## 2022–2023 Management of Cutaneous Melanoma

### Background

Skin melanoma (hereon simplified as "melanoma") accounts for 1.7% of global cancer diagnoses and is growing in incidence in developed countries (0.01% to 0.025% in Europe and 0.02% to 0.03% in the USA per 100,000 cases every year). Melanoma is responsible for over 80% of skin cancer deaths.[1,2] The 5-year overall survival (OS) of melanoma has risen to 93.3% in the US, but the survival rate for advanced disease remains only 30%.[2] There is no cure for advanced-stage melanoma, and the management goals focus on prolongation of survival and delay of progression.[3]

Melanoma exacts a substantial financial burden. The average annual cost of melanoma treatment increased by 288% from 2002 to 2006 and from 2007 to 2011, much higher than 25% for all other cancers combined. Melanoma skin cancer treatment costs $3.3 billion in the United States each year.[4]

The causes of start and progression of skin melanoma include oxidative stress, UV exposure, and perhaps alcohol consumption.[5-7] Current treatment modalities include surgery, radiotherapy, conventional chemotherapy, targeted therapy, and immunotherapy.[8] The current standard of care for stage I to resectable stage III melanoma is excision with/ without lymph node management (lymphatic mapping and sentinel lymph node biopsy and others applicable for each stage). For unresectable stage III, stage IV, and recurrent melanoma, the standard treatment options include intralesional therapy (talimogene laherparepvec [T-VEC]), immunotherapy (immune checkpoint inhibitors [ICI]), signal transduction inhibitors ( i.e., B-type Raf kinase [*BRAF*V600] with mitogen-activated protein kinase [MEK] inhibitors, briefly BRAF/MEK inhibitors), chemotherapy, and palliative local therapy (regional lymphadenectomy and radiotherapy).[9]

Based on mutational profiles, melanoma encompasses four major distinct subtypes, *BRAF*V600 mutation melanoma (in 45% of patients), neuroblastoma *RAS* (*NRAS*) mutation melanoma (15%), *KIT* mutation melanoma (5% to 10%), and wild-type melanoma. They differ in responses to treatment, which complicates management decision making.[10] With mutation-based subtypes identified, the current challenges for the treatment include resistance to BRAF/MEK inhibitors and ICI, and the toxicities induced by BRAF/MEK inhibitors therapies, among others.[11-13]

Despite the enormous effort of clinicians, diagnostic path and treatment should be improved during earlier stages to prevent/delay the progression of the disease.[11-13] Furthermore, awareness of recent clinical data in novel drug classes and combined therapies for late-stage disease should be improved in order to lower the death rate.

### The Expanding Treatment Paradigm

Recently, cancer experts have found that combining two or more drugs may treat advanced melanoma more effectively than either drug for certain patients.[14] Indeed, a leading clinician in cutaneous oncology and clinical immunotherapy has commented:

*Combination of immunotherapy is like a car at an intersection with three or four traffic lights in front that have to turn green for the car to progress through the intersection. In immunotherapy, an immune cell inside the cancer tumor needs one or perhaps more green lights (drugs) to be able to attack the cancer in front.*

Dr. Evan J. Lipson, MD
Associate Professor of Oncology
Johns Hopkins

However, despite the expert commentary, not all combination therapies have proven successful in phase 3 clinical trials. Clinicians need to be aware of updated data to make treatment decisions.[10]

**Gaps in Care**

The cutaneous melanoma clinician community is well-apprised of common diagnostic approaches and treatment pathways. However, currently the unstructured approach to skin melanoma early detection and treatment decision implies concerns in variable quality of care, sociodemographic inequalities, excision of many benign lesions (i.e. overdiagnosis), gaps in workforce training, and health system inefficiencies.[15] "To Improve Melanoma Outcomes, Focus on Risk Stratification, Not Overdiagnosis". - Robert A. Swerlick, MD.[16] This means that the optimal diagnostic pathway is not well-known. Furthermore, higher-volume hospitals are likely to result in higher survival rates of care compared with smaller volume counterparts.[17] Finally, clinicians may be unaware of new successes and failures of drug data obtained in phase 3 clinical trials or above to treat advanced melanoma.

