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The State of Melanoma: Emergent Challenges and Opportunities

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Abstract

Five years ago, the Melanoma Research Foundation (MRF) conducted an assessment of the challenges and opportunities facing the melanoma research community and patients with melanoma. Since then, remarkable progress has been made on both the basic and clinical research fronts. However, the incidence, recurrence and death rates for melanoma remain unacceptably high and significant challenges remain. Hence, the MRF Scientific Advisory Council and Breakthrough Consortium, a group that includes clinicians and scientists, reconvened to facilitate intensive discussions on thematic areas essential to melanoma researchers and patients alike - prevention, detection, diagnosis, metastatic dormancy and progression, response and resistance to targeted and immune-based therapy, and the clinical consequences of COVID-19 for melanoma patients and providers. These extensive discussions helped to crystalize our understanding of the challenges and opportunities facing the broader melanoma community today. In this report, we discuss the progress made since the last MRF assessment, comment on what remains to be overcome and offer recommendations for the best path forward.

Keywords

Melanoma; Prevention; Detection; Metastatic Dormancy; Targeted Therapy; Immunotherapy; COVID-19

INTRODUCTION

The incidence of melanoma continues to grow worldwide. Interest in melanoma and the care of patients who suffer from it has also grown. The advent of the clinical use of the

BRAF^{V600E} inhibitors vemurafenib and dabrafenib tremendously boosted the prospects and hopes of patients with melanoma, but it was the use of ipilimumab, nivolumab and pembrolizumab that made melanoma the poster child for immune checkpoint inhibitor treatment. Much has been accomplished over the last half decade in both the basic and clinical research arenas, and advances in our understanding and treatment of melanoma are now being applied to other forms of cancer. However, incidence, recurrence and death rates remain unacceptably high, and much remains to be done to address fundamental questions about melanoma prevention, detection, diagnosis, metastatic dormancy and progression, and response and resistance to targeted and immune-based therapy. In this report, leading melanoma investigators consider the challenges that the field must overcome to make progress in all of these key areas. We also discuss issues that clinicians, investigators and patients with melanoma face with respect to SARS CoV-2 infection. Finally, biomedical research is advancing at a breakneck pace, and we discuss the best ways to exploit new scientific and technical discoveries to facilitate the care and recovery of patients with melanoma.

PREVENTION

Primary prevention

Biological addiction in melanoma risk and prevention—Since ultraviolet (UV) radiation is established as a primary carcinogen for both melanoma and non-melanoma skin cancers, prevention strategies that seek to minimize UV mutagenesis are of clear significance. These prominently include UV avoidance (shade, protective clothing) and sunscreen usage, coupled with educational initiatives. Increased research on UV signaling responses in skin has shed light on potential mechanisms that may underlie sun-seeking behaviors. The UV-tanning pathway triggers p53-mediated induction of pro-opiomelanocortin expression, followed by cleavage into multiple bioactive peptides, which include melanocyte stimulating hormone (MSH) as well as β-endorphin. Production of both MSH and β-endorphin has been shown to produce behavioral changes of addictive-like dependency. Given the “paradoxical” linkage of UV-addiction to environmental mutagenesis, these findings suggest the existence of a powerful evolutionary driver, which may well be vitamin D. Studies are investigating potential linkage of vitamin D to opiate-like UV responses. However, it is critical to correct the misconception, sometimes suggested by the tanning industry, that UV is a “healthier” source of vitamin D than supplements.

Research is needed in order to better understand the role of vitamin D deficiency as well as various behavioral diagnoses (addictions, affective disorders, etc.) that may be associated with sun-seeking behavior. While some people might become addicted to tanning, there are no established clinical screening or diagnostic criteria for this behavior, and research in this area is ongoing. Another primary prevention strategy that has been suggested—though not proven—involves approaches to alter skin pigmentation from fair-skin (high pheomelanin-to-eumelanin ratio) towards darker skin pigmentation. While safety of such approaches is paramount, the principle of mimicking epidemiologically low-risk human pigmentation phototypes represents a potentially valuable research approach. For example, the ability to

potentially darken “amelanotic” melanocyte neoplasms might lead to earlier diagnoses and possible clinical benefit.

RECOMMENDED READINGS (1,2)

State of sunscreen safety and recommendations—The foundations of melanoma prevention include sun avoidance and routine sunscreen use. However, little is known about systemic absorption and toxicity of common sunscreens. In a pilot study, each of four sunscreen agents (avobenzone, oxybenzone, octocrylene, ecamsule) was applied to volunteers four times per day for four days to 75% body surface, and the sunscreen levels in their blood samples were quantified. In each case, blood concentrations of the applied sunscreen exceeded the Food and Drug Administration (FDA) threshold for waiving nonclinical toxicology studies. A follow-up expanded randomized clinical trial of six active ingredients led to essentially the same conclusions. While there is no evidence that the measured levels actually cause toxicity in humans, these studies clearly demonstrate that common commercial sunscreens can be absorbed through the skin. Considering the importance of sunscreens in sun safety practices and skin cancer prevention, long-term safety studies should be carried out, and will likely require participation from investigators from dermatology, pharmacology, toxicology, public health, and behavioral science. It is also critical that the FDA accelerates investigation and incorporation of additional UV filters that may have improved efficacy and favorable safety profiles.

Concerns about sunscreen toxicity also extend to aquatic life. A study by the State of Florida Office of Program Policy Analysis and Government Accountability found that oxybenzone and octinoxate in chemical sunscreens can have a negative effect on corals and other marine life, albeit following exposure to concentration levels generally not observed in nature. Another study assessed the concentrations of various UV filters and hormones in the surface seawater, sediment and coral tissue in Hawaii, and found trace concentrations of the UV-B filter oxybenzone in all of them. Although the actual biologic significance of findings such as these remains unknown, Hawaii became the first state to ban the use of sunscreens containing oxybenzone and octinoxate, effective January 1, 2021. Significant coral depletion over the last few decades has been linked to other factors, including ocean warming and acidification driven by climate change, overfishing and pollution. Nevertheless, the use of “environmentally-safe” compounds, such mineral-based sunscreens (i.e., zinc oxide or titanium dioxide), and sun-protective clothing can perhaps mitigate against further damaging this threatened ecosystem. Future studies should be aimed at determining the actual biological effects of chemical sunscreens in humans and on our environment.

The FDA regulates sunscreen as an over-the-counter drug; an unintended consequence of this policy is restrictons on the ability of students to carry or use sunscreens on school premises and/or at school activities in many school districts around the country. As of July 2019, 22 states have enacted legislation to allow students to possess and self-apply sunscreen at school, which improves opportunities for routine use (https://www.cdc.gov/cancer/skin/pdf/SkinCancerPreventionProgressReport-2019-508.pdf). Sun protective fabrics in clothing and hats provides an ultraviolet protection factor (UPF) that may be more effective, acceptable and/or serve as an adjunct to sunscreen use. An advantage of the UPF standard is

that both UVB and UVA are measured. A UPF of 50 blocks 98% of UVR, and activewear with this rating is readily available. Ongoing efforts to promote sunscreen as part of other sun protective behaviors, including sun avoidance at peak UV times and use of sun protective clothing, hats, and eyewear, are needed in public health messaging.

RECOMMENDED READINGS (3,4)

Implementing behavior change to enhance primary and secondary melanoma prevention through legislation and education—Empowering behavioral change for primary and secondary melanoma prevention remains challenging. Tanning via natural sunlight and/or indoor tanning bed use remains prevalent in our society, including among young people. To date in the US, legislation prohibiting indoor tanning by minors (under 18 years old) has been enacted in 21 states and the District of Columbia, an increase from only 2 states in 2012. Based on Centers for Disease Control (CDC) Youth Risk Behavior Survey data, indoor tanning use among high school students has decreased significantly over the past several years, now exceeding reduction targets set forth in the Healthy People 2020 initiative. Indeed, the observed 64% decrease in tanning bed use among high school students between 2009 and 2017 is encouraging, and is likely related to the above-noted statewide restriction of indoor tanning by minors as well as other initiatives. Use of indoor tanning facilities by adults has also been decreasing. According to National Health Interview Survey data, overall prevalence of indoor tanning dropped from 5.5% in 2010 to 3.5% in 2015 during the same interval, indoor tanning prevalence decreased for non-Hispanic white females 18–21 (31.8% to 20.4%), 22–25 (29.6% to 13.9%) and 26–29 (22.1 to 13.8).

Internationally, Australia, Brazil, and Iran restrict access to indoor tanning devices by all individuals; multiple other countries, most recently Spain and Poland, have enacted national laws that restrict use of indoor tanning devices by minors. An FDA regulation was proposed in 2015 that would restrict indoor tanning among all minors nationwide; however, as of Fall 2020 this regulation has not yet been finalized. Overall, changing social norms related to tanning increasingly involves novel approaches to reach the at-risk population, including social media messaging through ‘influencers’ and ongoing legislation to ban tanning beds outright, as has been done in Australia and other countries.

