Title: Systemic Anti-Cancer Therapy (SACT) guidelines for the management of malignant melanoma

Author(s): Dr Vicky Coyle Consultant Medical Oncologist & Dr Bode Oladipo Consultant Medical Oncologist
Co-authors: Dr O Dolan, Dr D Gordon, Dr T Lynch, Dr S McAleer, Dr M Walsh, Dr J O’Hare

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<td>Dr V Coyle &amp; Dr B Oladipo</td>
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<td>Treatment options for 1st and 2nd line treatment in metastatic disease updated.</td>
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<td>Dr V Coyle &amp; Dr B Oladipo</td>
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Authorisation of Systemic Anti-Cancer Therapy (SACT) guidelines for the treatment of malignant melanoma

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<td>Dr Vicky Coyle, Consultant Medical Oncologist Dr Bode Oladipo, Consultant Medical Oncologist</td>
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These SACT guidelines are being submitted by the authors on behalf of the Skin Clinical Reference group.
1. **Staging investigations**

- European and US guidelines recommend routine staging investigations for all patients excepting those with thin melanomas (Stage I - early Stage II disease).

- The following staging guidelines adopt a pragmatic approach based on clinico-pathological risk factors.

*Patients with Stage III or IV melanoma in whom radical surgical intervention is proposed should undergo staging PET scan to identify occult metastatic disease that may render the proposed management inappropriate.

**PET scan and brain imaging (CT or MR scan) should be performed after nodal resection in patients with Stage III melanoma prior to considering adjuvant therapy.

- BRAF mutation testing should be requested in node positive patients, relapsed disease, or those with unresectable locally advanced or metastatic disease who are being considered for systemic therapy. Secondary tissue testing is preferable.

*SACT for malignant melanoma V 5.1*
2. Surgical management

Surgical excision of primary lesion:

- Curative treatment of malignant melanoma is by surgical excision with adequate margins.

- UK guidelines recommend an initial excision biopsy of the whole tumour with a 2mm margin of normal skin and a cuff of fat. Punch or incision biopsy is not recommended.

- Wider surgical excision is performed to ensure complete removal of the primary lesion and micrometastatic disease.

- The size of the excision margins depends on the Breslow thickness of the melanoma while the depth has conventionally been to muscle fascia or deeper if feasible (Table 1).

- Determination of adequate margins should be confirmed histologically, although adjustment for shrinkage of 20% on average should be made.

- The final decision regarding surgical margins should be made after MDT discussion taking into consideration the anatomical site, likely functional outcome and patients' wishes after informed discussion.

Table 1: Recommended lateral margins

<table>
<thead>
<tr>
<th>Breslow thickness</th>
<th>Excision margins</th>
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<tbody>
<tr>
<td>in situ melanoma</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>≤1mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01-2.0mm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>2.01-4.0mm</td>
<td>2 cm</td>
</tr>
<tr>
<td>&gt;4mm</td>
<td>2 cm</td>
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</table>
Assessment of draining lymph node areas:

- Metastasis to regional lymph nodes is the strongest predictor of outcome in melanoma, with decreasing survival rates reported with increasing regional node involvement.

Sentinel node biopsy:

- Not commissioned in Northern Ireland.
- Provides staging and prognostic information in patients with melanoma without improvement in overall survival demonstrated to date.
- Failure to detect sentinel lymph node in 5% of patients.
- Further discussion on an individual basis.
Lymph node dissection:

- UK guidelines outline the extent of surgery that should be performed where feasible:
  
  - Axillary dissection level I - III is recommended.
  
  - Superficial inguinal nodal dissection can be considered where there is a single involved inguinal or femoral triangle node or a single positive superficial inguinal sentinel node.
  
  - Otherwise, an ilio-inguinal lymph nodal dissection can be considered where there is clinical or radiological evidence of more extensive nodal disease or where there is more than one microscopically involved node at sentinel node biopsy.
  