*Diagnosis pathways*

Early diagnosis of skin melanoma is crucial to reduce potential deaths. Indeed, early detected melanoma patients have better prognosis than those diagnosed at late stages. Late-stage diagnosed patients require much higher health system costs. [11-13,15] Yet early diagnosis is hard to implement because the USA is in short supply of dermatologists. Diagnosis is thus the responsibility of primary healthcare physicians (PHP). Most PHPs do not provide skin examinations and are not familiar with recent technologies.

The knowledge/behavior gaps of PHPs include:

- Not providing skin examinations. Such behavior of PHPs is hard to change if the education intervention is not intensive enough.[18]
- Not knowing/implementing new technologies for diagnoses. The most recent diagnostic tools include gene expression profiling tests, dermoscopy, artificial intelligence-assisted tools and teledermatology, etc.[19,20] Dermoscopy can be used to distinguish benign from invasive lesions.[21] Teledermatology can even help diagnoses in remote areas, where people are at high risk of skin melanoma and have less access to clinicians. A European consensus-based interdisciplinary guideline published in 2022 recommended tests of dermoscopic diagnosis, histopathologic diagnosis, and mutational tests, followed by encouraging eligible patients to participate in clinical trials before deciding their treatment options.[1,10]
- Implicit bias toward patients with darker skin, whose presentation of the disease differs from those of patients with lighter skin. Such educational content is only depicted in less than 5% of textbooks for physicians.[22]

***Needs Summary/Education Gap 1*:** Some primary care physicians (PCPs) may not provide enough screening for skin melanoma patients, and the knowledge and technologies of PCPs may not be up-to-date.

*New success and failures to treat advanced melanoma*

Physicians may be unaware of the recent successful and failed therapies shown in phase 3 trials for both

*BRAF*V600-wild type and *BRAF*V600 advanced melanoma.

American Society of Clinical Oncology (ASCO) guidelines published in 2020 recommended combotherapies as follows: In the adjuvant setting for patients with resected stage IIIA/B/C/D wild-type melanoma, nivolumab or pembrolizumab should be offered to adult and pediatric patients.[23] In resectable BRAF-mutant counterpart disease, either of those two agents or the combination of dabrafenib and trametinib should be offered.[24] These therapies were further proven successful as of 2022.[25,26]
In unresectable/metastatic stage wild-type melanoma, ipilimumab plus nivolumab, nivolumab alone, or pembrolizumab alone should be offered to patients. In BRAF-mutant disease of the same stage, those three regimens or triple therapy, i.e., combination with BRAF/MEK inhibitor therapy (dabrafenib/trametinib, encorafenib/binimetinib, or vemurafenib/cobimetinib) were recommended.

Furthermore, recent successful combotherapies included nivolumab plus relatlimab and nivolumab plus ipilimumab.[27,28] T-VEC plus pembrolizumab turned out to be an unsuccessful combotherapy.[29] A novel cell therapy tumor-infiltrating lymphocytes (TILs) emerged as a successful treatment.[30] For BRAF-mutant disease in the advanced stage, a triple therapy atezolizumab plus cobimetinib/vemurafenib] was approved but lacks mature evidence.[31-34] A failed triple therapy was spartalizumab plus dabrafenib/trametinib.[35,36]

***Needs Summary/Education Gap 2*:** Physicians may be unaware of the recent clinical data regarding new successful and failed therapies for advanced melanoma with different genetic types.

**Summary**

Standard of care or guidelines regarding skin melanoma should be updated more frequently due to the ever-changing landscape of skin melanoma care; e.g., European consensus-based interdisciplinary guidelines for melanoma published in 2022 did not include diagnoses of how to identify skin melanoma in patients with darker skin.[1,10] Furthermore, the PHP education needs to be improved in terms of content and format to reinforce sustainable practice changes.[37,38] The most common barriers reported by PHPs include lack of dermatologic training (89.4%), time constraints (70%), and competing comorbidities (51%).[39]

PHPs play a key role in early diagnoses and management of skin melanoma compared with specialists. Targeted educational content can equip PHPs with diagnostic pathways, technologies, and remove bias toward patients with darker skin, and maintain positive clinical practice changes. On the other hand, CME programs can target specialists with knowledge of novel therapies that can delay the progression of late-stage skin melanoma and ensure optimal patient outcomes.