Early detection strategies should ideally target the populations at highest risk for fatal melanoma: namely, middle-aged and older white men, and individuals of lower socioeconomic status (SES, for both sexes and across all racial-ethnic groups). The increasing burden of advanced melanoma in lower SES individuals highlights the need for improved community outreach, education, and awareness campaigns focused on melanoma risk and clinical warning signs, in tandem with novel care approaches (i.e., teledermatology/teledermoscopy) that can improve access to specialists for prompt diagnosis and treatment. Barriers to specialist access that impede early detection of melanoma are highlighted by health disparities in melanoma outcomes in rural areas in the US and abroad. Limited melanoma-specific knowledge and perceived general health competence is associated with thicker melanoma, highlighting the potential value of broader public health campaigns intended to raise awareness.

Population-based data from the CDC (US) and Queensland (Australia) demonstrate a persistent increasing incidence of melanoma in older adults, highlighting an ongoing unmet clinical need to enhance prevention efforts in this demographic. Remarkably, these data also demonstrate a decreasing incidence in younger adults, demonstrating the clinical impact of primary prevention efforts. Overall, there is significant opportunity to build on recent successes to continue to coordinate approaches to educate stakeholders on the dangers of UV radiation overexposure in support of legislative initiatives to restrict indoor tanning by minors at the US state, national and international levels, as well as a strong unmet clinical need to improve early detection strategies for those at highest risk.

Community-based efforts to improve primary and secondary melanoma prevention efforts are ongoing. For example, as part of a community-wide effort led by The University of Texas MD Anderson Cancer Center known as BeWellBaytown, the town of Baytown, Texas, is being mobilized to promote wellness and stop cancer before it starts (https://www.mdanderson.org/research/research-areas/prevention-personalized-risk-assessment/be-well-communities/be-well-baytown.html). As part of this initiative, evidence-based risk reduction strategies and programs are being employed to reduce UV radiation overexposure through: sun safe education and a district-wide sun safety policy; multi-faceted education sessions on sun-protective behaviors; training on sun-protective behaviors for city staff who work outdoors; community infrastructure improvements to reduce excessive exposure to UV radiation in preschools, elementary schools, the local college and at parks; and a city-wide health communication campaign to promote sun safe behaviors and increase sunscreen use.

RECOMMENDED READINGS (5–13)

Therapeutic prevention/chemoprevention—Sunscreens remain the only agents proven to reduce melanoma risk, as demonstrated by a randomized controlled trial in Australia. Given the limitations of applying topical products and other concerns related to sunscreens discussed above, if a safe and effective oral drug were available, it would likely be widely adopted as an alternative or adjunct to sunscreen. However, there are many obstacles to demonstrating efficacy of a new melanoma chemoprevention agent, including long latency of melanoma development, potential hazards of long-term drug administration, and large numbers of patients and high cost needed for a randomized controlled clinical trial.

Consequently, most of the work on melanoma chemoprevention has focused on repurposing drugs and natural products that may protect against one or more of the deleterious effects of acute UV exposure. For example, antioxidants have the potential to reduce UV-induced oxidative stress and consequent DNA damage although positive results in human studies are lacking. Oral N-acetylcysteine delayed development of UV-induced melanoma in a mouse model, but NAC did not protect nevi against UV-induced oxidative stress in human subjects. Broccoli sprout extract, which contains the antioxidant sulforaphane, protects against UV–induced skin damage and development of UV-induced squamous cell carcinoma in mice, and is currently being evaluated in patients with clinically atypical nevi. There is also some concern that antioxidants may promote melanoma metastasis based on studies in mice, but studies are lacking in patients with melanoma. Nicotinamide (NAM), the amide form of vitamin B3, was shown to reduce incidence of new keratinocyte carcinomas by 23% in

patients with prior history of skin cancer. Although equal numbers of melanomas developed in the treated and control groups, the study was not powered to detect an effect on melanoma incidence. Given the capacity of NAM to promote DNA repair in UV-treated melanocytes, and the association with T lymphocyte infiltration in melanomas in humans treated with NAM, there is some enthusiasm for pursuing NAM as a melanoma prevention agent. Finally, anti-inflammatory agents, such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), can target UV-induced inflammation and thereby potentially reduce oxidative stress and pro-carcinogenic signaling. However, studies on the effects of aspirin and NSAID use on melanoma risk are conflicting, and there has never been a prospective trial in high-risk subjects. In addition to their potential use as oral agents, there is also the possibility of combining these agents with sunscreen to enhance efficacy.

Members of the Melanoma Prevention Working Group published a comprehensive review in 2019 on candidate prevention agents and requirements for moving forward into phase 3 clinical trials, which is included in the recommended reading below.

RECOMMENDED READINGS (14,15)

Melanoma risk prediction

Genetic testing—There are increasing complexities and opportunities with multi-gene panel testing for germline mutations implicated in melanoma risk. Genetic risk counselors are now able to select 80 or more bona fide cancer susceptibility genes for evaluation in patients with a family history of melanoma. This reduces the likelihood of missing a pathogenic mutation in a known melanoma gene (e.g., *CDKN2A, CDK4, BAP1, MITF-E318K*). However, multi-gene panel testing also identifies a number of variants of unknown significance (VUS) and secondary findings (e.g., *BRCA2* mutation in a melanoma patient). The American College of Medical Genetics and Genomics have published recommendations for reporting of secondary findings in clinical exome and genome sequencing, and by extrapolation, those for multi-gene panel testing. In the latest (2019) American Academy of Dermatology Guidelines, genetic risk evaluation by a trained counselor is recommended for individuals with features of hereditary melanoma including melanoma tumor syndromes with germline mutations that confer risk for visceral malignancies (e.g., *CDKN2A* and pancreatic cancer, *BAP1* and mesothelioma, and *MITF-E318K* and translocation kidney cancer). Thus, testing should be performed by a broadly trained cancer risk genetic counselor, medical geneticist or other trained medical provider with access to care for other at-risk malignancies beyond melanoma (e.g., gastroenterologist for *CDKN2A* mutation carriers and breast cancer surgeon for *BRCA2* mutation carrier).

Because familial melanoma may result from shared environmental risk factors as well as heritable mutations, all patients with familial melanoma, regardless of genetic status, should continue to engage in strict sun protection and routine skin cancer surveillance. The lack of a detectable variant, even with panel testing, does not exclude the possibility of a high-risk mutation somewhere in the un-tested genome. Thus, individuals without identified germline pathogenic variants are not completely risk-free. If a variant is detected, there are multiple possible scenarios. First, a pathogenic mutation is identified in an “actionable” gene such as *CDKN2A*. The National Comprehensive Cancer Network (NCCN) recently endorsed annual

pancreatic cancer screening for individuals with germline *CDKN2A* pathogenic variants regardless of family history of pancreatic cancer, though this practice differs by institution. Individuals with deleterious germline *CDKN2A/p16* mutations should generally be referred to a gastroenterologist for a discussion regarding the implications of their carrier status on pancreatic cancer risk. Second, a pathogenic mutation may be detected in a secondary actionable gene, such as *BRCA2*. In this situation, genetic risk counselors and/or providers should be able to help refer the individual to the proper management team. Third, a pathogenic mutation may be found in a "non-actionable" gene such as *POT1*. There are currently no specific guidelines regarding the management of individuals with germline *POT1* mutations, and therefore the default surveillance for familial melanoma patients should suffice. Fourth, a VUS may be detected. In the absence of functional information, there is little that can be gleaned from the mutation alone. Strict sun protection and skin surveillance should be reinforced in patients with a VUS; however, additional screening for visceral malignancies is usually not warranted. Probands should be encouraged to inform other family members, especially if clinically actionable results are later found, since similar risks are shared by all carriers.

Direct-to-consumer or direct-to-physician marketing of genetic tests of melanoma susceptibility in the absence of training to understand the complexities of testing, such as VUS, may lead to harms such as unnecessary fear and concern as well as overuse of cancer screening diagnostic tests that may have limited impact on actual cancer outcomes. The American Academy of Dermatology melanoma clinical practice guidelines specifically recommend genetic counseling with a trained provider, in order to guard against misinformation and misguided clinical activities.

RECOMMENDED READINGS (16–19)

Melanoma underreporting to state cancer registries: generating a nationwide initiative to overcome this challenge—It is estimated that cutaneous melanoma underreporting to US state (and therefore national) cancer registries ranges from 30–70%. Lack of understanding the true melanoma incidence in the US adversely impacts resources needed to more effectively prevent, diagnose, and treat the condition. Nationwide initiatives, driven by organizations such as the American Association of Dermatology and state medical boards, could work to enhance practitioner awareness of state-based melanoma reporting requirements and to improve efforts by state cancer registries to facilitate reporting in community settings. For instance, diagnostic pathology/dermatopathology reports could highlight the responsibility of the practitioner establishing the diagnosis to report the melanoma, and offer guidance on the relevant state cancer registry information to aid the provider in doing so. This concept has already been successfully enacted in Arizona. Effective approaches to overcoming this challenge in the US may be useful to improve this issue worldwide.

