

Short-term Recommendations for Cutaneous Melanoma Management During COVID-19
(Contributions from City of Hope, Cleveland Clinic, Fred Hutchinson Cancer Research Center/Seattle Cancer Alliance, Huntsman Cancer Institute, Massachusetts General Hospital, MD Anderson Cancer Center, and Stanford Cancer Institute)

PRIMARY CUTANEOUS MELANOMA (CM):

Diagnostic Biopsy:

- Attempt excisional/complete saucerization biopsy whenever possible with intent to remove the clinical lesion. Histologic transection of the in-situ component at the peripheral margin is of less consequence.
- Broad (more superficial) shave biopsy should be performed for larger suspected melanoma in situ, lentigo maligna type lesions, i.e., melanoma on chronically sun-damaged skin (CSD melanoma).
- Arrange telehealth evaluation for new patients whenever possible; complete H&P on the day of surgery if needed.

Wide excision (WE) of in situ and invasive melanoma:

- Delay WE of melanoma in situ (MIS) for at least 3 months.
- Delay WE for up to 3 months for invasive melanomas of any depth, for which previous biopsy had clear margin or histologic peripheral transection of the in situ component.
- Delay WE for T1 melanoma (≤ 1 mm thickness) for up to 3 months even for positive margin on biopsy, as long as the biopsy removed the majority of the lesion. Otherwise, perform complete/excisional biopsy with narrow surgical margins or elliptical excision with 1 cm surgical margins in the office/outpatient setting.
- Depending on OR capabilities, offer sentinel lymph node biopsy (SLNB) for CM > 1 mm thickness, but defer SLNB for T1b melanoma (0.8-1.0 mm with or without ulceration), unless high risk features are evident (e.g., lympho-vascular invasion, very high mitotic rate, young patient age [≤ 40 years], or a combination of these factors).
- Surgical management of T3/T4 melanomas (> 2 mm thickness) should take priority over T1/T2 melanomas (≤ 2 mm thickness). The exception is any melanoma that is partially/incompletely biopsied in a which large clinical residual lesion is evident. Gross complete resection is recommended this case.
- Delay SLNB for up to 3 months, unless WE in the OR is planned, in which case WE/SLNB may be performed at the same time.
- Conduct all follow-up visits by telehealth with patient images sent to the provider (preferably using EHR systems in place).

STAGE III (REGIONAL NODAL) MELANOMA:

- As per current NCCN guidelines, defer completion lymph node dissection following a positive SLNB, and perform regional nodal ultrasound surveillance (if radiologic expertise available) or other imaging surveillance (CT, FDG PET-CT, MRI), as appropriate.

- Defer surveillance imaging (US, CT, FDG PET-CT, MRI) for 3-6 months in asymptomatic, surgically-resected patients, who are not on systemic therapy. Delay for 3 months for those who are clinically NED but on systemic adjuvant therapy.
- Defer therapeutic lymphadenectomy in the setting of clinically palpable regional nodes, and offer neoadjuvant systemic therapy immune checkpoint blockade (ICB) or BRAFi/MEKi instead.
- The NCCN Melanoma Panel does not consider neoadjuvant therapy as a superior option to surgery followed by systemic adjuvant therapy for stage III melanoma, but available data suggests this is a reasonable resource-conserving option during the COVID-19 outbreak.
- Neoadjuvant considerations include higher-dose pembrolizumab (400 mg IV x 1-2 cycles every 6 weeks), two cycles of nivolumab (480 mg IV every 4 weeks), BRAFi/MEKi x 8 weeks followed by surgery, or two cycles ipilimumab 3/mg/kg and nivolumab 1 mg/kg (or ipilimumab 1 mg/kg and nivolumab 3 mg/kg) pre-operatively. Surgery should be performed 8-9 weeks after initiation of neoadjuvant therapy. Short-interval monitoring with imaging (ultrasound, if available, vs CT, FDG PET-CT) may be indicated. For patients with clinical and/or radiologic response, consider ongoing immunotherapy over surgery.
- Metastatic resections (stages III and IV) should be placed on hold unless the patient is critical/symptomatic (assuming the hospital is not over capacity and the ORs are running); patients should be continued on systemic therapy.
- For clinical surveillance of stage III patients who are not on therapy, may delay oncologic surveillance visit up to 3-6 months and/or conduct by telehealth, per physician discretion.