  - In the case of cervical nodes a radical dissection performed by MDT surgeons with head and neck and melanoma expertise is recommended.

Distant metastatic disease:

- Surgical resection of metastatic disease may be of benefit to a minority of patients, for example solitary brain metastases or resectable lung metastases.
3. Systemic therapy

Adjuvant therapy:

- Interferon is the most evaluated adjuvant systemic therapy in melanoma and the only treatment to demonstrate an effect in this setting.
  
  - Data suggests modest benefits on recurrence-free survival but a small effect if any on overall survival (3% absolute survival benefit at 5 years (CI 1-5%) in recent metaanalysis).
  
  - No optimum dose, schedule or treatment duration has been identified. Consensus regarding use is lacking, and toxicity concerns are considerable.

- Adjuvant interferon could be discussed on an individual basis in selected patients with proven node positive disease following radical dissection.

- Clinical trial participation should be considered where available, and is the preferred option.

Systemic therapy for metastatic disease:

First line treatment:

- BRAF mutation status should be determined prior to starting treatment (if not already known)

- Choice of first line agent will depend on patient factors such as BRAF-mutation status, bulk of disease, performance status and comorbidity.

- Consider available clinical trials

- The following first line therapies can be considered:
  
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab
  - Vemurafenib or Dabrafenib for BRAF mutant melanoma
  - Dabrafenib + Trametinib for BRAF mutant melanoma
- Dacarbazine (or Temozolamide if CNS metastases as this has equivalent efficacy to DTIC and relatively high CNS penetration)
- Ipilimumab + Nivolumab

**Second and subsequent line treatment:**

- Choice of second line therapy will depend on patient factors including first line treatment, BRAF-mutation status, sites and volume of disease, performance status and comorbidity.
- Consider available clinical trials
- The following second and subsequent line therapies can be considered:
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab
  - Vemurafenib or Dabrafenib for BRAF mutant melanoma
  - Dabrafenib + Trametinib for BRAF mutant melanoma
  - Dacarbazine (or Temozolamide if CNS metastases as this has equivalent efficacy to DTIC and relatively high CNS penetration)
  - Ipilimumab + Nivolumab

**Unlicensed or non-funded therapeutic options**

- The melanoma treatment landscape is evolving rapidly, and novel drugs continue to show promise as single agent treatment or as combination therapy.
- Such new therapies may be available to clinically appropriate patients on an approved compassionate use/expanded access scheme, ahead of formal licensing and/or funding
- This will ensure patients can benefit from the most effective and safe evidence-based treatment options.
4. Radiotherapy

- Radiotherapy to primary cutaneous melanoma is rarely indicated, and generally performed where surgery is not possible.

- Radiotherapy can be indicated in the primary management of lentigo maligna and in the management of locoregional recurrence.

- Palliative radiotherapy may be useful in advanced disease e.g. brain or bone metastases.

Adjuvant radiotherapy:

- Consider adjuvant radiotherapy in high risk groups, but the clinical benefit is debatable for most patients:
  - Existing data suggests an improvement in local control but no benefit to overall survival (trend towards worse survival) and significant risk of increased toxicity.

- Radiotherapy to nodal areas may however be considered by the MDT if surgery is incomplete or not feasible. Systemic therapy may also be an option for these patients.

- Post-operative radiotherapy can be considered for head and neck melanoma, in particular mucosal melanoma of the nasal cavity or paranasal sinuses. The potential for morbidity is less than that for axillary or groin irradiation, but remains significant.

- The NCCN guidelines suggest post-operative radiotherapy for head and neck melanoma for patients with high risk features:
  - extracapsular disease
  - involvement of ≥2 neck nodes or intraparotid nodes
  - any node >3cm
  - neck excision without further nodal basin dissection
  - neck/soft tissue recurrence after initial surgical resection.
5. Specific clinical settings

Lentigo maligna:

- Typically occurs on head and neck in elderly patients, may progress to invasive lentigo malignant melanoma.
- Management is by surgical excision with 0.5cm margins.
- Topical therapy, for example imiquimod, is usually recommended only in the context of a clinical trial or after MDT discussion.

