INITIAL EVALUATION

- History and physical examination
- Review of prior surgical procedures
- Review of all relevant pathology reports (MD Anderson slide review preferred)
- Lifestyle risk assessment

CLINICAL PRESENTATION AND STAGING OF PRIMARY MELANOMA

In situ (Stage 0)

- No additional evaluation
- Consider baseline chest x-ray

TREATMENT

- Wide excision, 0.5 – 1 cm margin
- Wide excision, 1 cm margin

SURVEILLANCE

- Annual skin and nodal basin survey
- Physical exam with skin and nodal basin survey every 6 months for 2 years, then annually

Note: Consider Clinical Trials as treatment options for eligible patients.

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Cutaneous Melanoma

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1 See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

2 Consider function and cosmesis

3 Margins larger than 0.5 cm may be necessary for some, particularly large melanoma in situ, lentigo maligna type, lesions

4 Per AJCC 8th edition, the convention for rounding decimal values in the hundredth’s place is to round down those ending in 1 to 4 and to round up those ending in 5 to 9. For example, a melanoma measuring 0.75 mm in thickness would be recorded as 0.8 mm in thickness (i.e., T1b), and those measuring from 0.95 to 1.04 mm would be rounded to 1.0 mm (i.e., T1b)

5 Adverse features include: positive deep margins, lymphovascular invasion, young age or ≥ 2 mitoses/mm²

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Cutaneous Melanoma

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Note: Consider Clinical Trials as treatment options for eligible patients.

**INITIAL EVALUATION**

- History and physical examination
- Review of prior surgical procedures
- Review of all relevant pathology reports (MD Anderson slide review preferred)
- Lifestyle risk assessment

**CLINICAL PRESENTATION AND STAGING OF PRIMARY MELANOMA**

- \(< 0.8 \text{ mm in tumor thickness}\) and
  - ulceration (Stage 1B) and/or
  - with adverse features (consider additional diagnostic biopsy if significant residual lesion)
- Consider baseline chest x-ray

**TREATMENT**

- Wide excision, 1 cm margin
- Consider LM/SLNB (obtain preoperative lymphoscintigraphy if ambiguous lymphatic drainage or at the discretion of surgeon)

**SURVEILLANCE**

- Physical exam with skin and nodal basin survey every 6 months for 2 years, then annually

**CNS imaging**

Consider CLND on selective basis

**CLND** = complete lymph node dissection
**LM** = lymphatic mapping
**SLNB** = sentinel lymph node biopsy

1. See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice.
2. Per AJCC 8th edition, the convention for rounding decimal values in the hundredth’s place is to round down those ending in 1 to 4 and to round up those ending in 5 to 9. For example, a melanoma measuring 0.75 mm in thickness would be recorded as 0.8 mm in thickness (i.e., T1b), and those measuring from 0.95 to 1.04 mm would be rounded to 1.0 mm (i.e., T1b).
3. Adverse features include: positive deep margins, lymphovascular invasion, young age or ≥ 2 mitoses/mm²
4. Consider function and cosmesis
5. Randomized trials have failed to demonstrate survival benefit for routine CLND following a positive SLN. Although CLND is associated with improved regional control and in a minority of patients upstaging might impact clinical decision-making, post-hoc forest plot analyses of MSLT-2 have not definitely identified any subgroups of patients likely to derive a survival benefit; therefore, the vast majority of patients are no longer routinely offered CLND. One possible exception to this approach is for patients with limited access to follow-up. Overall, this remains an area of active investigation and dialogue.

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Randomized trials have failed to demonstrate survival benefit for routine CLND following a positive SLN. Consider function and cosmesis. Per AJCC, a possible exception to this approach is for patients with limited access to follow-up care. This algorithm should not be used to treat pregnant women.

**CLINICAL PRESENTATION AND STAGING OF PRIMARY MELANOMA**

- Consider preoperative ultrasound of regional nodal basin(s) if primary tumor greater than 4 mm or for ambiguous/equivocal regional basin(s) physical examination
- Baseline chest x-ray
- Consider cross-sectional imaging as clinically indicated for symptoms or T4b primary

**TREATMENT**

- Wide excision with the following margins\(^2\) based on tumor thickness\(^1\):
  - \(\leq 1\) mm: 1 cm margin
  - \(> 1-2\) mm: 1-2 cm margin
  - \(> 2\) mm: 2 cm margin
- LM/SLNB (obtain preoperative lymphoscintigraphy if ambiguous lymphatic drainage or at the discretion of surgeon)