RECOMMENDED READING (20)

Secondary prevention

Melanoma screening efforts—The success of early detection as a secondary prevention modality is dependent on identification and treatment of early, pre-lethal melanoma. This requires an approach that: 1) reaches individuals at risk and educates them about skin self-exams and melanoma clinical warning signs, 2) assures access to healthcare providers who can identify melanoma at its early stages, and 3) results in appropriate curative treatment. An ideal early detection program must also assure that the benefits of early detection exceed the harms, including minimizing biopsy of benign lesions and overtreatment of relatively indolent skin cancers that can drive up costs of screening with little added benefit. Early detection programs have been attempted in Germany, Australia, Belgium, France, and the US. A recent evidence-based review has concluded that collectively, the data suggest that screening programs are beneficial, but that the evidence is not strong. We await additional data from these screening programs, especially Germany's nationwide effort, to determine whether the detection of thinner primaries translates to meaningful reductions in overall melanoma mortality.

The Oregon statewide War On Melanoma™ early detection effort has developed a three-pronged approach to reach the lay public, skin service professionals (e.g., massage therapists, hairdressers, aestheticians, etc.), and primary care providers (www.WarOnMelanoma.org). Outreach is through an unbranded public health campaign and includes in-person and online educational resources at www.StartSeeingMelanoma.com. Specific strategies in Oregon to improve access to dermatologic care includes e-visits, e-consults, teledermoscopy, and mobile app mole-tracking with MoleMapper. The program is testing the hypotheses that implementation of this campaign will increase awareness and intention to self-screen, improve prognosis at the time of diagnosis, reduce mortality due to melanoma, and reduce the cost of care for melanoma. Early efforts for expansion to other states within the US have begun in California (entitled Wipe Out Melanoma – California), Arizona, Missouri, Utah, Texas, Georgia, and Massachusetts.

The University of Pittsburgh Medical Center implemented a program that educated primary care physicians about skin cancer detection and encouraged an annual skin cancer screening examination of any patient age 35 and older presenting for a routine visit. This initiative resulted in an increased rate of melanoma detection as well as diagnosis of thinner melanomas among screened vs. unscreened individuals. Although concerns about causing patient anxiety have been raised as a possible harm of skin cancer screening, a survey of patients found that in comparison to patients who did not have a full skin examination, those who did undergo a full skin examination did not differ on negative psychosocial measures and actually scored higher on measures of positive psychosocial wellbeing. Screening was also not associated with an increase in dermatology visits or skin surgeries.

Establishing a successful early detection program requires a broad range of expertise and technology. Funding for dissemination and implementation science is needed to assure that progress is made through cooperation across the entire spectrum of stakeholders including patients and patient advocates, primary care and melanoma specialists, laboratory scientists, public health and population scientists, and engineers.

RECOMMENDED READINGS (7, 21–26)

Role of digital imaging, non-invasive technologies and artificial intelligence (AI) in melanoma diagnosis—Digital imaging has become ubiquitous in society following the rapid development of high-resolution mobile devices (up to 108 megapixel sensors). Two-dimensional and 3-D total body photography (TBP) using semi-automated devices continue to be developed with the goal of increasing image quality and speed of acquisition. Digital follow-up with serial imaging has also proven to be useful in the surveillance of high-risk populations by providing the added benefit of not overlooking cutaneous melanomas that have few dermoscopic criteria, while minimizing the excision of benign lesions. The benefits of TBP and serial dermoscopic imaging have been endorsed by recent consensus recommendations from pigmented lesion experts in the US. Efforts are underway to execute the first randomized clinical study to compare routine clinical care with an intensive skin surveillance program consisting of 3-D TBP, sequential digital dermoscopy, and melanoma-risk stratification in a high-risk melanoma cohort in Australia. While digital images accurately document the appearance of skin lesions, they can also represent a threat to patient privacy. Therefore, proper measures need to be in place to safeguard this sensitive data. A lack of standardization in image acquisition and storage limits the current utility of this technology.

With the continued expansion of imaging databases, and recent developments in computer science, the implementation of artificial intelligence (AI) in the melanoma diagnostic field is gaining interest. Access to large data pipelines is the primary barrier to developing clinical level AI, as the development and training of such algorithms requires large datasets of standardized images tagged with a ‘ground truth’ diagnosis. AI implies that computers can simulate intelligent behavior, while machine learning is the application of AI to allow the system to learn on its own and improve over time. Augmented intelligence is the intersection of machine learning and other advanced applications to work with and enhance human tasks. In the AI arena, machine learning and computer vision are particularly applicable to cutaneous melanoma diagnosis – aiming to augment clinician decision-making, enhance human intelligence, and optimize the physician-patient relationship.

Multiple publications have demonstrated that various convolutional neural networks, a type of deep learning algorithm, can do well in binary clinical or dermoscopic image classification (benign vs. malignant) of skin neoplasms, including melanoma, and keratinocyte cancers, with the convolutional neural networks consistently performing as well if not better than selected groups of expert clinicians. However, studies to date have been done in an experimental setting (‘in silico’) and have not yet been applied to the real-world clinical setting.

The creation of standardized and safe imaging documentation represents a powerful opportunity to enhance serial skin self-examination and facilitate objective and accurate skin cancer screening by medical providers. It also creates a critical tool for following patients with atypical nevus phenotype, and establishes robust databases for the development of reliable machine learning algorithms for early melanoma identification. All AI platforms require prospective clinical testing and randomized controlled trials to assess their diagnostic

capabilities vs. that of the health provider, and must demonstrate improved sensitivity, specificity and cost effectiveness before becoming part of routine clinical practice.

In addition to the implementation of standardized digital imaging (with and without AI support), there has been an explosion of other non-invasive imaging and molecular diagnostic technologies designed to provide a “bedside” diagnosis of cutaneous melanoma. These include existing FDA-approved technologies (e.g., reflectance confocal microscopy, electrical impedance spectroscopy), and emerging technologies (e.g., optical coherence tomography, polarized light, photoacoustic imaging, Raman spectroscopy, elastic scattering spectroscopy). Current molecular diagnostic techniques include adhesive patch gene expression profiling, utilizing *PRAME* and *LINC*. These technological advances have the potential to positively impact the field by providing better access, improved triage, and more accurate diagnosis for patients; however, they require vigilance to ensure that they are clinically implemented following appropriate validation. Specifically, these modalities must be tested against “real world” clinical interpretation (i.e., dermatologist visual inspection with dermoscopy, utilization of total body photography/mole mapping and/or serial digital dermoscopy in patients with high-risk nevus phenotypes). As yet, they do not replace the gold standard of histopathologic examination.

It is anticipated that effective integration of prospectively validated non-invasive diagnostic devices, including AI and augmented AI platforms, will be paradigm-changing for automated diagnosis of skin cancer, including melanoma, and may greatly enhance primary care-based diagnoses and prioritize patient referrals to dermatologists in rural areas with specialist shortage.

RECOMMENDED READINGS (27–29)

Need for increased specificity in melanoma diagnosis: healthcare cost implications—Provider sensitivity for diagnosis of cutaneous melanoma is not perfect; low provider sensitivity results in melanomas diagnosed at more advanced stages, which necessitates more intensive therapeutic courses, incurs additional personal and financial morbidity for the patient, and has a higher mortality risk. Appropriately validated quality metrics are important to guide continuous improvements in early melanoma detection as they quantify performance with melanoma screening examinations, identify opportunities for additional educational intervention, and measure changes in provider diagnostic sensitivity associated with introduction of novel diagnostic support technologies. Despite these potential benefits, quality metrics for cutaneous melanoma diagnosis have remained elusive. The most commonly cited metric is the “number needed to biopsy” (i.e., how many skin biopsies are necessary for a melanoma diagnosis). This gives an approximation of the provider’s positive predictive value, but is of limited practical application when the provider’s sensitivity, specificity, and melanoma prevalence are unknown.

Development of clinically appropriate, feasible, and validated quality metrics for melanoma detection, including sensitivity, is best guided by the clinician end-users, yet the absence of structured clinical and pathology data limits practical metric development. Advances in Native Language Processing offer opportunity for evaluation of structured pathology

diagnosis fields, but interpretation of more heterogeneous clinical impression data fields remains challenging for this technology. Measurement of overlooked melanomas (false negatives) remains particularly challenging, as the “diagnostic moment” of the full skin examination is not currently captured. Similarly, the absence of an International Classification of Diseases, Tenth Revision (ICD-10) code structure for “skin cancer screening” examinations hinders efforts to retrospectively identify patients who received screening examinations, thus complicating efforts to quantify “number needed to screen” or similar outcomes measures.

Performance metrics, when paired with opportunities for clinical practice improvement, have the potential to optimize patient comfort and satisfaction, improve clinicians’ self-efficacy regarding noninvasive diagnosis, improve busy clinicians’ allocations of time and effort (for both dermatologists and pathologists), and reduce health care costs. The cost of adjuvant systemic therapy (e.g., one year of adjuvant pembrolizumab estimated at over $160,000 for drug cost alone) vs. the cost of one diagnostic biopsy (approximately $259), suggests that increasing allocation of resources to comprehensive early detection initiatives may be worth considering in order to reduce total healthcare costs.