Locoregional recurrence:

- Surgical excision is the mainstay of treatment, excision should be complete but wide margins are not necessary.
- For multiple lesions, small skin lesions can be treated by CO₂ laser therapy.
- For larger or deeper lesions, regional chemotherapy with isolated limb infusion (ILI) or perfusion (ILP) are potential treatment options. With the advent of more effective systemic therapies, the role of these procedures are becoming less well defined.
- Regional therapies are not performed in Northern Ireland at present, but referral to specialist centres could be considered in the absence of other options.
- Radiotherapy can be considered for disease which is not controlled by other modalities.
Primary melanoma at other sites:

**Mucosal melanoma**

- Primary mucosal melanoma occurs rarely but is associated with a poor prognosis.
- Treatment is by wide surgical excision with clear margins.
- Radiotherapy is often used for mucosal melanoma, particularly for head and neck tumours.

**Subungual melanoma**

- Small minority of malignant melanomas which are managed surgically, conserving function where possible.

Brain metastases:

- Dexamethasone is usually given as immediate treatment, particularly in the presence of symptoms and/or perilesional oedema
- Surgical resection or stereotactic radiotherapy can be considered for solitary or small number (typically up to three) metastases, usually for lesions up to 3cm in size.
- Whole brain radiotherapy is an option for larger volume and/or multiple brain metastases with good symptomatic improvement in headache/neurological deficit reported.
- Patients with BRAF mutation positive disease and brain metastases may receive a BRAF inhibitor as initial treatment rather than radiotherapy, as there is a high response rate and potential for rapid clinical improvement.
- BRAF mutation negative patients with asymptomatic, small volume brain metastases may also be successfully treated with initial systemic therapy, enabling deferral of cranial radiotherapy.
5. **MDM discussion**

- All patients newly diagnosed with malignant melanoma should be discussed at an appropriate multidisciplinary team meeting.

- Patients with a new, single primary, adult, non-metastatic, melanoma up to and including stage IIA disease who are not for approved clinical trial participation may be discussed at the appropriate local or specialist skin MDT.

- Specialist skin MDT discussion is required for the following patients:
  
  o Stage IIB – IV melanoma
  o Patients with newly diagnosed metastatic or recurrent disease
  o Patients <19 years at diagnosis
  o Patients with melanoma being managed by other site specialist teams, such as gynaecological, mucosal or head and neck (excluding ocular)
  o Patients planned for approved clinical trial entry

- For less common or atypical primaries such as gynaecological or mucosal melanomas, or for particular sites of recurrence being considered for resection, it may be more appropriate for more than one MDT to be involved in the treatment decisions:

- This is consistent with the best practice measures in the Manual for Skin Cancer Services and NICE Quality Standards:

6. **Oncology referral**

- All referrals should be made via the MDM to include the following patients:
  
  o Stage IIB – IV melanoma
6. Genetics referral

- A small minority of melanomas are thought attributable to genetic mutations.
- Consider clinical genetics referral in the following patients:
  - Individuals from families with 3 or more cases of melanoma or pancreatic cancer.
  - Individuals from families with 2 cases of melanoma in first degree relatives, with multiple primary melanomas in at least one case.
  - Individuals from families with 1 case of melanoma and pancreatic cancer in a first degree relative.
7. Follow-up

Stage Ia
- Good prognosis (5YS 97%).
- 2 - 4 visits over 12 months to teach self-examination then discharge.

