# A phase III, Randomized Trial of Surgical Resection With or Without BCG versus Best Medical Therapy as Initial Treatment in Stage IV Melanoma

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This study will establish the role of surgical versus nonsurgical approaches in patients whose melanoma has spread to distant sites. Results will help clinicians develop a standardized initial approach that prolongs survival and optimizes quality of...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Epidermal and dermal conditions |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON36748

**Source**
ToetsingOnline

**Brief title**
MORD-STG4SURG-049

### Condition

- Epidermal and dermal conditions

**Synonym**
melanoma, skin cancer

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** John Wayne Cancer Institute

**Source(s) of monetary or material Support:** John Wayne Cancer Institute;Los Angelos;USA

## Intervention

**Keyword:** Melanoma, Stage IV

## Outcome measures

### Primary outcome

This study is open to patients with Stage IV metastatic melanoma who are able to have all sites of known disease surgically removed or ablated and have metastases in no more than 3 visceral organs. Patients with brain or bone metastases are not eligible for the study. Eligibility for resection must be confirmed by a participating surgeon who confirms the potential to resect all known disease.

### Secondary outcome

1. To determine whether surgical resection with or without BCG as initial therapy for Stage IV metastatic melanoma will prolong melanoma-specific survival (MSS) as compared to initial BMT. Melanoma-specific survival is defined as the time from randomization to death from melanoma.

2. Time to progression of initial metastatic sites: To determine whether surgical resection with or without BCG as initial therapy for Stage IV metastatic melanoma will prolong progression-free survival (PFS) relative to best medical treatment as initial therapy. For this study, PFS is defined as the time from randomization to disease recurrence at initial metastatic site in patients rendered disease-free by surgery, or time from randomization to RECIST-defined progression of target lesions in patients receiving best medical

therapy or those having residual disease following surgery.

3. Time to development of new metastatic sites: To determine whether surgical resection with or without adjuvant BCG as initial therapy for Stage IV metastatic melanoma will prolong time to the development of new metastatic sites of disease relative to best medical therapy. This endpoint is defined as the time from randomization to disease recurrence at new metastatic sites in patients rendered disease-free by surgery, or time from randomization to the development of new metastatic sites of disease in patients in the best medical therapy group. Progression of existing lesions in the best medical therapy arm will not be considered an event for this endpoint (see progression-free survival above, #2).

4. To determine whether adjuvant treatment with intradermal Bacillus Calmette-Guérin (BCG) will improve melanoma-specific or disease-free survival in patients undergoing resection of melanoma metastases.

5. To evaluate the correlation between tumor volume doubling time and PFS as well as melanoma-specific survival (MSS) in patients with surgery or medical therapy.

6. To determine whether surgical resection as initial therapy for Stage IV metastatic melanoma will improve quality of life (QOL) relative to best medical treatment as initial therapy.

7. To determine the 7. prognostic and predictive value of molecular blood biomarker measurements of circulating tumor cells (CTC) and circulating DNA after randomization and after resection in the surgery arm.

8. To determine what proportion of all stage IV patients at the time of initial

diagnosis of distant metastases are possible candidates for surgical resection of all metastatic disease and what proportion of those undergoing surgery can be completely resected.

9. To discover predictive immune and molecular biomarkers in patients with Stage IV metastatic melanoma that may correlate with prognosis and help select patients for best outcomes following medical or surgical therapy.61, 62

10. To determine whether surgical resection of Stage IV metastatic melanoma will alter immune responsiveness to urinary tumor associated antigen (UTAA), ganglioside, or other melanoma antigens relative to best medical therapy without resection

## Study description

**Background summary**

This study will establish the role of surgical versus nonsurgical approaches in patients whose melanoma has spread to distant sites. Results will help clinicians develop a standardized initial approach that prolongs survival and optimizes quality of life. Results also will indicate whether Bacillus Calmette-Guerin (BCG) postoperative immunotherapy significantly improves the outcome of patients treated with surgery.