**SURVEILLANCE**

- Sentinel node(s) negative

  • Clinical trial
  • Nivolumab
  • Pembrolizumab
  • Dabrafenib with trametinib (\(BRAF\ V600E/K\) mutations)
  • Observation

- Physical exam with skin and nodal basin survey every 3-4 months for 2 years, then every 6 months for 3 years, then annually
  - Consider chest x-ray, interval CT chest, abdomen, and pelvis with IV/PO contrast or PET-CT (with IV contrast if available) as well as MRI brain with IV contrast based on signs/symptoms as well as the pattern and extent of disease

- SLN-negative melanomas 0.8-1 mm (see Page 2, Box A)

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**CLINICAL PRESENTATION/STAGING**

<table>
<thead>
<tr>
<th>Local recurrence, unknown primary melanoma (presenting as dermal, subcutaneous or nodal disease) or in-transit metastasis</th>
<th>Refer to Pages 1-3 for clinical presentation, staging, and treatment of primary melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequately treated primary (local persistence or margin positive resection)</td>
<td>Refer to Pages 1-3 for clinical presentation, staging, and treatment of primary melanoma</td>
</tr>
<tr>
<td>Resectable (isolated or limited) non-nodal locoregional metastasis</td>
<td>Refer to Pages 1-3 for clinical presentation, staging, and treatment of primary melanoma</td>
</tr>
<tr>
<td>Clinical nodal and/or non-nodal locoregional metastasis, see Page 5</td>
<td>Refer to Pages 1-3 for clinical presentation, staging, and treatment of primary melanoma</td>
</tr>
<tr>
<td>Distant metastasis, see Pages 6-8</td>
<td>Refer to Pages 1-3 for clinical presentation, staging, and treatment of primary melanoma</td>
</tr>
</tbody>
</table>

**TREATMENT**

- **Sentinel node(s) negative**
  - Consider observation, clinical trial or adjuvant therapy options (see Box B below)

- **Sentinel node(s) positive**
  - Consider clinical trial of neoadjuvant therapy or local excision, negative margin
  - Consider LM with SLNB
  - Consider local postoperative adjuvant radiation therapy

**SURVEILLANCE**

- Physical exam with skin and nodal basin survey and chest x-ray every 3-4 months for 2 years, then every 6 months for 3 years, then annually
- CT chest, abdomen and pelvis with IV PO contrast or PET-CT (with IV contrast if available) as well as MRI brain with IV contrast at scheduled follow-up visits and/or based on signs/symptoms as well as pattern and extent of disease

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1 Note: If patient presents with clinically suspicious lymph node or nodule, or history of melanoma, consider fine needle aspiration and/or core needle biopsy to establish the diagnosis prior to excision to facilitate definitive treatment planning

2 Tumor mutation analysis includes at a minimum BRAF, NRAS and KIT. Consider MD Anderson approved melanoma biomarkers (click here).

3 Includes in-transit and/or satellite metastasis

4 Randomized trials have failed to demonstrate survival benefit for routine CLND following a positive SLN. Although CLND is associated with improved regional control and in a minority of patients upstaging might impact clinical decision-making, post-hoc forest plot analyses of MSLT-2 have not definitely identified any subgroups of patients likely to derive a survival benefit; therefore, the vast majority of patients are no longer routinely offered CLND. One possible exception to this approach is for patients with limited access to follow-up. Overall, this remains an area of active investigation and dialogue.

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Cutaneous Melanoma

Clinical nodal and/or non-nodal locoregional metastasis

- Review of all relevant pathology reports (MD Anderson slide review preferred)
- CT chest, abdomen, pelvis with IV/PO contrast or PET-CT (with IV contrast if available)
- CNS imaging [MRI brain (with IV contrast) preferred]
- Tumor mutation testing
- LDH
- Other clinical chemistries as clinically indicated

Distant metastasis (resectable or unresectable)/unresectable locoregional metastasis, see Pages 6-8

- Consider clinical trial of neoadjuvant therapy
- LND
  - Consider parotidectomy if head/neck primary tumor and
  - Consider adjuvant radiation therapy for high risk features (with pretreatment dental consult if head/neck radiation therapy planned)
- Consider adjuvant therapy (see Box B on Page 4)
  - Note: If recurrence on prior adjuvant therapy, consider switching agents

Resectable clinical regional nodal metastasis with or without resectable (isolated or limited) non-nodal locoregional metastasis

- Consider clinical trial of neoadjuvant therapy
- LND
  - Consider parotidectomy if head/neck primary tumor and
  - Consider adjuvant radiation therapy for high risk features (with pretreatment dental consult if head/neck radiation therapy planned)
- Consider adjuvant therapy (see Box B on Page 4)
  - Note: If recurrence on prior adjuvant therapy, consider switching agents

Multiple and/or unresectable satellite and/or in-transit metastases with or without clinical regional nodal disease

- Consider clinical trial
- Systemic therapy as recommended on Pages 7-9
  - Talimogene laherparepvec (T-VEC) (intralesional)
  - ILI/ILP with systemic and/or intralesional agents (clinical trial)

Note: Consider Clinical Trials as treatment options for eligible patients.