Stage Ib-IIc
- 5YS rates of 85% to 53% for T1b to T4b N0 melanoma respectively.
- Three monthly clinical review for 3 years then 6 monthly review until 5 years.
- No routine investigations required in asymptomatic patients.
  CT CAP and brain 6-monthly x 3 years for stage IIc disease

Stage IIIa/IIIB/IIIC or Stage IV
- Stage III melanoma five-year survival rates of 78%, 59% and 40% are reported for Stage IIIa, IIIb and IIIc melanoma respectively.
- Three-monthly clinical review for 3 years, 6-monthly review years 4 and 5 and yearly review years 5-10.
- CT CAP and brain 6-monthly x 3 years

Unresected Stage III or Stage IV
- Follow-up and investigation based on clinical need
8. **Appendix 1: 2009 AJCC staging**

TNM staging categories and anatomic stage groupings [25]

<table>
<thead>
<tr>
<th>Classification</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
<th>Stage grouping</th>
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<tbody>
<tr>
<td>Tis</td>
<td>N/A</td>
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<td></td>
</tr>
<tr>
<td>T1</td>
<td>≤1.00</td>
<td>a. Without ulceration and mitosis &lt;1/mm²</td>
<td>IA</td>
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<tr>
<td></td>
<td></td>
<td>b. With ulceration or mitoses ≥1/mm²</td>
<td>IB</td>
</tr>
<tr>
<td>T2</td>
<td>1.01-2.00</td>
<td>a. Without ulceration</td>
<td>IIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. With ulceration</td>
<td>IIB</td>
</tr>
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<td></td>
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<td></td>
<td>b. With ulceration</td>
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<table>
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<tr>
<td>N2</td>
<td>2-3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>≥4 nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes</td>
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<tr>
<th>Site</th>
<th>Serum LDH</th>
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<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>N/A</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
<td>Normal</td>
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<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
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*Micrometastases are diagnosed after sentinel lymph node biopsy

**Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically*
9. Appendix 2: Systemic therapy regimens

### Adjuvant Interferon (Kirkwood regimen)

**Treatment**
- Paracetamol 1g 30mins prior to Interferon
- Interferon α-2b 20 miu/m² IV in 100 ml N.Saline over 20 mins, weeks 1-4
- Interferon α-2b 10 miu/m² SC Mon/Wed/Fri, weeks 5-52

**Investigations**
- FBC/WCC/ONC profile weekly week 1-4
- FBC/WCC/ONC profile monthly, weeks 5-52
- If ANC <0.5 or LFT >5-10 X ULN, withhold dose till ANC >0.5 and LFTS <5 X ULN then resume at 50% dose
- If ANC <0.25 or LFTS >10 X ULN, discontinue therapy
- Follow up imaging during and after treatment as per protocol

### Ipilimumab

**Treatment**
- Ipilimumab 3mg/kg IV on day 1, every 3 weeks for 4 cycles

**Investigations**
- FBC/WCC/ONC profile/TFTs/Cortisol day 1 each cycle
- Proceed if blood tests are within protocol parameters
- Assess response with CT CAP +/- brain after 4 cycles. May need further short interval imaging to assess for delayed response
- Education and prompt management of immune-related adverse events essential
- High caution in pre-existing autoimmune disease. May not be appropriate if prognosis <3-4 months or high steroid dependency
Pembrolizumab

**Treatment**
- Pembrolizumab 2mg/kg IV on day 1, every 3 weeks until disease progression

**Investigations**
- FBC/WCC/ONC profile/TFTs/Cortisol day 1 each cycle
- Proceed if blood tests are within protocol parameters
- Assess response with CT CAP +/- brain after every 4 cycles. May need further short interval imaging to assess for delayed response
- Education and prompt management of immune-related adverse events essential
- High caution in pre-existing autoimmune disease. May not be appropriate if high steroid dependency

Nivolumab

**Treatment**
- Nivolumab 3mg/kg IV on day 1, every 2 weeks until disease progression

**Investigations**
- FBC/WCC/ONC profile/TFTs/Cortisol day 1 each cycle
- Proceed if blood tests are within protocol parameters
- Assess response with CT CAP +/- brain after every 4 cycles. May need further short interval imaging to assess for delayed response
- Education and prompt management of immune-related adverse events essential
- High caution in pre-existing autoimmune disease. May not be appropriate if high steroid dependency
Ipilimumab + Nivolumab