RECOMMENDED READINGS (30–31)

Tertiary prevention as it relates to melanoma survivorship

Tertiary prevention focuses on avoiding or reducing the sequelae of a disease process once established in an individual. It may be integrated into treatment considerations and has considerable overlap with “survivorship.” Recent statistics from the American Cancer Society indicate that there are over 1.3 million melanoma survivors living in the US; nearly half of those survivors are under the age of 65. Advances in treatment of systemic disease with immunotherapy and targeted therapies have caused dramatic decreases in mortality from melanoma: in the years 2013–2017, the American Cancer Society reports a 7% decrease in melanoma deaths annually for patients aged 20–64 and a 5–6% decrease in melanoma deaths annually for those over 65. However, survivorship can pose multiple issues, including those of second primary melanomas, increased risk of other skin cancers, and long-term consequences from treatment of melanoma. Immunotherapy with PD-1 (programmed cell dealth protein 1 receptor) inhibitors, for example, can cause permanent autoimmune adverse effects, including hypothyroidism, adrenal insufficiency, and diabetes. Current work in this area focuses on guidelines for management of these and other side effects of therapy, while maintaining the efficacy of treatment. The development, documentation, and implementation of formal survivorship plans for individuals treated with curative intent is another approach to decrease associated morbidity and improve patient quality of life.

RECOMMENDED READINGS (32, 33)

PREVENTION & EARLY DETECTION RECOMMENDATONS: Table 1

TUMOR CELL DORMANCY AND METASTASIS

The clinical importance of defining dormancy and its underlying mechanisms

Clinical cancer dormancy is the period of time a patient who ultimately recurs was clinically free of detectable disease, defined in melanoma from the time of treatment of the primary lesion until the appearance of metastasis or other recurrences. But dormancy is more than simply subclinical growth – the concept implies a period of time where clinically undetectable residual tumor persists but does not actively proliferate. In melanoma, there are many cases where patients recur after a disease-free interval spanning a decade or more after initial removal of the primary, but whether the underlying mechanism(s) for this prolonged disease-free interval truly reflects dormant cells (as opposed to slow but steady growth of a very small inoculum of residual tumor cells) has never been determined. Traditionally, studies of dormancy were largely based on cultured cells, mouse models or patients who were untreated or subjected to rather ineffective treatments. As staging and prognostication become more precise and treatments become more effective, a large fraction of patients with resected Stage III and someday even Stage II disease are expected to be subjected to adjuvant therapy, typically for up to a year. Adjuvant therapy may alter the kinetics of growth of any residual cells, and cells entering dormancy might retain a degree of sensitivity to the treatment administered but survive long enough to recur after treatment discontinuation. Understanding this phenomenon is therefore critical to the rational design of both adjuvant therapy regimens and salvage treatments in patients recurring after completion of adjuvant therapy.

Here we highlight pending questions in the context of melanoma dormancy that provide exciting opportunities for research and innovation at basic and clinical levels. In addition to understanding what drives the onset of dormancy, we need to identify signatures that maintain the dormant state(s), and conversely, those that allow for “awakening” of dormant cells. The extent to which persister cells may evolve with time (genetically and epigenetically) is an active area of research. It is also unclear how the fate of dormant tumor cells is modulated in an organ-specific manner. For example, are mechanisms governing asymptomatic, or “silent” metastasis in the brain similar to those in lung, liver or other distal sites?

Another unresolved question is the role of the immune system with respect to dormant vs. active metastasis. Below we offer some ideas as to how to leverage models and human sample analysis to help address these unmet needs. In particular, we discuss opportunities for developing strategies to detect disseminated melanoma cells and to monitor their presence as dormant or active cells in patients.

Animal models to visualize and characterize melanocytes and melanoma progression

One of the challenges with studying dormancy in vivo is the paucity of imaging tools and physiologically-relevant animal models. These limitations are being addressed by using highly sophisticated models in zebrafish as well as in genetically engineered mouse (GEM) models. In both settings it is now possible to trace tumor cells in living animals and assess the contribution of various risk factors such as UV or aging. Other mouse models are being

generated to monitor specific roles of the vasculature and distinct components of the tumor microenvironment. The development of GEMs for depletion of selective immune cells or modification of stromal compartments is also expanding our ability to analyze cell-cell interactions. Similarly, new tools for intravital imaging in zebrafish and the possibility of cost-effective genetic and pharmacological screens in these animals represent great platforms for in depth studies of melanocytic cell populations and their differential potential to self-renew and enter into programs of cellular quiescence (dormancy). They also offer the opportunity to monitor proliferation of such cells in basal conditions or in response to intrinsic and/or extrinsic pro-oncogenic signals.

Detection, isolation and monitoring of dormant melanoma: human to mice and vice-versa

Animal models may be very useful in defining mechanistic aspects of melanocyte biology and tumor cell dormancy/awakening as mentioned above, but a main challenge is to translate this knowledge into reliable prognostic biomarkers and response indicators. Progress in this field will necessarily involve a comprehensive and multidisciplinary characterization of human specimens (primary lesions, liquid biopsies and recurrent/metastatic tumors).

Tissue collection—The question of what/when tissues should be collected in retrospective vs. prospective analyses is always an important one. This has become critical as larger cohorts of patients are proceeding to neoadjuvant intervention, where agents are administered before local treatment and before detection of clinical visceral metastases. Consensus is building that sampling should go beyond the primary lesion and sentinel lymph nodes. Bone marrow may represent a screening platform if dormancy cues and regulators identified in model systems can be validated in comprehensive studies in human patients.

Regarding markers for monitoring disseminated melanoma cells, pigmentation-associated markers could be used to identify tumor cells in sentinel lymph nodes and bone marrow. This could also be the case to detect circulating tumor cells in blood. A consideration, however, is that pigmentation markers may be lost as melanoma cells switch into invasive phenotypes. Consequently, methods to detect specific genetic alterations such as gains, losses, or translocations characteristic of melanoma may allow the pinpointing of amelanotic cancer cells. Technologies for single cell analyses in situ or in dissociated biopsies are likely to represent a tractable platform for gene discovery, but there is a need for systematization/homogenization of protocols and bioinformatics analyses. Access to biobanks or repositories of specimens linked to clinical trials are also key. In particular, probing the cellular state of residual tumor cells may help understand long-term effects of immunotherapy agents that may drive melanoma cells into dormancy.

Liquid biopsies—An area of further research in melanoma and other cancers is the use of blood or serum to monitor for active and dormant residual disease. The mutational status of cell-free DNA (cfDNA) can be explored as a strategy to predict or anticipate a soon-to-occur relapse. This may also be the case for DNA or RNA contained in exosomes. Analysis of samples obtained at the time of surgery will be important as a baseline control, but also at multiple timepoints during follow up, to determine if patients carry dormant or proliferative disseminated cells after surgery or after adjuvant treatment. Limitations with respect to

sensitivity should be addressed, and consideration should be taken into account that dormant lesions may not necessarily shed circulating cells to the same extent as actively proliferating tumors. Therefore, from a clinical perspective, it may be more practical to pursue circulating tumor cells in the context of drug response in advanced Stage IV patients, rather than in Stage II-III tumors.

Given the considerations posed above for the detection of circulating cells, an alternative possibility to gauge the potential for tumor cell relapse is to test for proteins in serum that have been linked to dormancy induction/maintenance (i.e., WNT5A, SOX9, N2RF1 or TFGB2) or that have been linked to dormancy break (i.e., uPAR, FBXW7, FAK or DKK1). Conceptually, it should be possible not only to probe tumor-associated mutations or gene signatures, but also to assess secreted factors from the host. Such an approach has not yet been tested.

Rapid autopsy programs—Rapid autopsy programs have been set up in some academic medical centers in order to sample many organ sites immediately post mortem to collect metastastic tumors and clinically uninvolved tissues, where subclinical disseminated tumor cells may reside. These efforts could improve our understanding of the complexity of end-stage disease and the systemic nature of melanoma spread. In studies of prostate cancer, rapid autopsy programs have provided information regarding the extent of metastatic disease. However, studies of dormancy with post-mortem biopsies have not been performed in melanoma. As for other sampling procedures, the question remains of whether characterizing dormant cells that never reactivated in deceased patients will be clinically informative for other prospective studies. Similarly, it will be important to determine whether disseminated tumor cells identified at a given time point reflect the actual (epi)genetic changes that happened at the site of origin years earlier (i.e., to study tumor cell evolution). In this context, it will be useful to compare disseminated tumor cells in patients with detectable metastases to those identified only post-mortem, looking at cases who had complete resection vs. those who had previously responded to a systemic therapy but then relapsed. This would perhaps distinguish different stages of dormancy from irreversible arrest programs such as senescence.

In summary, the field of tumor dormancy is nascent but burgeoning. Outstanding needs include more physiological animal models for in vivo studies and a better knowledge of the plasticity of human melanomas in naïve vs. treated patients. Intriguing data are emerging regarding aspects of tumor cell tropism to different organs, but it will be important to dissect in more detail the impact of the microenvironment at large. From a clinical perspective, the field needs more sensitive imaging tools for the detection of micrometastases, as well as for the processing of liquid biopsies. What and when to collect specimens for analyses in patients who have remained asymptomatic for years or after long-term treatment is also a challenge. Moreover, biopsies should be considered beyond the primary tumor that may inform about (pre)metastatic niches. As we design therapies to address tumor dormancy, we need to be aware of long-term effects of sustained treatment. Overall, addressing the potential of dormant tumor cells to grow and colonize distal sites will be critical to overcoming the burden of recurrent disease.