This study is designed to examine the impact of surgical resection versus medical therapy as initial treatment therapy for patients with Stage IV melanoma. Surgical resection is thought to be efficacious in highly selected patients with solitary metastases, but not in patients with multiple sites of metastases. Even in those with solitary metastases, there is considerable debate among major melanoma centers over whether undergoing initial systemic medical therapy prior to surgical resection should be preferred to initial surgical resection upon Stage IV diagnosis. According to Dr. Dan Coit, Co-leader of the Melanoma Disease Management Team at Memorial Sloan Kettering Cancer Institute in New York, a trial of initial medical therapy is their standard approach on the multidisciplinary melanoma service even for patients with solitary distant metastases (personal communication, 15 Dec 2009). Many who favor upfront medical therapy believe that delay before surgical

resection may avoid unnecessary surgery by identifying patients who progress early due to the outgrowth of occult metastases at multiple sites, which may make the patient unresectable.
This is a Phase III, randomized, international, multicenter study of metastasectomy with or without BCG versus best medical therapy as initial therapy in Stage IV melanoma. This study has three arms: surgical resection plus BCG as an immune adjuvant, surgical resection plus observation, and best medical therapy (BMT). Since no systemic medical therapy has been demonstrated to be superior to DTIC and multiple new therapies are being evaluated, the choice as to what constitutes best medical therapy will be determined by the individual investigator based on the standard of care for systemic medical therapy at that particular multicenter site. Best systemic medical therapy may include clinical trials of new agents or standard non-protocol treatments (e.g., DTIC or Temodar according to the standard of care at the multi-center site).
Patients who progress on the best medical treatment arm may switch to a different medical therapy or, if appropriate, have surgical therapy; similarly, surgery patients may have additional surgical resection or receive medical therapy.
(see prototcol Backroundinformation and scientific rationale pp 15-26)

**Study objective**

This study will establish the role of surgical versus nonsurgical approaches in patients whose melanoma has spread to distant sites. Results will help clinicians develop a standardized initial approach that prolongs survival and optimizes quality of life. Results also will indicate whether Bacillus Calmette-Guerin (BCG) postoperative immunotherapy significantly improves the outcome of patients treated with surgery.
(see prototcol Study objectives pp 27-28))

**Study design**

This is a Phase III, randomized, international, multicenter study of metastasectomy versus best medical therapy as initial therapy in Stage IV melanoma. This study has three arms: surgical resection plus BCG as an immune adjuvant, surgical resection plus observation, and best medical therapy.
Prior to enrolling in this study, patients with Stage IV melanoma will undergo a screening phaseto determine if their disease is resectable, thus making them potentially eligible for the trial. Patients will be assessed clinically and radiographically to determine the extent of disease, and all patients must be evaluated by a participating surgeon to determine resectability as an eligibility criterion (see Chart 1 in Section 4.10.1).
Patients who enroll in the study will be randomly assigned to undergo initial therapy either by surgical resection (+/- BCG) or best

medical therapy. Since no systemic medical therapy has been demonstrated to be superior to DTIC and multiple new therapies are being evaluated, the choice as to what constitutes best medical therapy will be determined by the individual investigator according to the
standard of care for systemic medical therapy at that particular multicenter site. Best systemic medical therapy may include clinical trials of new agents or standard non-protocol treatments, such as DTIC or high-dose IL-2. See Section 5.3 for discussion of BMT.
All patients will be followed for up to 5 years for clinical and correlative endpoints, including overall survival, time to development of new metastatic sites of disease, progression-free survival, melanoma-specific survival, quality of life, and correlative laboratory studies, including
tumor volume doubling time and development of anti-melanoma antibodies. Patients receiving BCG will also undergo immunologic evaluations to determine reactivity to PPD skin testing. Patients in the surgical resection arms should have their operations completed within 3 weeks after randomization. If upon operation, these patients are found to have unresectable disease, they will receive best available medical or radiation therapy. Two post-surgery visits will be required for BCG administration. The first dose of BCG will be given no earlier than 4 weeks
after surgery, and the second BCG dose will follow 2 weeks later. Follow-up visits will then occur at months 2, 4, 6, 8, 10, and 12 in year 1; months 3, 6, 9, and 12 in year 2; months 4, 8 and 12 in year 3; then every 6 months for years 4 and 5. The follow-up schedule will be based
on the patient*s surgery date (Day 0) and, for BCG patients, recovery from surgery (see Study Calendar, Appendix 1). The treatment schedule for medical therapy patients will be determined by the regimen they receive, but they should be examined and scanned at least as often as the
above stated follow-up regimen.
Patients receiving medical therapy will follow the treatment schedule according to theirdesignated regimen, but will still need to be seen at a participating study site for follow-up visits at least every 2 months in year 1; every 3 months in year 2; every 4 months in year 3; and every
6 months for years 4-5 (see Study Calendar, Appendix 1, for a detailed schedule). The followupschedule will be based on the patient*s start date for medical therapy (Day 0).
Patients in any treatment arm whose disease progresses or recurs after initial treatment may undergo salvage therapy as appropriate. Salvage treatments may include additional surgical resection for those in the surgery arms whose disease, according to the judgment of the clinical investigator, is still resectable. Those in the surgery arms whose disease is not resectable will receive the best available medical therapy. Patients in the best medical therapy arm who progress and/or recur may continue with a different medical therapy or may undergo surgical
resection if their disease is still resectable, according to the judgment of the clinical investigator. The medical and surgical oncologist team will determine whether patients with stable disease orpartial responses should