**Treatment**
- Ipilimumab 3mg/kg IV and Nivolumab 1mg/kg IV on day 1 every 3 weeks for 4 cycles
  - Followed by
- Nivolumab 3mg/kg IV on day 1 every 2 weeks until disease progression

**Investigations**
- FBC/WCC/ONC profile/TFTs/Cortisol day 1 each cycle
- Proceed if blood tests are within protocol parameters
- Assess response with CT CAP +/- brain after 4 cycles. May need further short interval imaging to assess for delayed response
- Education and prompt management of immune-related adverse events essential
- High caution in pre-existing autoimmune disease. May not be appropriate if prognosis <3-4 months or high steroid dependency

Dabrafenib (BRAF-mutation positive metastatic disease)

**Treatment**
- Dabrafenib 150mg bd orally continuous dosing until disease progression

**Investigations**
- FBC/WCC/ONC profile day 1 each cycle
- ECG day 1 of cycles 1-3
- Proceed if blood tests/ECG are within protocol parameters
- Baseline skin assessment, and at 8 weekly intervals
- Assess response with CT CAP +/- brain after cycle 2, and every 2-3 months thereafter.
- Reduce dose for grade 2+ toxicities as per protocol
- Caution: Drug interactions
Vemurafenib (BRAF-mutation positive metastatic disease)

Treatment

• Vemurafenib 960mg bd orally continuous dosing until disease progression

Investigations

- FBC/WCC/ONC profile day 1 each cycle
- ECG day 1 of cycles 1-3
- Proceed if blood tests/ECG are within protocol parameters
- Baseline skin assessment, and at 8 weekly intervals
- Assess response with CT CAP +/- brain after cycle 2, and every 2-3 months thereafter.
- Reduce dose for grade 2+ toxicities as per protocol
- Caution: Drug interactions

Dabrafenib + Trametinib (BRAF-mutation positive metastatic disease)

Treatment

• Dabrafenib 150mg bd + Trametinib 2mg od orally continuous dosing until disease progression

Investigations

- FBC/WCC/ONC profile day 1 each cycle
- ECG day 1 of cycles 1-3. BP monitoring as per protocol.
- Echocardiogram at baseline and at 4 weeks, then every 3 months.
- Proceed if blood tests/ECG/echo are within protocol parameters
- Baseline skin assessment, and at 8 weekly intervals
- Assess response with CT CAP +/- brain after cycle 2, and every 2-3 months thereafter.
- Reduce dose for grade 2+ toxicities as per protocol
- Caution: Drug interactions
### Dacarbazine (metastatic melanoma)

**Treatment**
- Dacarbazine 850mg/m² iv on day 1 (21 day cycle for up to 6-9 cycles)

**Investigations**
- FBC/ONC D1 each cycle
- Proceed if ANC>1.5, Plt>100, Bil<2xULN, AST/ALT<3xULN
- Assess response (CT CAP) after 2-3 cycles
- Caution in hepatic and renal impairment

### Temozolamide (metastatic melanoma - in place of DTIC if CNS metastases)

**Treatment**
- Temozolamide 200mg/m² po once daily day 1 - 5 (28 day cycle for up to 6 cycles)

**Investigations**
- FBC/ONC D1 each cycle
- Proceed if ANC>1.5, Plt>100, Bil<2xULN, AST/ALT<3xULN
- FBP/DWCC C1 D22 only: if ANC<1.0 or Plt<50 the next cycle should be dose reduced by 50mg/m²
- Assess response (CT CAP and brain imaging) after 2 cycles
10. Appendix 3: References


SACT for malignant melanoma V 5.1
Burmeister, B., et al., Adjuvant radiotherapy improves regional (lymph node field) control in melanoma patients after lymphadenectomy: Results of an Intergroup randomized trial (TROG 02.01/ANZMTG 01.02). Int J Radiat Oncol Biol Physics, 2009. 75(3): S2.


