PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for the TIDAL Melanoma Study: Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II, Single Centre, Randomised, Pilot Study.
AUTHORS	Read, Tavis; Webber, Scott; Thomas, Janine; Wagels, Michael; Schaider, Helmut; Soyer, H. Peter; Smithers, B. Mark

VERSION 1 - REVIEW

REVIEWER	Richard Joseph Mayo Clinic Florida
REVIEW RETURNED	17-Mar-2017

GENERAL COMMENTS	This is not a manuscript but a clinical trial protocol. I'm never peer reviewed a protocol before and don't feel it is appropriate.

REVIEWER	Gudula Kirtschig Marburg University, Dept of Dermatology Germany
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	this is an interesting approach and certainly worth a trial that will allow to answer the primary outcome However, I feel a few details are missining, please see questions in enclosed file The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Murat Durdu Başkent University Faculty of Medicine, Department of Dermatology, Adana Hospital, Seyhan, 01130, Adana, TURKEY
REVIEW RETURNED	04-May-2017

GENERAL COMMENTS	This is a nice study aimed to investigate the topical immunotherapy of cutaneous in-transit Melanoma Metastases.

VERSION 1 – AUTHOR RESPONSE

Reviewer 2

- This is a non-superiority trial and the comparison to isolated limb infusion is to demonstrate the estimated difference in cost. ILI is the existing standard of care at our institution, relatively expensive and commonly used for this condition world-wide. The topical treatments and ILI are selected for patients where surgery is inappropriate (has failed) and I believe that a comparison to surgery alone would introduce a significant bias as these patient sub-groups may have substantially different treatment and long-term outcomes.
- To clarify, the primary outcome is complete response, measured up to 12 months following the start of treatment. I have detailed this within the time sub-heading and methods sections. Disease-free survival begins from the point of complete response. You are correct in noting that the measurement of progression-free survival begins from the time of first clinical response. The minimum planned follow-up duration is 12 months from the time of best response or from the last treatment at 12 months (total of 24 months from treatment commencement).
- Patients that progress on the trial will be treated in accordance with the existing standard of care at the time (currently isolated limb infusion) or when disease is systemic and considered non-resectable, patients will be considered for enrolment in other clinical trials or under care of the medical oncologists using systemic therapies. Given this is a non-superiority, proof of concept pilot trial, it is not powered to permit a direct comparison with these therapies in terms of clinical efficacy or long-term outcomes.
- This is correct, if a patient experiences a complete response treatment is discontinued. There is no clear evidence concerning the effect of continuing the therapy after this point. Further treatment is therefore arbitrary and may confound the calculation of time to progression, progression-free and disease-free survival within this study.
- Both investigational agents can be adjusted individually. For example, DPCP treatment begins with a 0.005% concentration cream and can be up-titrated in terms of both total dose applied and the frequency of application to provide a sustained mild-moderate dermatitis. These details are summarised in Table 1 and explained further under the sub-headings ‘Investigational Agents’ and ‘Treatment Schedule.’

The Editor

- I have now modified the title and emphasised within the manuscript text that this is a protocol for a pilot study. The revised title is: "Protocol for the TIDAL Melanoma Study: Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II Single Centre Randomised Pilot Study."
- Further details are provided in the methods section describing the rationale for recruiting fifteen patients into each treatment arm.
- Enclosed is the completed SPIRIT Checklist.

Once again, thank you for your recommendations, I believe these changes improve the readability of the article and address your specific comments.

VERSION 2 – REVIEW

REVIEWER	Gudula Kirtschig Marburg University Department of Dermatology Marburg Germany
REVIEW RETURNED	06-Jun-2017

GENERAL COMMENTS	In your accompanying letter you say:

	- Patients that progress on the trial will be treated in accordance with the existing standard of care at the time (currently isolated limb infusion) or when disease is systemic and considered non-resectable, patients will be considered for enrolment in other clinical trials or under care of the medical oncologists using systemic therapies. Given this is a non-superiority, proof of concept pilot trial, it is not necessary to have it powered to permit a direct comparison with these therapies in terms of clinical efficacy or long-term outcomes. : Do not quite agree with the wording, but understand what you mean: – you still want to show efficacy, your primary end point is complete response rate of treated lesions I find one point confusing: Here (abstarct first para, see enclosed file) you say that you want to compare DPCP or imiquimod treatment to surgery. The next paragraph says the new local treatments will be compared to ILI. Do I understand it correctly: You are looking for alternative treatment for patients with IT metastasis who are not suitable for surgery. These alternatives are either DPCP or imiquimod. Your primary end point is complete response rate of treated lesions, the direct comparison will be done between DPCP and imiquimod. Now the confusion: the results regarding efficacy (primary endpoint) will be compared a) between the two new local treatments and b) compared to previous results you obtained from earlier treatments with isolated limb infusion (primary end point efficacy and sec. endpoint costs, but no direct comparison, no three arm study)? Means you will have at least three outcomes: -treatment effects comparing the two treatments in question (primary endpoint) -the two treatments in question compared to ILI -economic evaluation for patients with IT metastases who are not suitable for surgery (inclusion criterion)? Imiquimod Patients are treated using 5% topical imiquimod applied as a mixture within an aqueous cream. This concentration remains constant for the duration of treatment. A local inflammatory response is produced with application once daily, five days per week, with two rest days. The solution is applied with a 0.5cm margin surrounding lesions and left overnight for 8 hours duration. The treatment is continued so that a mild to moderate dermatitis is maintained with sequential treatments and this includes the provision to reduce the treatment frequency (Table 1). Comment: my experience with imiquimod for the treatment of lentigo maligna is, that some patients need twice daily applications before they develop inflammation, however, you may have your own experience with the metastases. The reviewer also provided a files in addition to these comments. Please contact the publisher for full details.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

- Yes, as you correctly note, this is a proof of concept study and is not powered to detect a statistically significant difference. However, we do want to establish the clinical efficacy based on high quality

data collection within a prospective randomised study – this is because varying response rates have been reported in the literature. To achieve this, the primary outcome we are using is the complete response rate of treated lesions. I have amended the PICO and study rationale sections to clarify this point.
- Yes you are right, we are evaluating two topical treatments (imiquimod or DPCP) in patients with superficial cutaneous in-transit melanoma metastases who are unsuitable for surgery. The results from this study, including the primary outcome (complete response) data will be used to provide more accurate power calculations. These results may then be used with greater confidence to design a superiority trial attempting to show a significant difference in efficacy by directly comparing imiquimod with DPCP within a larger trial open for recruitment at multiple institutions.
- Put simply, isolated limb infusion (ILI) is the standard of care at our institution and we have high quality long-term data available that would be interesting to review (as an ad hoc historical control). The study is not powered to compare the efficacy of either topical therapy with ILI at this stage. Given that ILI is also quite labour intensive and expensive, we will record the relative health-care associated costs involved with the new topical therapies as this will make for an interesting discussion.
- Thank you for this feedback, it is interesting to hear your experience with topical imiquimod for lentigo maligna. The dermatologists involved with this study report that most patients tend to experience moderate reactions using 5% topical imiquimod 5 days per week. However, this is part of the rationale for starting with a small pilot study – we need more high quality data about the treatment regimen and clinical response rates!

Once again, thank you for your recommendations. I have made several other minor changes to improve the readability of the article as indicated.

VERSION 3 – REVIEW

REVIEWER	Gudula Kirtschig Marburg University Germany
REVIEW RETURNED	07-Jul-2017

GENERAL COMMENTS	Thank you - no further comments