**References**

1. Garbe C, Amaral T, Peris K, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022. *European Journal of Cancer*. 2022;170:236-255.
2. Saginala K, Barsouk A, Aluru JS, Rawla P, Barsouk A. Epidemiology of melanoma. *Medical sciences*. 2021;9(4):63.
3. Steininger J, Gellrich FF, Schulz A, Westphal D, Beissert S, Meier F. Systemic therapy of metastatic melanoma: on the road to cure. *Cancers*. 2021;13(6):1430.

4. Tripp MK, Watson M, Balk SJ, Swetter SM, Gershenwald JE. State of the science on prevention and screening to reduce melanoma incidence and mortality: The time is now. *CA: a cancer journal for clinicians*. 2016;66(6):460-480.
5. Emanuelli M, Sartini D, Molinelli E, et al. The double-edged sword of oxidative stress in skin damage and melanoma: From physiopathology to therapeutical approaches. *Antioxidants*. 2022;11(4):612.
6. Ding L, Gosh A, Lee DJ, et al. Prognostic biomarkers of cutaneous melanoma. *Photodermatology, photoimmunology & photomedicine*. 2022;38(5):418-434.
7. Zhai Z, Yamauchi T, Shangraw S, Hou V, Matsumoto A, Fujita M. Ethanol Metabolism and Melanoma. *Cancers*. 2023;15(4):1258.
8. Zeng L, Gowda BJ, Ahmed MG, et al. Advancements in nanoparticle-based treatment approaches for skin cancer therapy. *Molecular Cancer*. 2023;22(1):10.
9. National Cancer Institute. Melanoma Treatment (PDQ®)–Health Professional Version. National Cancer Institute. Accessed Nov. 17, 2022. [Online]. Available: https://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq#_862_toc
10. Garbe C, Amaral T, Peris K, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment-Update 2022. *European Journal of Cancer*. 2022;170:256-284.
11. Dulgar O, Kutuk T, Eroglu Z. Mechanisms of resistance to BRAF-targeted melanoma therapies. *American Journal of Clinical Dermatology*. 2021;22:1-10.
12. Haas L, Elewaut A, Gerard CL, et al. Acquired resistance to anti-MAPK targeted therapy confers an immune-evasive tumor microenvironment and cross-resistance to immunotherapy in melanoma. *Nature Cancer*. 2021;2(7):693-708.
13. Sibaud V, Baric L, Cantagrel A, et al. Gestion des toxicités des inhibiteurs BRAF et MEK dans le mélanome métastatique. *Bulletin du Cancer*. 2021;108(5):528-543.
14. Melanoma Research Alliance. Combination Therapy for Melanoma. Melanoma Research Alliance. Accessed August, 2023. [Online]. Available: https://www.curemelanoma.org/patient-eng/melanoma-treatment/combination-therapy-for-melanoma
15. Janda M, Olsen CM, Mard VJ, Cust AE. Early detection of skin cancer in Australia–current approaches and new opportunities. *Public health research & practice*. 2022;32(1)
16. Swerlick RA. Melanoma screening—intuition and hope are not enough. *JAMA dermatology*. 2022;158(5):483-485.
17. Huo J, Lairson DR, Du XL, et al. Hospital case volume is associated with improved survival for patients with metastatic melanoma. *American journal of clinical oncology*. 2016;39(5):491.
18. Dolan NC, Ng JS, Martin GJ, Robinson JK, Rademaker AW. Effectiveness of a skin cancer control educational intervention for internal medicine housestaff and attending physicians. *Journal of general internal medicine*. 1997;12:531-536.
19. Ahuja S, Briggs SM, Collier SM. Teledermatology in rural, underserved, and isolated environments: a review. *Current dermatology reports*. 2022;11(4):328-335.
20. Adelson P, Eckert M. Skin cancer in regional, rural and remote Australia; opportunities for service improvement through technological advances and interdisciplinary care. *Australian Journal of Advanced Nursing, The*. 2020;37(2):25-30.
21. Tran T, Cyr PR, Verdieck A, et al. Expert consensus statement on proficiency standards for dermoscopy education in primary care. *The Journal of the American Board of Family Medicine*. 2023;36(1):25-38.
22. Rizvi Z, Kunder V, Stewart H, et al. The bias of physicians and lack of education in patients of color with melanoma as causes of increased mortality: a scoping review. *Cureus*. 2022;14(11)
23. Seth R, Messersmith H, Kaur V, et al. Systemic therapy for melanoma: ASCO guideline. *Journal of Clinical Oncology*. 2020;38(33):3947-3970.