RECOMMENDED READINGS (34–38)

DORMANCY/METASTASIS RECOMMENDATIONS: Table 2

TARGETED THERAPY

With the publication of large-scale genomic data in cutaneous melanoma and uveal melanoma as part of The Cancer Genome Atlas (TCGA) and other large studies that included cutaneous as well as mucosal and acral melanoma subtypes, the landscape of targetable mutations in melanoma is coming into focus. While translation has only led to therapeutic breakthroughs in patients whose tumors harbor $BRAF^{V600}$ mutations, ongoing research is underway to determine how to optimally target these alternative genetic aberrations. Additional targetable mutations could be addressed over the coming years to maximize the benefit of targeted therapy for patients with melanoma.

Clinical experience for BRAF-targeted therapies

The past decade has been an unquestioned success with the development of effective BRAF-targeted therapy for patients with $BRAF^{V600}$ mutant melanoma. The safety and efficacy data of combined BRAF-MEK inhibition has led to regulatory approval of three regimens (dabrafenib + trametinib; vemurafenib + cobimetinib; encorafenib + binimetinib) in the metastatic setting and one (dabrafenib + trametinib) in the adjuvant setting for Stage III melanoma. Further, recent long-term data from three phase III trials (co-BRIM, pooled data from COMBI-V and COMBI-D) of BRAF-MEK combinations show 5-year progression free survival (PFS) in 14–19% of patients, with 5-year overall survival (OS) of 31% and 34%, respectively for vemurafenib + cobimetinib and dabrafenib + trametinib. These numbers are even better for patients with a normal vs. elevated LDH (5-year PFS 18–25% vs 8–10%), those with a performance status of 0 and those with fewer than 3 organs involved with melanoma. Further, 5-year follow-up results from the adjuvant study of dabrafenib + trametinib vs. placebo (COMBI-AD) showed a 16% absolute difference in the percentage of patients who were relapse-free after the application of combination BRAF-MEK inhibition in the adjuvant setting compared to patients undergoing observation. And yet, despite this success, there are several issues that must be addressed to optimally use these agents.

First, there are no data that indicate whether any of the three different BRAF-targeted therapy regimens are superior in efficacy. Data suggest that efficacy is similar across regimens, with each regimen showing similar relative efficacy compared to single agent vemurafenib in randomized phase III trials. Interestingly, the COLUMBUS trial included an arm of single agent encorafenib, which demonstrated superiority to vemurafenib. Thus, single-agent encorafenib may be more efficacious than single-agent vemurafenib; however, it is not clear from the data across trials that encorafenib + binimetinib is more effective than vemurafenib + cobimetinib. Thus, the key distinguishing features of the regimens are number of pills per day, timing of administration vis-à-vis food intake, toxicity and pharmacokinetics/half-life.

Second, the great success of BRAF-targeted therapy has been overshadowed by immune checkpoint inhibitor data, either single-agent PD-1 inhibition or combined anti-PD-1 and

anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) inhibition. With 5-year OS of 44% and 52%, respectively, and an enhanced ability to maintain disease control after stopping therapy, immunotherapy has become favored as initial therapy for patients with $BRAF^{V600E}$ melanoma. However, results from ongoing randomized trials comparing the sequence of combined immune checkpoint inhibition to BRAF-targeted therapy at disease progression or the reverse sequence (DREAM-seq, NCT02224781; SECOMBIT, NCT02631447) are needed to provide level 1 evidence to support optimal therapy choices in the front-line setting. Unfortunately, there are no widely adopted pretreatment biomarkers that can be used to help select patients with $BRAF^{V600}$ melanoma most likely to benefit from immunotherapy or BRAF-targeted therapy. It is hopeful that the two clinical trials launched to address the question of "which type of therapy first?" will also help answer the more nuanced question of "which therapy for which patient?".

Third, while as many as 15–25% of patients, depending on risk factors, may remain progression-free 5 years after starting treatment with BRAF-MEK inhibitors, the majority of these patients remain continuously on treatment. Data has suggested that 40–50% of patients who discontinue treatment either voluntarily or due to toxicity while still in response will experience disease progression within 6–9 months. While many of such patients can respond to resumption of therapy, data are limited and anecdotal. More information is needed to determine which and when patients can safely stop BRAF/MEK targeted therapy and what the impact of stopping is on patient outcome and quality of life.

Fourth, translational research studies have consistently shown that BRAF/MEK inhibition is associated with increased CD8+ T cells, T cell cytotoxicity and melanoma differentiation antigen expression, as well as decreased immunosuppressive cytokines within metastatic melanoma deposits. These data have been used to support the development and testing of triplet combination regimens involving BRAF/MEK and PD-1 pathway inhitibion. Recent results from the IMSPIRE 150 and Keynote 022 trials show that these triple combinations can produce improved median PFS and duration of response relative to targeted therapy alone. However, despite these encouraging correlative studies and clinical results, it remains unclear whether the tumor biopsy findings are a consequence of enhanced antitumor immunity or merely tumor cell death and depletion and whether the early clinical findings result from syngergistic, additive or even subadditive effects of the combination. More research is needed on the impact of BRAF/MEK inhibition on antitumor immunity and deterrmining how the triplet combinations compare to ipilimumab + nivolumab immunotherapy with subsequent targeted therapy upon progression in terms of critical endpoints such as OS, cost, toxicity and the ability to allow treatment-free survival (time without treatment or toxicity).

Finally, there are also no data to help determine which patients with resected Stage III BRAF mutant melanoma should preferentially be offered adjuvant BRAF-targeted therapy or anti-PD-1 therapy. The COMBI-AD trial comparing adjuvant dabrafenib + trametinib to placebo showed a 5 year recurrence-free advantage of 52% vs 36% compared to placebo, suggesting that a significant proportion of Stage III patients with BRAF mutant melanoma harboring minimal residual disease may be cured with a year of adjuvant targeted therapy. Identifying who these patients are and if they differ from those getting long-term benefit

from adjuvant immunotherapy is a critical unmet need. In addition, we need information regarding the optimal duration of therapy in the adjuvant setting, a risk-benefit analysis of BRAF-targeted vs. anti-PD-1 therapy, and more data regarding whether these regimens may be as or more effective in the neoadjuvant setting. Notably, several small neoadjuvant trials have demonstrated that major response or pathologic complete response (CR) is associated with objective clinical endpoints such as recurrence-free survival. This suggests that the neoadjuvant setting may be a place to vet promising targeted therapy regimens using pathologic CR as a key metric of potential efficacy, along with a number of correlative endpoints to better understand the effects of therapy on the tumor and its microenvironment.

Non-BRAF—targeted therapies

The second most common oncogenic driver mutation in melanoma occurs in *NRAS*, a target that presently lacks a specific inhibitor. Preclinically, inhibitors of the MAPK pathway, particularly pan-RAF, MEK and ERK inhibitors, have shown promising efficacy. Unfortunately, despite modest benefits of MEK and ERK inhibitors in small trials in patients with NRAS mutant melanoma, a randomized phase III trial of the MEK inhibitor binimetinib compared to dacarbazine demonstrated only a modest benefit in PFS and no difference in OS. Based on these data, the clinical testing of single agent MAPK inhibitors in this setting was discontinued. Large-scale national basic research efforts (see below) are focused on identifying novel inhibitors of activated KRAS pathway, raising the possibility that such efforts may ultimately benefit patients with NRAS melanoma.

Targeted therapy resistance

The great majority of patients with BRAF mutant melanoma treated with targeted therapy ultimately will require additional therapy due to primary (intrinsic) or secondary (acquired) resistance. A deeper understanding is needed to better address resistance in all melanoma subtypes and to inform future therapy development. It is key that patients treated with standard of care BRAF-targeted therapy are enrolled into correlative protocols that allow, when feasible, serial biopsies and blood analyses, and that clinical trials of targeted therapies build in mandated biopsies and blood analyses. Such collection of patient samples in a dedicated fashion is necessary to more fully understand the therapeutic resistance landscape. Preclinical studies informed by clinical samples followed by translation of preclinical breakthroughs are expected to lead to next generation, transformative therapies.

Molecular landscapes

In recent years, sequencing studies have revealed that cutaneous melanomas, which commonly arise from sun-exposed surfaces of the body, harbor a high mutational burden and a UV mutation signature but infrequent structural rearrangements. In contrast, mucosal and acral melanomas have a low mutational burden and rarely display a UV mutation signature. The most common genetic alterations present in cutaneous melanoma provide a rationale for genomic subclassification of these patients. Specifically, BRAF, NRAS and NF1 mutations, which are largely mutually exclusive drivers of MAPK activation, comprise three genomic subtypes established by TCGA in cutaneous melanoma. A fourth, so-called triple wild-type (WT) tumors, comprise cases that lack these mutations. Nevertheless, even triple WT tumors show an activated MAPK pathway due to autocrine and paracrine growth factor stimulation.

BRAF mutation classifications—*BRAF*^{V600} (class I) mutations are the most prevalent in melanoma, and in light of the availability of specific inhibitors represent the only clinically actionable genetic subtype to date. Class II BRAF mutations are RAS-independent, with intermediate to high kinase activity. In contrast, class III BRAF mutations are RAS-dependent, with low kinase activity. Class II and III mutations are generally not sensitive to current BRAF-targeted agents.

