MelMarT Melanoma Margins Trial

A Phase III, multi-centre, multi-national randomised control trial investigating 1cm v 2cm wide excision margins for primary cutaneous melanoma

ANZMTG 03.12

Background and Rationale
Patients with an invasive primary melanoma are recommended to undergo excision of the primary lesion, with a secondary wide local excision around the original biopsy scar. There is evidence that less radical margins of this secondary excision may be just as safe as wider margins. This randomised controlled trial will review a 1 cm versus 2 cm margin of the wide local excision of the primary lesion, for adult patients with a primary cutaneous melanoma >=1mm thick. This will determine differences in the rate of local recurrence and melanoma specific survival. The impact upon quality of life for patients and the change in use of healthcare resources will also be ascertained.

Study Objectives
This study will determine whether there is a difference in local recurrence rates and melanoma-specific survival rates for patients treated with either a 1cm excision margin or 2cm margin for both intermediate & high risk melanomas. The study is designed to be able to prove or disprove that there is no difference in risk of the tumour recurring around the scar or anywhere else in the body between the two groups of patients. This study is designed to show that the risk of long-term pain associated with surgery can be halved. If the study shows no risk of the tumour recurrence then we will also be able to determine how much of an impact the narrower excision has on patients in terms of improved quality of life and reduced side effects from the surgery and melanoma disease. This trial will also evaluate and determine the economic impact of narrower excision margins on the health services and society in general.

Study Hypothesis
There is no difference in local recurrence rates or melanoma-specific survival for patients treated with either a 1cm or 2cm excision margin for intermediate and high risk primary melanoma. A 1cm excision margin will halve the risk of long-term pain and will improve surgical complication rates. A 1cm excision margin will have an impact on improved quality of life for patients and change the use of local healthcare resources.

Study Design
This is a randomised, controlled, multi-centre, non-inferiority, internationally recruiting, phase III clinical trial.
<table>
<thead>
<tr>
<th><strong>MELMART TRIAL SCHEMA</strong></th>
<th><strong>TRIAL PHASE</strong></th>
<th><strong>TIME</strong></th>
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</thead>
<tbody>
<tr>
<td>Diagnosis of Primary Cutaneous Melanoma pT2-pT4 (N0M0) AJCC Stage IB-IIC</td>
<td>Screening</td>
<td>No more than 120 days prior to randomisation</td>
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<tr>
<td>Confirmation of Diagnosis – Pathology review at Specialist MDT (Trial Centre) Informed Consent</td>
<td>RANDOMISATION (Stratification Factors: Risk Group; Age; Sex; Site)</td>
<td>Total patients = 9,684</td>
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<tr>
<td><strong>ARM A:</strong> Experimental Arm</td>
<td><strong>ARM B:</strong> Control Arm</td>
<td><strong>ARM A:</strong> Experimental Arm</td>
</tr>
<tr>
<td>Wide Local Excision = 1cm Margin</td>
<td>Wide Local Excision = 2cm Margin</td>
<td>Wide Local Excision = 1cm Margin</td>
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<tr>
<td>+ Sentinel Lymph Node Biopsy +/- Reconstruction</td>
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<tr>
<td>N=3,484</td>
<td>N=3,484</td>
<td>N=1,448</td>
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<tr>
<td>At participating sites: QOL component (FACT-M, EQ-5D-5L and Neuropathic Pain (PainDetect)) &amp; Health economic component (Form BE)</td>
<td>Intervention (ie. 1 or 2 cm wide local excision)</td>
<td>Day 0 + &lt;14 days</td>
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<td><strong>FOLLOW UP</strong></td>
<td></td>
<td></td>
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<tr>
<td>Clinical Information &amp; Health Status</td>
<td>Annually after 12 months according to National Guidelines of Trial Centre</td>
<td>From 12 months until Trial Completion (max. 120 months)</td>
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<tr>
<td>At participating sites: Follow Up Employment Questionnaires</td>
<td>At 3, 6 and 12 months</td>
<td>Day 0 to 12 months</td>
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<tr>
<td>At participating sites: FACT-M, EQ-5D-5L, PainDetect (Neuropathic pain) and Follow Up Cost Questionnaire completion</td>
<td>At 3, 6, 12, 24 &amp; 60 months</td>
<td>Day 0 – Month 60 (Year 5)</td>
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<tr>
<td>Melanoma Recurrence(s)</td>
<td>At the time of Recurrence</td>
<td></td>
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<tr>
<td>Death</td>
<td>At the time of Death</td>
<td></td>
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<tr>
<td><strong>ENDPOINTS</strong></td>
<td></td>
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<tr>
<td>Local Melanoma Recurrence Melanoma Specific Survival</td>
<td>Primary Endpoints</td>
<td>Day 0 until Trial Completion (max. 120 months)</td>
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<tr>
<td>Recurrence-Free Survival Overall Survival</td>
<td>Secondary Endpoints</td>
<td>Day 0-12 months &amp; 60 months</td>
</tr>
<tr>
<td>FACT-M, EQ-5D-5L and Neuropathic Pain (PainDetect) Questionnaires, Health economics (Employment and Cost Questionnaires) and Surgical Complication Rate</td>
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Patient Accrual
The aim is to recruit 9,684 patients (6,968 in the intermediate risk group and 2,896 in the high risk group) worldwide accrued over five years. The initial 400 patients will be accrued during the pilot phase of the study.

