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# FAST FACTS

**S2015 - Melanoma Margins Trial (MelMarT-II): A Phase III, multi-centre, multi-national randomised control trial investigating 1cm v 2cm wide excision margins for primary cutaneous melanoma**

## Patient Population

It is expected that patients will be recruited from treatment centres specialising in the surgical care of melanoma patients. Recruiting institutions will be required to demonstrate an adequate annual caseload of primary melanoma and will need to be performing a minimum of 30 -SLNBs per annum. Patients eligible for the trial should be assessed by the specialist multidisciplinary teams (or tumour board) including pathology slide review to confirm the diagnosis of primary melanoma. The following patients would be eligible for the trial:

### *Inclusion Criteria*

Patients may be included in the study if they meet **ALL** of the following criteria:

1. Patients must have a Stage II primary invasive cutaneous melanoma (pT2b-pT4b, AJCC 8th edition) with Breslow thickness >1.0mm to 2.0mm; >2.0mm to 4.0mm or >4.0mm with ulceration, or >2.0mm to 4.0mm; or >4.0mm without ulceration (Table 1) as determined by diagnostic biopsy (narrow excision, incision, shave or punch biopsy) and subsequent histopathological analysis.
2. Must have a primary melanoma that is cutaneous (including head, neck, trunk, extremity, scalp, palm or sole).
3. An uninterrupted 2cm margin must be technically feasible around biopsy scar or primary melanoma.
4. Surgical intervention (which refers to the staging -SLNB and WLE as these are both to be done on the same day) must be completed within 120 days of the original diagnosis. Surgical intervention must also be performed within 28 days of randomisation.
5. Patients must be 18 years or older at time of consent.
6. Patient must be able to give informed consent and comply with the treatment protocol and follow up plan.
7. Life expectancy of at least 5 years from the time of diagnosis, not considering the melanoma in question, as determined by the PI.
8. Patients must have an ECOG performance score between 0 and 1 at screening.
9. A survivor of prior cancer is eligible provided that **ALL** of the following criteria are met and documented:
    - The patient has undergone potentially curative therapy for all prior malignancies,
    - There has been no evidence of recurrence of any prior malignancies for at least FIVE years *(with the exception of successfully treated uterine/cervical or non-melanoma skin cancers (SCCs/BCCs) with no evidence of recurrence*), **and**
    - 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 WLE at the site of the primary index lesion.
3. Patient unable or ineligible to undergo staging SLNB of the primary index lesion.
4. Perineural invasion or neurotropic melanoma: Neurotropism or perineural invasion in any type of melanoma is an exclusion. Perineural invasion does not include entrapment of nerves within the main primary tumour mass.
5. Desmoplastic melanoma: with any patient where pathology determines melanoma as PURE desmoplastic (as per WHO definition of >90% desmoplasia), they are not eligible for this study. However melanomas with less than 90% desmoplasia or mixed desmoplastic subtypes are eligible unless there is neurotropism present (perineural invasion)
6. Microsatellitosis (a nest of metastatic tumour cells found to be growing away from the primary tumour) as per AJCC 8$^{th}$ edition definition is an exclusion.
7. Subungual melanoma.
8. 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.
9. History of previous or concurrent (i.e., >1 primary melanoma) invasive melanoma.
10. Melanoma located distal to the metacarpophalangeal joint; on the tip of the nose; the eyelids or on the ear; genitalia, perineum or anus; mucous membranes or internal viscera.
11. Physical, clinical, radiographic or pathologic evidence of satellite, in-transit, regional, or distant metastatic melanoma.
12. Patient has undergone surgery on a separate occasion to clear the lymph nodes of the probable draining lymphatic field, including -SLNB, of the index melanoma.
13. Any additional solid tumour or hematologic malignancy during the past 5 years (*with exception of non- melanoma skin cancers (T1 skin lesions of squamous cell carcinoma (SCCs), basal cell carcinoma (BCCs)), or uterine/cervical cancer*).
14. Melanoma-related operative procedures not corresponding to criteria described in the protocol.
15. 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.
16. History of organ transplantation.
17. Oral or parenteral immunosuppressive agents (not topical or inhaled steroids) at enrolment or within 6 months prior to enrolment.