NRAS mutations—*NRAS* mutations are typically alterations of the Q61 residue, which hyperactivates its ability to phosphorylate downstream targets. Advances in the understanding of RAS structures, interactors, post-translational modifications and activity have led to a variety of promising preclinical strategies to develop RAS-targeting agents, but no RAS-targeted agents are yet approved for clinical use.

NF1 mutations—*NF1* loss-of-function mutations are also core melanoma drivers. NF1 enhances hydrolysis of RAS-bound GTP to restrain downstream MAPK activity. *NF1* mutations frequently co-occur with mutations in RASopathy genes, such as *RASA2*, *PTPN11*, encoding *SHP2* and *MAP2K1/2*. These co-occurring mutations are thought to further amplify MAPK signaling to drive tumorigenesis, where NF1 loss of function alone may be insufficient. Despite MAPK activation as a critical driver of NF1 mutant melanoma, there is scant evidence that MEK inhibitors or other targeted agents are efficacious in NF1 mutant melanoma. SHP2 inhibitors represent a promising class of targeted therapies for RAS-GTP-dependent cancers, including those with NF1 mutation or class 3 BRAF mutations. SHP2 functions downstream to integrate growth factor signaling and RAS activity. Allosteric SHP2 inhibitors designed to subvert RAS activity are currently in early clinical development.

Triple wild-type melanomas—Triple WT tumors can harbor *KIT* amplification, mutation or structural rearrangement, or mutations in *HRAS*, *KRAS*, *GNAQ* or *GNA11*. *KIT* alterations are found most frequently in acral or mucosal melanomas. Tumors with activating *KIT* mutations in exons 9 or 11, though not amplification, have responded to tyrosine kinase inhibitors that target KIT, such as imatinib, which are largely ineffective against other melanomas. In addition to the main core driver mutations described above, other common alterations have been documented, which may be actionable with existing drugs in clinical use or development. Alterations in cell cycle regulators (i.e., *CDKN2A* loss, *CDK4* or *CCND1* amplification, *ALK* translocations) provide a rationale to combine CDK4/6 inhibitors such as palbociclib and ribociclib. Palbociclib monotherapy has shown efficacy in patients with acral melanomas with CDK alterations, as well as synergy with BRAF and MEK inhibitors in cell line models. Similarly, genetic alterations in the PI3K/AKT/PTEN pathway have supported preclinical studies with PI3K inhibitors. Unfortunately, none of these small molecules have shown promise as either single agents or combinations against metastatic melanoma. Alterations in the MDM2/p53 axis are relatively less common in melanoma (<20% of patients) but could be targeted with second generation MDM2 or MDMX inhibitors that restore p53 levels and/or function, such as ALRN-6924, currently in Phase I clinical trials.

Various analytical approaches have nominated a number of additional potential therapeutic targets. Recurrent point mutations in *IDH1* at R132 are observed in several cancer types, including 3–5% of melanomas. Ivosidenib is an inhibitor of mutant IDH1 that was recently approved for use in acute myeloid leukemia. Efficacy in IDH1 mutant melanoma has not been established. A hot-spot mutation in *RAC1* (P29S/L), a Rho GTPase, confers hyperactivity, and is nearly melanoma-specific. Numerous strategies to develop Rho GTPase inhibitors have been pursued but have not yet achieved clinical success. Neurotrophic tyrosine receptor kinase (NTRK) fusions have also been noted in melanoma, in particular spitzoid lesions, and may be targetable with newly approved NTRK inhibitors such as entrectinib.

Uveal melanomas (along with very rare melanomas arising from blue nevi) are characterized by mutually exclusive activating mutations in *GNAQ* or *GNA11*, encoding heterotrimeric Gαq family members. Preclinical studies have found that GNA11 mutant uveal melanomas are initially sensitive to BET inhibitors, and that combined FGFR inhibition overcomes the emergence of resistance to BET inhibitors. Recent studies have found that Gαq stimulates YAP via FAK, identifying these as suitable therapeutic targets in uveal melanoma. A new generation of orally bioavailable FAK inhibitors are currently being tested in Phase I trials, offering new promise for patients with metastatic uveal melanoma.

Molecular heterogeneity and phenotypic plasticity

In addition to the diversity of oncogenic driver mutations, there is abundant heterogeneity of melanoma cells between patients, between lesions from the same individual, and within individual tumors. Controversial cancer stem cell models initially reported for melanoma have ceded to models in which phenotypic plasticity of melanoma cells is thought to be a consequence of different transcriptional or cell states. Highly plastic melanoma cells can switch between these different cell states. This cell state switching likely serves to engage specific tumorigenic properties in response to microenvironmental cues or when otherwise needed for tumor growth or survival. Through bulk transcriptional analyses of both patient tumors and cell culture models, transcriptional states characterized by high expression of either *AXL* or *MITF*, among other genes, were established. These cell states have been described as ‘invasive’ and ‘proliferative’ classes, respectively. The MITF/AXL cell states have also been characterized by properties related to drug sensitivity. The AXL-high cell state, compared to the MITF-high state, is reported to possess relative resistance to MAPK pathway inhibitors but sensitivity to ferroptosis-inducing agents, such as GPX4 inhibitors. These cell states were recently confirmed to coexist intratumorally by single cell RNA sequencing of patient tumors. It is expected that additional single cell RNA sequencing, spatial profiling and other advanced phenotypic and functional characterization will further clarify different classes of cells in patient tumors. Specific subpopulations representing a given cell state may exist prior to therapy, for example NGFR/EGFR^{+} cells, or develop during therapy leading to resistance. Thus, for complete eradication of a tumor, we may need to develop dual strategies that target both the bulk of the tumor and more resistant subpopulations. Due to the apparent heterogeneity and plasticity of melanomas, the aim should be to focus on common pathways, many yet to be discovered. Potential candidate

pathways could relate to pigment cell differentiation and to neural crest-like dedifferentiation.

Models for therapy resistance

Melanoma cells have inherently or develop resistance to small molecule inhibitors that are in clinical use. This intrinsic and/or acquired resistance can be seen and modeled both in vitro in melanoma cell lines and in vivo in human cell line xenografts, patient-derived xenografts (PDX) and GEM models of melanoma. To maintain continuous drug pressure on tumor, mice are fed a diet containing the appropriate inhibitors, achieving drug concentrations in the circulation similar to those used in patients. Xenograft and GEM models have confirmed the correlative studies from patient tissues. In vivo models are ideal to assess mechanisms of resistance and point to main dependencies and vulnerabilities of melanoma cells to better develop new strategies for second-line or rescue therapy. Each type of in vivo model has advantages and weaknesses. The weakness of GEM models is their relative paucity of genetic aberrations, while human xenografts lack a typical tumor microenvironment because their immunocompromised murine hosts lack most immune cells. To overcome the latter, investigators have been working on humanizing the mice by reconstituting them with human hematopoietic stem cells that could differentiate into all blood cell lineages. Ideally, the immune cells and the tumor cells should come from the same patient. However, collecting hematopoietic stem cells from melanoma patients in sufficient numbers needed for experimental studies in mice is not feasible. A potential alternative is the generation of immune cells from patients through a series of dedifferentiation steps to obtain induced pluripotent stem cells that can then be differentiated to hematopoietic stem cells and thymic progenitor cells. Those technologies are still underdeveloped but urgently needed to better understand the role of immune cells in the tumor microenvironment for resistance against signaling inhibitors.

Preclinical → clinical development

Ultimately, any potentially transformative preclinical development needs to make it into the clinic. In the past decade, one example of this is the development of combined BRAF-targeted therapy with anti-PD-1/anti-PD-L1 (programmed death-ligand 1) therapy. The initial discovery that BRAF and/or MEK inhibition led to increased melanocytic antigen expression in vitro and in vivo, as well as increased CD8+ T cells and other pro-inflammatory changes in patient samples, led to several clinical trials of triplet BRAF/MEK/anti-PD-L1 drugs. Moving forward, a number of key factors for clinical development of promising preclinical findings need to be considered. First, each new trial needs a strong rationale from experimental models, not only cell lines but xenograft/PDX and/or GEM models and if possible patient samples. Those data need to convincingly show at least tumor stasis or optimally regression. Second, biomarkers should be developed to optimally select patients for trials based on the relative likelihood of benefit or toxicity. Third, with combination therapies gaining favor, it is becoming increasingly critical to reassess timing, sequence and dose of treatments. To achieve these ambitious objectives, it will become important for clinical and research centers to collaborate, as large-scale trials on highly selected patients are only possible when conducted in multiple centers. Optimally those multicenter trials would be supported by both pharmaceutical companies and federal

agencies, facilitating the ability to acquire requisite pre-treatment, multiple on-treatment, and post-treatment samples. Particularly, complex combination trials need extensive evaluation of both the host immune and tumor responses. New findings should be evaluated and validated in experimental models to support future planning for clinical trials. The more information we can gather from each trial, the better we can plan for subsequent trials.

RECOMMENDED READINGS (39–46)

TARGETED THERAPY RECOMMENDATIONS: Table 3

IMMUNOTHERAPY

Resistance to immune checkpoint inhibitors

Immunotherapy with checkpoint inhibitors has markedly improved and extended the lives of many patients with advanced or metastatic melanoma. While in the early 2000s median OS was 6–9 months, recent clinical trials show 3 to 5 year survival rates exceeding 50%. However, approximately 70% of patients still experience disease progression within 5 years. This includes both de novo (primary) resistance in 30–50% of patients and an additional 20–30% with progression after initial benefit (secondary resistance). Further improvements in outcomes from immunotherapy of patients with melanoma will require additional scientific, clinical and societal advances.