Stage III adjuvant therapy:

- May initiate up to 12 weeks from time of surgical resection of melanoma.
- Choose regimens that are the least taxing on the health system and patient. With less-frequent clinic visits/infusions, telehealth interval symptom checks by staff are recommended.

Options include:

- Nivolumab 480 mg IV q 4 weeks x one year
- Pembrolizumab, 200 IV q 3 weeks x one year
- Pembrolizumab, 400 mg IV q 6 weeks x one year (Lala et al, ASCO 2018, Abstr 3062)
- BRAFi/MEKi as per current NCCN cutaneous melanoma guidelines
- While dabrafenib/trametinib is the evidence-based option, alternative BRAFi/MEKi regimens (encorafenib/benimetinib or vemurafenib/cobimetinib) may be substituted if drug supply is limited.

STAGE IV MELANOMA:

- Carefully consider the toxicity of the regimen selected; decisions about ICB should be individualized, with preference for agents with the lowest toxicity profile.
- It is currently unknown how patients infected with SARS-CoV-2 on ICB will react to the expected immune-related adverse events (irAEs). It is possible that patients on ICB could

experience more severe treatment-related adverse events during their treatment course.

- Single agent PD-1 should be considered for every patient without brain metastasis.
- Nivolumab/ipilimumab combination induces grade 3-4 irAEs more than twice as often as PD-1 monotherapy, frequently necessitating the use of high-dose and prolonged steroid or other immunosuppressive agents. Therefore, decisions about combination vs monotherapy need to be tailored to patient characteristics and with awareness of constrained capacity to manage toxicities.
- A regimen of ipilimumab 1 mg/kg and nivolumab 3 mg/kg every 3 weeks for 4 infusions, with subsequent consideration for nivolumab monotherapy, is associated with lower rates of immune-mediated toxicity compared to the FDA standard.

Stage IV melanoma with brain metastasis:

- Nivolumab/ipilimumab combination has a high rate of intracranial durable responses (55%), comparable to the extracranial activity of these agents. The risk of irAEs is the same as patients without brain metastasis and may be lessened by the alternate dosing of ipilimumab 1 mg/kg and nivolumab 3 mg/kg in the 4 cycles of induction therapy.
- In patients with BRAF-wild type melanoma, this may be the most reasonable approach for patients with small (<2-3 cm), asymptomatic metastases who do not require steroids for perilesional edema.
- Patients with larger, symptomatic and/or steroid-dependent metastases should receive stereotactic radiosurgery (SRS) as a component of initial therapy (ideally first), and come off steroids, followed by single-agent PD-1 blockade.
- Whole brain radiation therapy is not recommended for melanoma metastatic to the brain.
- For patients with BRAF V600-mutated melanoma and brain metastasis, consideration should be given to BRAFi/MEKi, with an intracranial response rate of up to 58%. However, clinicians should take into account that the duration of response is limited, with median PFS around 5 months

General recommendations related to drug supply:

- The melanoma panel recognizes that drug resources may become limited over the course of the pandemic, and therefore we can make the following recommendations:
- Encorafenib/benimetinib or vemurafenib/cobimetinib combinations can be substituted for dabrafenib/drametinib in the adjuvant setting.
- Single agent BRAF inhibitors can be used in the event of MEK inhibitor shortages.
- For patients progressing beyond standard ICB and targeted therapy:
- Hospice care conversation is recommended since chemotherapy is only of limited benefit and palliative in nature.
- Oral temozolomide is the preferred option if palliative chemotherapy treatment is selected as it would limit resource utilization and contact with the medical system. For other regimens please refer to the current melanoma guideline version.