LDH = lactate dehydrogenase  LND = lymph node dissection
ILI = isolated limb infusion  ILP = isolated limb perfusion

1 Tumor mutation analysis includes at a minimum BRAF, NRAS and KIT. Consider MD Anderson approved melanoma biomarkers (click here).
2 Includes in-transit and/or satellite metastasis
3 High-risk nodal features include:
   - Extracapsular extension
   - Nodal deposit ≥ 3 cm
   - ≥ 4 nodes
   - Recurrent regional nodal or soft tissue recurrence

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Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION/STAGING

- Review of all relevant pathology reports (MD Anderson slide review preferred)
- CT chest, abdomen, pelvis with IV/PO contrast or PET-CT (with IV contrast if available)
- CNS imaging [MRI brain (with IV contrast) preferred]
- Tumor mutation testing\(^1\)
- LDH
- Other clinical chemistries as clinically indicated

Distant metastasis (resectable or unresectable)/unresectable locoregional metastasis

CNS involvement?

- Yes
- See Page 9

- No

\(\text{BRAF V600 mutation}\)\(^1\)?

- Yes
- See Page 7

- No
- See Page 8

\(^1\) Tumor mutation analysis includes at least minimum \(\text{BRAF}, \text{NRAS}, \text{and KIT}\). Consider MD Anderson approved melanoma biomarkers (click here).

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### CLINICAL PRESENTATION/STAGING

<table>
<thead>
<tr>
<th>First-line therapies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial</td>
</tr>
<tr>
<td>Anti-PD-1 monotherapy (nivolumab or pembrolizumab)</td>
</tr>
<tr>
<td>Ipilimumab with nivolumab</td>
</tr>
<tr>
<td>BRAF inhibitor with MEK inhibitor²</td>
</tr>
<tr>
<td>Intrallesional injection with talimogene laherparepvec (T-VEC)</td>
</tr>
<tr>
<td>Consider surgery for resectable (isolated or limited) distant metastasis with or without post-operative adjuvant therapy</td>
</tr>
<tr>
<td>Consider TIL harvest for future therapy on clinical trial</td>
</tr>
</tbody>
</table>

#### Second/subsequent-line therapies:

|● Clinical trial                        |
|● BRAF inhibitor with MEK inhibitor if refractory to anti-PD-1 based therapy |
|● Anti-PD-1 or ipilimumab with nivolumab if refractory to BRAF inhibitor with MEK inhibitor |
|● Ipilimumab or ipilimumab with nivolumab if refractory to anti-PD-1 based therapy |
|● Consider TIL harvest for future therapy on clinical trial |
|● High-dose interleukin-2               |
|● Consolidative surgery after response to systemic therapy |
|● Surgical and/or regional therapy for limited and/or symptomatic disease (e.g., surgery, infusional therapy, radiation therapy, or liver-directed therapy) |
|● Intrallesional injection with talimogene laherparepvec (T-VEC) |
|● Chemotherapy¹ or biochemotherapy¹ |

---

**TIL =** tumor-infiltrating lymphocytes

¹Tumor mutation analysis includes at a minimum **BRAF, NRAS and KIT.** Consider **MD Anderson approved melanoma biomarkers (click here).**

²Regimens:

- Dabrafenib with trametinib or
- Vemurafenib with cobimetinib or
- Encorafenib with binimetinib

³Chemotherapy: CVD (cisplatin, vinblastine, dacarabazine), carboplatin in combination with paclitaxel, nab-paclitaxel, dacarabazine or temozolomide

⁴Biochemotherapy: CVD plus interleukin-2 and interferon alpha

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Follow-up evaluation at least every 3 months, or individualized based on extent of disease, response to therapy or clinical trial protocol, and includes periodic CT chest, abdomen, and pelvis with IV/PO contrast or PET-CT (with IV contrast if available) and MRI brain with IV contrast

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Note: Consider Clinical Trials as treatment options for eligible patients.