Clinical definitions—Immunotherapy approaches and drug development are evolving rapidly. New agents are commonly evaluated for activity in patients with melanoma who have shown primary or secondary resistance to an immune checkpoint inhibitor. However, because of unique patterns of response and the lack of consistency in the clinical definitions of what constitutes a treatment-refractory patient, the design of clinical trials of new agents and interpretation of results remains a significant challenge. To address this unmet need, the Society for Immunotherapy of Cancer convened a taskforce to generate consensus clinical definitions for resistance to immune checkpoint inhibitors in three distinct scenarios: primary (or de novo) resistance, secondary (or acquired) resistance, and resistance after therapy has been discontinued. According to the taskforce, the definition of primary resistance to a single agent requires that the patient had received adequate exposure, defined as at least 6 weeks of therapy, and developed either confirmed radiographic progression with two imaging tests at least 4 weeks apart or unequivocal clinical evidence of progression within 6 months of starting treatment and while on therapy. Secondary resistance assumes that the patient had exposure to therapy for at least 6 months, obtained initial clinical benefit (CR, partial response or stable disease for at least 6 months), and had either confirmed radiographic progression with two imaging tests at least 4 weeks apart or unequivocal clinical progression. Resistance after stopping therapy, whether after completion of adjuvant/neoadjuvant therapy, following attainment of maximal benefit or due to severe toxicity, is considered to behave similarly to either primary or secondary resistance, depending on the initial response and the length of time since the last treatment, with 12 weeks being the consensus cutoff between primary and secondary resistance. The goal of this effort was to provide guidance for clinical trial design and to support analyses of data related to mechanisms of resistance.

RECOMMENDED READING (47)

Mechanistic underpinnings—While the mechanisms for primary and secondary resistance may overlap, they could also be quite different. Understanding the mechanism of the immune response can provide a context for the development of resistance. Cytotoxic T cell responses are critical to initial tumor destruction and play a central role in preventing recurrence; however, there is increasing evidence for a role of other lymphocyte populations including B and NK cells in either enhancing or sustaining the initial immune response. Humoral immune responses to tumor antigens has improved patient outcomes coinciding with the presence of tertiary lymphoid structures within the tumor; these are examples of B cell contributions. Antibodies targeting membrane antigens can mediate antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity, which may sustain tumor cell destruction. It is still unknown whether B cells are simply surrogate markers of a productive antitumor T cell response or are contributing in a meaningful way to the elimination of residual tumor. In addition, NK cells can be activated in response to cytokines released by reinvigorated T cells following checkpoint inhibitor therapy and serve to eliminate residual tumor cells devoid of surface HLA molecule expression.

Mechanisms of primary resistance—Primary resistance can occur even in cases where T cells are present in the tumor microenvironment (“warm” tumors). The immune destruction of tumor cells may be inhibited directly by expression of non-PD-1 pathway inhibitory checkpoints (e.g., TIM-3, VISTA, LAG-3), the presence of immunosuppressive cytokines (e.g., TGFβ, IL-6), or through the recruitment of immunosuppressive cells (e.g., regulatory T cells, myeloid-derived suppressor cells, tumor-associated macrophags [type 2]). Lastly, the absence of immune cells in the tumor microenvironment (“cold” tumors) either through loss of antigen expression, lack of T cell chemokines to prevent migration to tumor sites, or active exclusion triggered by activation of WNT-β-catenin expression or loss of PTEN are all well-established causes of primary resistance.

Mechanisms of secondary resistance—Tumor cells can lose expression of target antigens (shared or neoantigens) or downregulate expression of components of the antigen-processing machinery, including HLA restriction elements. Alternatively, tumor cells may lose expression of PD-L1 via abnormal signaling through the interferon-γ pathway. While these resistance mechanisms are well accepted, the resistance mechanisms in the majority of cases remain unknown.

RECOMMENDED READINGS (48,49)

Rational combination strategies—Ideally, combination immunotherapy should involve complementary or synergistic mechanisms that increase the effectiveness of therapy without escalating adverse events. With more consistent definitions, both clinical and mechanistic, combinatorial approaches can more rationally target an appropriate mechanism of resistance.

The presence of a high frequency of tumor-infiltrating “exhausted” CD8+ T cells expressing PD-1 and CTLA-4 is highly predictive of anti-PD-1 response in patients with metastatic melanoma. However, recent research has shown that even PD-1 blockade produces only a

limited burst of T cell proliferation in many animal models. Similarly, circulating peripheral exhausted T cells were found to be only transiently reinvigorated during anti-PD-1 therapy of melanoma. Prolonging this activation through combination of an anti-PD-1 antibody with an anti-CTLA-4 antibody, a 41BB or GITR agonist antibody or cytokine stimulation to produce longer lasting metabolically competent effector cells could result in enhanced T cell survival and tumor clearance. Ipilimumab, a clinically available anti-CTLA-4 antibody, is thought to act via enhanced T cell priming, although there is data that Treg depletion or stimulation of exhausted T cells may also play a role.

Given that many melanomas lack tumor-infiltrating lymphocytes, an obvious possibility for combination immunotherapy is an inflammatory signal that attracts cDC1 or cDC2, T cells or NK cells to the tumor site and sets up an IFN-γ/IL-12 cascade. This may be achieved by approaches that include intratumoral injections of oncolytic viruses, STING, TLR7/9, as well as cytokines such as IL-12, which can polarize the tumor microenvironment in a Th1 direction.

Finally, another direction for combination immunotherapy is to generate tumor selective T cells with peptide, RNA or DNA vaccines. While cancer vaccine research has shown limited progress to date, promising new directions such as personalized neoantigen or shared antigen vaccines using existing or novel adjuvants are being actively pursued.

RECOMMENDED READINGS (50–53)

Current issues in the management of advanced melanomas

In the treatment-naïve setting, there are currently two main systemic immunotherapy options for patients with advanced unresectable melanoma: anti-PD-1 monotherapy (nivolumab, pembrolizumab), and anti-PD-1 plus anti-CTLA-4 combination therapy (nivolumab + ipilimumab). Other FDA approved immunotherapies may be reasonable in specific populations such as talimogene laherparepvec (TVEC) or TVEC coadministered with an immune checkpoint inhibitor, though the latter remains under study.

Brain metastases—Melanoma has the highest propensity of all common malignancies to metastasize to the brain, with 40% of patients expected to develop brain metastases following the diagnosis of metastatic disease and up to 70% by the time of death from the disease. Therapeutic strategies for melanoma brain metastases have been largely restricted to stereotactic radiosurgery or neurosurgical resection. Whole brain radiation therapy has shown little therapeutic benefit compared to its benefit in other malignancies.

Combination anti-CTLA-4/anti-PD-1 immunotherapy has demonstrated impressive clinical activity with objective response rates of 50–60% and median OS that has not yet been reached in up to 5 years in Phase 2/3 studies. This combination in asymptomatic patients with silent melanoma brain metastases not requiring corticosteroids produced an intracranial response rate of 55% with 29% CR. Further, the intracranial PFS rate at 9 months was 67%, far exceeding what has been observed with other therapies. However, the combination still has substantial systemic toxicities with serious adverse events in as many as 55% of patients, encouraging the pursuit of equally effective but less toxic combinations. While anti-

CTLA-4/anti-PD-1 combinations involving different doses and schedules have shown improved toxicity profiles with comparable efficacy in extracranial melanoma metastases, these less toxic regimens have not been studied in patients with melanoma brain metastases. Similar, promising novel anti-PD-1 based combinations have not yet been investigated in melanoma patients with brain metastases.

In addition, nivolumab + ipilimumab has shown much less activity in patients with symptomatic melanoma brain metastases, possibly related to the immunosuppressive effects of corticosteroids necessary to control the edema around the brain lesions. The development of alternatives to corticosteroids for controlling central nervous system edema, such as the VEGF antibody, bevacizumab, is urgently needed. Also stereotactic radiosurgery has historically improved the outcomes of patients with melanoma brain metastases and may be synergistic with immunotherapy. Efforts to determine how best to combine these two effective treatment approaches remain a high priority.

Finally, leptomeningeal disease remains a frequent site of treatment failure and source of death in patients with melanoma. Understanding whether leptomeningeal disease results from altered tumor biology or is an immune sanctuary is critical to developing effective treatment. Opportunities exist for intrathecal immunotherapy with checkpoint inhibitors alone and in combination, but such studies are complicated by the requirements for multidisciplinary involvement in the treatment, the relative rarity of the entity, patient co-morbidities and often rapid clinical decline. Lacking an effective treatment, studies to determine if immunotherapy applied in earlier stages of melanoma can prevent the development of this devastating entity will be critical.