continue their medical therapy.
(see prototcol Study design29-30)

**Study burden and risks**

Surgery: Potential risks from undergoing surgery for this study are the standard risks of surgical resection and depend on the site of the metastases to be resected.
BCG; Nearly all patients receiving BCG experience local erythema, induration, and inflammation of the skin at the injection sites. When injected intradermally, the expected reaction is a small red papule that scales, forms a localized abscess, ulcerates and dries, leaving a small pink or bluish sc
Systemic treatment: Potential risks from medical therapy will vary depending on the regimen used and individual patient sensitivity but generally include weight loss, loss of appetite, nausea and/or vomiting, fatigue, decrease in blood counts, hair loss, as well as others specific to individual drugs. Additional side effects depend on the regimen of drugs to be used for the chosen medical or adjuvant therapy.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Inclusion Criteria
All of the following inclusion criteria must be met and certification of eligibility must be obtained from the Principal Investigator in order for the patient to be eligible. A completed, signed and dated consent form is also required prior to randomization and prior to the performance of any protocol-related procedures.;1. Patients must be at least 18 years of age and have a minimum life expectancy
(excluding melanoma) of 5 years.
2. All known disease must be surgically resectable in the opinion of a participating surgeon.
3. Patients must have a histologic diagnosis of Stage IV melanoma arising from a primary cutaneous site or visceral metastasis from an unknown primary site and be within 4 months of initial stage IV diagnosis.
4. Patients may have up to 3 visceral organs involved. Any number of lesions up to 6 is allowed.
5. Patients must provide informed written consent for participation.
6. Patients must have ECOG performance status of 0 or 1.
7. Patients must be in good general health with no serious co-morbid illness. Good clinical judgment must be exercised in careful selection of patients who are candidates for surgical resection of distant metastases.
8. Laboratory values within 30 days of randomization:
a. WBC >3,000/mm3
b. Lymphocytes >800/mm3
c. Platelets >100,000/mm3
d. Creatinine <2.0 mg/dL
e. Bilirubin <2.0 mg/dL
f. Alkaline phosphatase < 2X upper
g. SGOT < 2X ULN
h. SGPT < 2X ULN
i. LDH < 1.5X ULN

## Exclusion criteria

Exclusion Criteria
If any of the following exclusion criteria is met, the patient is ineligible for the study.
1. Unresectable metastatic disease or more than 4 months since stage IV diagnosis.

2. Brain or bone metastatic sites.
3. History of primary uveal or mucosal melanoma.
4. Another concomitant diagnosis that limits life expectancy to less than 5 years.
5. Chronic immunosuppression due to inherited, acquired or iatrogenic immune defect. This includes active HIV, hepatitis, or use of immunosuppressive medications as a component of anti-rejection therapy for organ transplant, as treatment for an autoimmune disease.
6. More than 3 involved visceral organ sites or more than 6 metastatic lesions.
7. Psychiatric disorder or organic brain syndrome that might preclude participation in the protocol.
8. Diagnosis of other malignancy in the past 5 years except adequately treated low grade malignancies such as basal cell carcinoma, cutaneous squamous cell carcinoma, carcinoma-in-situ of the cervix, or other neoplasm that will not limit life expectancy to less than 5 years.
9. Serious cardiac, gastrointestinal, hepatic or pulmonary disease that would make surgical resection high-risk.
10. Pregnancy

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Observational non invasive |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Treatment

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 01-11-2011 |
| Enrollment: | 20 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |

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|---|---|
| Brand name: | TICE (r) Strain Bacillus Calmette-Guerib (BCG) from Organon Teknika |

## Ethics review

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|---|---|
| Approved WMO Date: | 27-01-2011 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2010-021030-56-NL |
| ClinicalTrials.gov | NCT01013623 |
| CCMO | NL31661.042.10 |