Inclusion Criteria
Patients may be included in the study only if they meet all of the following criteria:

1. Patients must have a primary invasive cutaneous melanoma of Breslow thickness greater than 1 millimetre as determined by diagnostic biopsy (narrow excision, incision or punch biopsy) and subsequent histopathological analysis.
2. Patients must have had the invasive primary completely excised, including any in situ component but excluding melanocytic atypia, with a narrow margin, either in one stage or more than one stage in the case where an incision or punch biopsy has previously been performed. This information, including measured margins of lateral and deep clearance must be documented on the pathology report.
3. Must have a primary melanoma that is cutaneous (including head, neck, trunk, extremity, scalp, palm, sole).
4. An uninterrupted 2cm margin must be technically feasible around biopsy scar or primary melanoma.
5. Randomisation and the primary study intervention, including staging sentinel node biopsy, must be completed by 120 days of original diagnosis.
6. Patients must be 18 years or older at time of consent.
7. Patient must be able to give informed consent and comply with the treatment protocol and follow-up plan.
8. Life expectancy of at least 10 years from the time of diagnosis, not considering the melanoma in question, as determined by the PI.
9. Patients must have an ECOG performance score between 0 and 1.
10. A survivor of prior cancer is eligible provided that ALL of the following criteria are met and documented:
    o The patient has undergone potentially curative therapy for all prior malignancies,
    o There has been no evidence of recurrence of any prior malignancies for at least FIVE years (except for successfully treated cervical or non-melanoma skin cancer with no evidence of recurrence), and
    o The patient is deemed by their treating physician to be at low risk of recurrence from previous malignancies.

Exclusion Criteria
Patients will be excluded from the study for any of the following reasons:
1. Uncertain diagnosis of melanoma i.e. so-called ‘melanocytic lesion of unknown malignant potential’.
2. Patient has already undergone wide local excision at the site of the primary index lesion.
3. Patient unable or ineligible to undergo staging sentinel lymph node biopsy of the primary index lesion.
4. Desmoplastic or neurotropic melanoma.
5. Microsatellitosis as per AJCC 2009 definition.
7. Patient has already undergone a local flap reconstruction of the defect after excision of the primary and determination of an accurate excision margin is impossible.
8. History of previous or concurrent (i.e., second primary) invasive melanoma.
9. Melanoma located distal to the metacarpophalangeal joint, on the tip of the nose, the eyelids or on the ear, mucous membranes or internal viscera.
10. Physical, clinical, radiographic or pathologic evidence of satellite, in-transit, regional, or distant metastatic melanoma.
11. Patient has undergone surgery on a separate occasion to clear the lymph nodes of the probable draining lymphatic field, including sentinel lymph node biopsy, of the index melanoma.
12. Any additional solid tumour or hematologic malignancy during the past 5 years except T1 skin lesions of squamous cell carcinoma, basal cell carcinoma, or uterine/cervical cancer.
13. Melanoma-related operative procedures not corresponding to criteria described in the protocol.
14. Planned adjuvant radiotherapy to the primary melanoma site after Wide Local Excision is not permitted as part of the protocol and any patients given this treatment would be excluded from the study.
15. History of organ transplantation.
16. Oral or parenteral immunosuppressive agents (not topical or inhaled steroids) at any time during study participation or within 6 months prior to enrolment.