**Cutaneous Melanoma**

**CLINICAL PRESENTATION**

- TIL = tumor-infiltrating lymphocytes

- **First-line therapies:**
  - Clinical trial
  - Anti-PD-1 monotherapy (nivolumab or pembrolizumab)
  - Ipilimumab with nivolumab
  - Intralesional injection with talimogene laherparepvec (T-VEC)
  - Consider surgery for resectable (isolated or limited) distant metastasis with or without post-operative adjuvant therapy
  - Consider TIL harvest for future therapy on clinical trial

- **Second/subsequent-line therapies:**
  - Clinical trial
  - Ipilimumab or ipilimumab with nivolumab if refractory to anti-PD-1 based therapy
  - Consider TIL harvest for future therapy on clinical trial
  - FDA-approved KIT inhibitor for patients with targetable KIT mutation
  - High-dose interleukin-2
  - Consolidative surgery after response to systemic therapy
  - Surgical and/or regional therapy for limited and/or symptomatic disease (e.g., surgery, infusional therapy, radiation therapy, or liver-directed therapy)
  - Intralesional injection with talimogene laherparepvec (T-VEC)
  - Chemotherapy\(^2\) or biochemotherapy\(^3\)

- **Follow-up evaluation** at least every 3 months, or individualized based on extent of disease, response to therapy or clinical trial protocol, and includes periodic CT chest, abdomen, and pelvis with IV/PO contrast or PET-CT (with IV contrast if available) and MRI brain with IV contrast

---

\(^1\) Tumor mutation analysis includes at a minimum *BRAF*, *NRAS* and *KIT*. Consider MD Anderson approved melanoma biomarkers (click here).

\(^2\) Chemotherapy: CVD (cisplatin, vinblastine, dacarabazine), carboplatin in combination with paclitaxel, nab-paclitaxel, dacarabazine or temozolomide

\(^3\) Biochemotherapy: CVD plus interleukin-2 and interferon alpha

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**CLINICAL PRESENTATION/STAGING**

**Brain metastases** (with or without extracranial disease)

- **BRAF V600 mutation?**
  - Yes
    - Consider multidisciplinary MD Anderson Brain Metastasis Clinic or
    - Clinical trial or
    - Ipilimumab with nivolumab, unless contraindicated<sup>2</sup> or
    - BRAF inhibitor with MEK inhibitor<sup>3</sup> or
    - Anti-PD-1 monotherapy (nivolumab or pembrolizumab) or
    - Chemotherapy (temozolomide) or
  - No
    - Surgery +/- adjuvant radiation therapy if resectable and/or
      - Stereotactic radiation therapy +/- immunotherapy or
      - Whole brain radiation therapy +/- immunotherapy

- **CNS metastases** (with or without extracranial disease)
  - Is there evidence of LMD?
    - Yes
      - LMD with or without brain metastasis (with or without extracranial disease)
        - **BRAF V600 mutation?**
          - Yes
            - Consider multidisciplinary MD Anderson Brain Metastasis Clinic or
            - Clinical trial or
            - Ipilimumab with nivolumab, unless contraindicated<sup>2</sup> or
            - Anti-PD-1 monotherapy (nivolumab or pembrolizumab) or
            - Chemotherapy (temozolomide) or
          - No
            - BRAF inhibitor with MEK inhibitor<sup>3</sup> or
            - Intrathecal interleukin-2 or
            - Chemotherapy (temozolomide) or
            - Palliative radiation therapy
    - No

---

**Note:** Consider Clinical Trials as treatment options for eligible patients.

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**CNS** = central nervous system

**LMD** = leptomeningeal disease

<sup>1</sup>Tumor mutation analysis includes a minimum BRAF, NRAS and KIT. Consider MD Anderson approved melanoma biomarkers (click here).

<sup>2</sup>Contraindications: receiving corticosteroids (at least dexamethasone 4 mg daily or equivalent) or is symptomatic requiring intervention

<sup>3</sup>Regimens:
- Dabrafenib with trametinib or
- Vemurafenib with cobimetinib or
- Encorafenib with binimetinib

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STAGING


SURGERY FOR SENTINEL LYMPH NODE BIOPSY AND LIMB PERFUSION


SUGGESTED READINGS

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SUGGESTED READINGS - continued

RADIATION THERAPY


SYSTEMIC THERAPY: CHEMOTHERAPY, IMMUNOTHERAPY, AND TARGETED THERAPY


Continued on next page
Cutaneous Melanoma

Systemic Therapy: Chemotherapy, Immunotherapy, and Targeted Therapy


Suggested Readings - continued

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SYSTEMIC THERAPY: CHEMOTHERAPY, IMMUNOTHERAPY, AND TARGETED THERAPY - continued


ADJUVANT THERAPY FOR HIGH-RISK MELANOMA


INTRATUMORAL THERAPY

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This practice algorithm is based on the majority expert opinion of the Melanoma Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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