24. Atkinson V, Robert C, Grob JJ, et al. Improved pyrexia-related outcomes associated with an adapted pyrexia adverse event management algorithm in patients treated with adjuvant dabrafenib plus trametinib: Primary results of COMBI-APlus. *European Journal of Cancer*. 2022;163:79-87.
25. Long GV, Luke JJ, Khattak MA, et al. Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial. *The Lancet Oncology*. 2022;23(11):1378-1388.
26. Eggermont AM, Kicinski M, Blank CU, et al. Five-year analysis of adjuvant pembrolizumab or placebo in stage III melanoma. *NEJM Evidence*. 2022;1(11):EVIDoa2200214.
27. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *New England Journal of Medicine*. 2022;386(1):24-34.
28. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *Journal of Clinical Oncology*. 2022;40(2):127-137.
29. Lawrence L. No Survival Benefit With T-VEC in Advanced Melanoma. Cancer Therapy Advisor. Accessed Nov. 11, 2022. [Online]. Available: https://www.cancertherapyadvisor.com/home/cancer-topics/skin-cancer/no-survival-benefit-with-t-vec-in-advanced-melanoma/
30. Rohaan MW, Borch TH, van den Berg JH, et al. Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma. *N Engl J Med*. Dec 8 2022;387(23):2113-2125. doi:10.1056/NEJMoa2210233
31. Haanen J, Rohaan M, Borch T, et al. LBA3 Treatment with tumor-infiltrating lymphocytes (TIL) versus ipilimumab for advanced melanoma: Results from a multicenter, randomized phase III trial. *Annals of Oncology*. 2022;33:S1406.
32. Schmitt AM, Dumas L, Larkin J. Atezolizumab, cobimetinib, and vemurafenib as first-line treatment for unresectable metastatic BRAF V600 mutated melanoma. *Expert Review of Anticancer Therapy*. 2022;22(1):17-25.
33. Stenger M. Addition of Atezolizumab to Vemurafenib/Cobimetinib in Unresectable Advanced BRAF V600–Mutant Melanoma. ASCO Post. Accessed Oct. 19, 2022. [Online]. Available: https://ascopost.com/issues/august-25-2020/addition-of-atezolizumab-to-vemurafenibcobimetinib-in-unresectable-advanced-braf-v600-mutant-melanoma/
34. Switzer B, Puzanov I, Skitzki JJ, Hamad L, Ernstoff MS. Managing metastatic melanoma in 2022: a clinical review. *JCO Oncology Practice*. 2022;18(5):335-351.
35. Dummer R, Long GV, Robert C, et al. Randomized phase III trial evaluating spartalizumab plus dabrafenib and trametinib for BRAF V600–mutant unresectable or metastatic melanoma. *Journal of Clinical Oncology*. 2022;40(13):1428.
36. Tawbi HA, Robert C, Brase JC, et al. Spartalizumab or placebo in combination with dabrafenib and trametinib in patients with BRAF V600-mutant melanoma: exploratory biomarker analyses from a randomized phase 3 trial (COMBI-i). *Journal for immunotherapy of cancer*. 2022;10(6)
37. Fee JA, McGrady FP, Rosendahl C, Hart ND. Training primary care physicians in dermoscopy for skin cancer detection: a scoping review. *Journal of Cancer Education*. 2020;35(4):643-650.
38. Posada EL, Lauck KC, Tran T, Krause KJ, Nelson KC. Educational interventions to support primary care provider performance of diagnostic skin cancer examinations: a systematic literature review. *Journal of Cancer Education*. 2022;37(6):1579-1588.
39. Najmi M, Brown AE, Harrington SR, Farris D, Sepulveda S, Nelson KC. A systematic review and synthesis of qualitative and quantitative studies evaluating provider, patient, and health care system-related barriers to diagnostic skin cancer examinations. *Archives of Dermatological Research*. 2022;314(4):329-340.