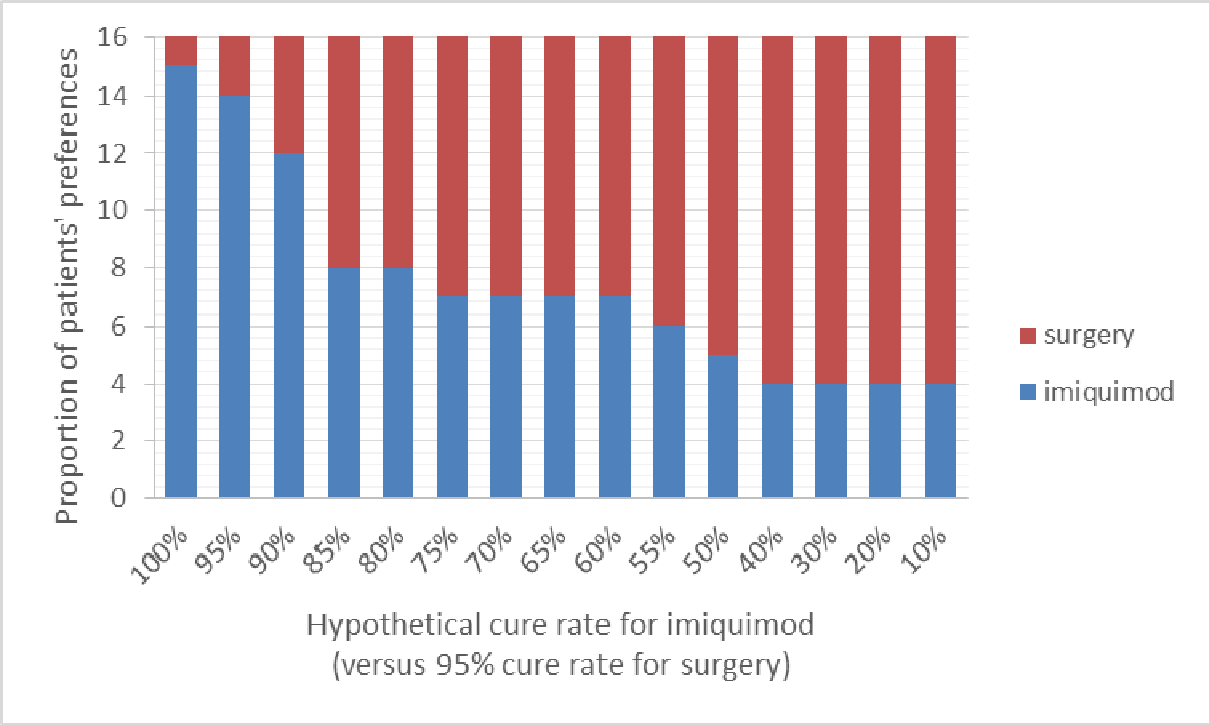

Figure 3 –User Opinion Questionnaire

Bar chart depicting the number of patients (y-axis) reporting preference for either surgery (red) or imiquimod (blue) for varying hypothetical imiquimod cures rates (x-axis) versus a fixed surgical cure rate of 95%. Patients were surveyed having experienced both treatments.