***Please note:***

- Pregnancy is not a specific exclusion criterion for this trial, though it may not be clinically appropriate to perform a wide excision and SLNB until the pregnancy has been completed, which may exclude the patient due to violation of inclusion criterion 4.
- We would advise careful counselling of the patient prior to enrolment, which would include a discussion at the treating centre's multidisciplinary team meeting or tumour board and the central trial office.

Table 3: Summary of Inclusion/Exclusion criteria

| Inclusion criteria | Ineligible | Eligible |
|---|---|---|
| Stage II primary invasive cutaneous melanoma as per pT2b-pT4b, AJCC 8th edition see table 1 | | X |
| Cutaneous primary melanoma | | X |
| An uninterrupted 2cm margin must be feasible around biopsy scar or primary melanoma | | X |
| Surgical intervention must be completed within 120 days of the original diagnosis and within 28 days of randomisation. | | X |
| Patients must be 18 years or older at time of consent | | X |
| Patient must be able to give informed consent | | X |
| Life expectancy of at least 5 years from the time of diagnosis | | X |
| ECOG performance score between 0 and 1 at screening. | | X |
| **A survivor of prior cancer is eligible provided that ALL of the following criteria are met and documented** | | |
| * patient has undergone potentially curative therapy for all prior malignancies | | X |
| * no evidence of recurrence of any prior malignancies for at least FIVE years | | X |
| * patient is deemed by their treating physician to be at low risk of recurrence from previous malignancies. | | X |

| Exclusion criteria | Ineligible | Eligible |
|---|---|---|
| Uncertain diagnosis | X | |
| Prior WLE at primary index lesion site | X | |
| Unable or ineligible to undergo staging SLNB of the primary index lesion | X | |
| Perineural invasion or neurotropic melanoma: Neurotropism or perineural invasion in any type of melanoma | X | |
| Desmoplasia >90% | X | |
| Desmoplasia <90% | | X |
| Desmoplasia mixed subtype | | X |
| Desmoplasia <90% plus Neurotropism or perineural invasion | X | |
| Desmoplasia mixed subtype plus Neurotropism or perineural invasion | X | |
| Satellitosis/Microsatellites | X | |
| Subungual melanoma | X | |
| Prior local flap reconstruction of the defect after excision of the primary lesion and determination of an accurate excision margin is impossible | X | |
| History of previous or concurrent invasive melanoma | X | |
| Melanoma located distal to the metacarpophalangeal joint; on the tip of the nose; the eyelids or on the ear; genitalia, perineum or anus; mucous membranes or internal viscera | X | |
| Prior surgery to clear the lymph nodes of the probable draining lymphatic field, including -SLNB, of the index melanoma | X | |
| Any additional solid tumour or hematologic malignancy during the past 5 years (excl. SCC/BCC or uterine/cervical cancer) | X | |
| Melanoma-related operative procedures not corresponding to criteria described in the protocol | X | |
| 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. | X | |
| Organ transplantation recipient | X | |
| Oral or parenteral immunosuppressive agents (not topical or inhaled steroids) at enrolment or within 6 months prior to enrolment | X | |

***Exclusion criterion exceptions***

The screening process is critical for both patient safety and the integrity of the MelMarT-II trial, however as this trial is a pragmatic in design it is understood that some eligibility exceptions must be allowed for. Below are two scenarios where participants meeting exclusion criterion 4, 5 and or 6 may remain on trial.

1. Participants randomised in good faith and deemed eligible at point of randomisation and intervention. Exclusion criterion 4, 5 and or 6 (e.g. microsatellites/PNI) discovered in wide local excision or discovered after post-hoc review of primary melanoma and/or patient.
   **Outcome**: Participant to stay on trial. No other action. Included in final analysis.

2. Participants randomised in error (ineligible meets exclusion criterion 4, 5 and or 6 (eg microsatellites/PNI)), undergoes trial intervention then error discovered.
   **Outcome**: Participant stays on study and follow-up data only (not PROMs) to be collected. Included in a sensitivity analysis, specifically for this group, but not included in main analysis. Serious breach notification to sponsor and ethics.
   In the UK, de-identified patient data will also be sent to the British ethics committee. Historic patients have been withdrawn in the UK but will be reconsented.

**SCHEMA**