

Short-Term Recommendations for Cutaneous Melanoma Management During COVID-19 Pandemic

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PLEASE NOTE: The following short-term guidance may depend on prevalence of COVID-19 in the practitioner's region. However, an abundance of caution should be exercised to reduce the transmission and impact of SARS-CoV-2.

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 (without visible residual pigmentation or large clinical residual lesion) is of less consequence.
- Broad (more superficial) shave biopsy should be performed for larger suspected melanoma in situ (MIS) and lentigo maligna type lesions (ie, melanoma on chronically sun-damaged skin [CSD melanoma]).
- Arrange telehealth evaluation for new patients whenever possible; complete history and physical (H&P) on the day of surgery if needed.

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

- Delay WE of MIS for up to 3 months.
- 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. If a large clinical residual lesion is evident (including concern for thicker melanoma), perform complete/excisional biopsy with narrow surgical margins or elliptical excision with 1 cm surgical margins in the office/outpatient setting.
- Delay WE for up to 3 months for invasive melanomas of any depth, for which previous biopsy had clear histologic margins or only peripheral transection of the in situ component. Most time-to-treat studies show no adverse patient outcomes following a 90-day treatment delay, even for thicker CM.
- Surgical management of T3/T4 melanomas (> 2 mm thickness) should take priority over T1/T2 melanomas (≤ 2 mm thickness). As above, the exception is any melanoma that is partially/incompletely biopsied in which large clinical residual lesion is evident. Gross complete resection is recommended in this case.
- Depending on operating room (OR) capabilities, discuss sentinel lymph node biopsy (SLNB) for CM > 0.8 mm thickness (as per NCCN Guidelines for Cutaneous Melanoma). Sentinel lymph node biopsy may be delayed for up to 3 months unless WE in the OR is planned, in which case WE/SLNB may be performed at the same time.

- Defer follow-up screening/clinical surveillance visits in surgically resected, asymptomatic patients with localized melanoma (stages 0, I, II) for at least 3–6 months.
- Conduct all follow-up visits by telehealth with patient images sent to the provider (preferably using electronic health record [EHR] systems in place).
- Defer imaging surveillance (eg, chest x-ray, CT, FDG PET/CT in stage IIB/IIC patients) in asymptomatic stage IIB/IIC patients for at least 3–6 months.

STAGE III (REGIONAL NODAL) MELANOMA:

- As per current NCCN Guidelines for Cutaneous Melanoma, defer completion lymph node dissection (CLND) following a positive SLNB, and perform regional nodal ultrasound (US) surveillance (if radiologic expertise is 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 without evidence of disease (NED) but who are 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 BRAF/MEK inhibitors instead. Exceptions are when metastatic node(s) are invading or encroaching upon a vital structure (eg, carotid artery or skull base), such that delayed resection may result in significantly increased morbidity, when neoadjuvant therapy is not possible and/or the patient has already failed systemic therapy.
- 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 suggest 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)
 - BRAF/MEK inhibitors x 8 weeks followed by surgery
 - Two cycles of ipilimumab 3 mg/kg and nivolumab 1 mg/kg (or ipilimumab 1 mg/kg and nivolumab 3 mg/kg) preoperatively
 - Surgery should be performed 8–9 weeks after initiation of neoadjuvant therapy.
- Short-interval monitoring with imaging (US, 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), and patients should be continued on systemic therapy. Given hospital-intensive resources, the use of talimogene laherparepvec (TVEC) for cutaneous/nodal/in-transit metastasis should be cautiously considered and, if possible, deferred until the COVID-19 crisis abates. A single dose of palliative radiation therapy may be useful for larger/symptomatic metastasis, as appropriate.

- For clinical surveillance of stage III patients who are not on therapy, the physician may delay the oncologic surveillance visit up to 3 months and/or conduct by telehealth, per physician discretion.

Stage III adjuvant therapy:

- Therapy may be initiated up to 12 weeks from time of definitive surgical resection of melanoma. Adjuvant therapy has not been shown to improve melanoma-specific survival and should be deferred during the COVID-19 pandemic for patients with <50% chance of disease relapse.
- Choose regimens that are the least taxing on the health system and patient.
- Adjuvant options include:
 - Nivolumab 480 mg IV every 4 weeks for 1 year
 - Pembrolizumab 200 IV every 3 weeks for 1 year
 - Pembrolizumab 400 mg IV every 6 weeks for 1 year*
 - BRAF/MEK inhibitors as per current NCCN Guidelines for Cutaneous Melanoma
- While dabrafenib/trametinib is the evidence-based option, alternative BRAF/MEK inhibitor regimens (encorafenib/binimetinib or vemurafenib/cobimetinib) may be substituted if drug supply is limited.
- With less-frequent clinic visits/infusions, telehealth interval symptom checks by staff are recommended.

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. Single-agent anti-PD-1 is recommended over combination ipilimumab/nivolumab at present due to:
 - more substantial inflammation/possible exacerbation of COVID-19,
 - need for steroids/other immunosuppressants that may adversely affect SARS-CoV-2–infected individuals, and
 - increased resource utilization for visits related to toxicities/monitoring.
- 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 AEs during their treatment course and that treatment of irAEs with steroids/other immunosuppressants may adversely affect SARS-CoV-2–infected individuals.
- Single-agent PD-1 should be considered for every patient without brain metastasis.
- As with adjuvant or neoadjuvant therapy, consider the lowest frequency dosing schedule of available regimens, including:
 - Nivolumab 480 mg IV every 4 weeks
 - Pembrolizumab 400 mg IV every 6 weeks*
- 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, as well as possible inpatient hospitalization and emergency department (ED) visits. Therefore, decisions about combination versus

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 for 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 (<1 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 checkpoint blockade.
- For patients with *BRAF* V600-mutated melanoma and brain metastasis, consideration should be given to BRAF/MEK inhibitors, with an intracranial response rate of up to 58%. However, clinicians should take into account that the duration of response is limited, with median progression-free survival (PFS) of around 5 months.

General recommendations related to drug supply:

Drug resources may become limited over the course of the pandemic; therefore, we can make the following recommendations:

- Encorafenib/binimetinib or vemurafenib/cobimetinib combinations can be substituted for dabrafenib/trametinib in the adjuvant setting.
- Single-agent BRAF inhibitor 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 version of the NCCN Guidelines for Cutaneous Melanoma.

*This regimen was granted accelerated approval by the FDA on 4/28/2020,^{1,2} based on pharmacokinetic modeling and exposure-response analyses (comparing predicted exposure of pembrolizumab 400 mg every 6 weeks to pembrolizumab 2mg/kg every 3 weeks, 200 mg every 3 weeks, and 10 mg/kg every 2 weeks), and additional exposure-response analyses across the pembrolizumab development program and in a cohort of patients enrolled in KEYNOTE-555 (NCT03665597).³

References

1. FDA approves new dosing regimen for pembrolizumab. April 29, 2020. Available at: <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-new-dosing-regimen-pembrolizumab>. Accessed: May 1, 2020.
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3. Lala M, Akala O, Chartash E, et al. CT042 - Pembrolizumab 400 mg Q6W dosing: First clinical outcomes data from Keynote-555 cohort B in metastatic melanoma patients. AACR Virtual Annual Meeting I, presented April 28, 2020. Available at: <https://www.abstractsonline.com/pp8/#!/9045/presentation/10751>.