RECOMMENDED READING (54)

Adjuvant therapy

Recent studies in adjuvant immunotherapy have changed the treatment landscape for patients with resected stage III or stage IV melanoma. Phase III studies have shown that adjuvant ipilimumab is superior to placebo in terms of OS, and that pembrolizumab is superior to placebo and nivolumab is superior to ipilimumab in terms of recurrence-free survival. More recently, a Phase II trial found that adjuvant nivolumab + ipilimumab was superior to nivolumab alone in patients with stage IV resected melanoma in terms of recurrence-free survival. Results of a Phase III trial of adjuvant nivolumab + ipilimumab vs. nivolumab alone are awaited, but the initial release of information from an analysis of low PD-L1 expressing tumors showed no significant difference between the two arms in recurrence-free survival. Ongoing Phase III trials are determining whether the benefits of nivolumab or pembrolizumab can be extended to patients with high-risk stage II disease. Also the impact of these adjuvant immune therapies on OS (essentially, the survival benefit of initiating treatment postoperatively vs. waiting and treating only those who relapse) is eagerly awaited.

Despite this progress, adjuvant treatment continues to present several unique challenges, including the unmet need for biomarkers to guide who requires treatment, treatment duration and intensity. Also, the management of recurrence after adjuvant immunotherapy is an issue

of increasing importance since the numbers of relapsing patients will grow due to the expanded use of adjuvant therapy. Finally, there is a significant financial toxicity associated with these treatments that societies will need to address in order to optimize access to such therapies.

Predictive biomarkers for improved patient selection—While several studies have highlighted candidate markers for selecting patients in need of further systemic therapy, more extensive prospective studies are necessary for rigorous validation using standard clinicopathologic prognostic factors as a comparator. In general, blood-based soluble biomarkers offer several advantages including their amenability to longitudinal monitoring and their ability to sample heterogeneous tumors without the sampling bias intrinsic to tumor tissue-based assays. However, reported blood-based soluble markers, cfDNA and plasma-derived tumor exosomes still require additional prospective validation in larger multicenter clinical trials. Ultimately, it appears likely that a combination of approaches will be required to identify patients most likely to benefit from adjuvant therapy. An improved understanding of underlying mechanisms of melanoma dormancy and reactivation could help guide further development of these markers (see above).

Prediction of immune-related adverse events—An area that is particularly relevant to adjuvant immunotherapy is the prediction of immune-related adverse events (irAEs), since the acceptable risk:benefit ratio is much lower in this clinical setting. There is a pressing need for the development of biomarkers capable of identifying those patients at higher risk for severe life-threatening toxicities such as myocarditis. There is emerging data implicating auto-antibodies, T cell-derived cytokines and neutrophil-related markers as predictive of specific irAEs in the metastatic disease setting; however, additional studies are needed to validate these data and verify that these are relevant to the adjuvant treatment setting. This process may be complicated by the diverse underlying pathogenesis of the various irAEs.

Duration of adjuvant treatment—While the current recommended adjuvant treatment duration is 1 year, additional studies are needed to more clearly define the most appropriate duration of adjuvant therapy for the individual patient in order to minimize both financial and clinical toxicity. Current adjuvant treatment approaches are for 12 months but it may be that much shorter durations will be equally effective with reduced costs and toxicity, especially those with early stage III disease where the risk of melanoma relapse is greatly reduced.

RECOMMENDED READINGS (55–57)

Neoadjuvant therapy

Traditionally, surgery has been a preferred option for patients with locoregionally advanced melanoma. However, the development of effective systemic therapies has led to clinical trials of immunotherapy or targeted therapy preceding surgery in resectable or borderline resectable patients. Recent studies showed that a single dose of anti-PD-1 produced a pathologic CR in 30% of treated patients, further supporting the idea that less than one year

of adjuvant therapy might be sufficient. In other studies, two doses of combination anti-PD-1 + anti-CTLA-4 produced pathologic CRs in up to 60% of subjects, and pathologic CR was associated with freedom from subsequent relapse without need for postoperative adjuvant therapy. Recent studies examining whether this approach could be used to limit surgery to the resection of a marked “index” node rather than a complete node dissection show encouraging early results. Studies are also exploring whether information obtained from examination of that index lymph node could be used to guide subsequent treatment choices such as additional surgery, continued adjuvant therapy or switching to a different systemic therapy. Based on this work, one can foresee the role of surgery in patients with stage III and oligometastatic stage IV melanoma shifting from an attempt at definitive treatment to obtaining information about the interplay between tumor and the immune system that can guide upfront therapy, along with salvage resection of residual, non-responding disease when necessary.

In addition, neoadjuvant therapy offers an unparalleled opportunity for interrogating tumor tissue to better define mechanisms of an effective immune response and the means of tumor escape for various therapies. As such, it is a great tool for the rational development of combination immunotherapy regimens. As early data suggest that a pathologic CR in a regional lymph node portends long-term disease-free survival, an opportunity exists for using this endpoint to identify promising combination regimens, potentially accelerating drug development by limiting the need for expensive large-scale randomized phase III trials. These advantages may be recognized by regulatory agencies and parallel the drug development pathways in other tumor types such as breast cancer.

RECOMMENDED READINGS (58–61)

Current challenges for melanoma clinical trials

Beyond basic scientific and clinical questions, there are other important clinical issues that have emerged from the success of therapy.

Financial toxicity—The financial toxicity (i.e., the personal impact of the cost of treatment borne directly by the patient) of modern melanoma therapy, especially immunotherapy, is related in large part to the duration of therapy and number of infusions administered. Currently there is insufficient information on which to base the decision of when to stop therapy in the absence of toxicity or disease progression. Many questions exist: (1) Can treatment be stopped after a radiologic CR? (2) Is a radiologic CR a reliable measure of disease disappearance? (3) Is it too restrictive or too insensitive? Clinical trials provide minimal data to shed light on these questions. Randomized trials assessing the optimal duration of therapy are difficult to perform as they require large numbers of patients to confirm equivalent treatment outcomes and have garnered little support from the pharmaceutical industry. Absent trial data, the incidence of late toxicity may influence the balance favoring more or less treatment. Furthermore, is there a better way to assess the presence of residual disease after treatment in those who display a PR or SD with standard imaging? The answer may provide further evidence for stopping treatment earlier. The potential approaches are numerous and include PET-CT scans with/without directed

biopsies, blood markers (e.g., cfDNA, exosomes), and assays for circulating tumor cells. The development of various non-invasive techniques should be prioritized and potential funding sources should be identified and engaged.

Clinical trial accrual and completion—Critically important to our capacity to further improve outcomes for patients with melanoma is the need to limit the focus of clinical trials to the major hypotheses of the day, expedite the development of these trials in multicenter studies and cooperative groups and assess treatments in the neoadjuvant setting where pathologic response may provide more rapid evidence of clinical activity of a new agent or a new combination for early FDA approval. With the current broad spectrum of approved treatments for patients with melanoma, clinical research is often viewed as less of a necessity. However, it remains essential if we are to make further advances and better select patients for specific treatments. Therefore, it is even more critical than ever to identify means to incentivize referrals of patients for such clinical trials.

Raising the OS bar further—Biomarkers in melanoma are needed to select best regimens for specific cohorts of patients, based on a single or multiple biologic markers. For those unlikely to respond we must define alternate or combination regimens ideally based on a better understanding of the underlying mechanism of immune resistance. These efforts require broad collaborations, harmonized definitions and coordinated clinical trial portfolios that utilize all existing resources of cooperative groups, pharma and academic collaborations to accelerate the pace of progress for patients with melanoma.

RECOMMENDED READINGS (62, 63)

IMMUNOTHERAPY RECOMMENDATIONS: Table 4

MELANOMA AND COVID-19

The COVID-19 pandemic created unprecedented obstacles and challenges in providing medical care to our melanoma patients. We have been forced into making decisions about surveillance visits, surgery and treatment that we have not previously considered, sometimes delaying patient care in order to protect patients, their families and our staff from contracting COVID-19. This pandemic has forced us to adapt quickly and develop alternative strategies and solutions for patient management. This experience has raised many questions and provided us with few answers. We continue to learn and evolve our care practices every day so as to provide safe, seamless and comprehensive care, despite the unknown duration of this new environment. This section details some of the changes that have been made and questions that merit future inquiry.

Screening for early melanoma

During the initial peak in the COVID-19 pandemic, non-essential workers were told to shelter in place. Most private dermatology offices were closed, so routine total body skin exams on established patients and evaluations of patients presenting with new suspicious lesions were delayed. A number of questions have now arisen as a result of these unanticipated delays: (1) What will be the impact of delayed diagnosis of a primary

melanoma? (2) Now that precautions are in place and dermatologists are back in the office, have we seen an increase in the stage at presentation of newly diagnosed patients? (3) Will a 3- to 6-month delay in diagnosis or surveillance visits have a significant impact on disease stage at presentation or ultimate outcomes?

Telemedicine was thrust into the forefront due to this outbreak. It provided a platform for safely assessing and managing a patient's most acute issues. Patients could engage their care team via the internet and often providers could remotely visualize any skin lesions of concern to the patient. In some instances, a remote assessment could allay a patient's fears until an in-person visit could be scheduled. This technology does not, however, allow for routine screening to be performed and so potentially suspicious lesions not recognized by the patient are not routinely assessed. Furthermore, it remains unclear to what degree atypical skin lesions can be accurately assessed via telemedicine so as to prioritize in-person visits. The potential for AI or machine learning to assist in the virtual evaluation of skin lesions also remains unclear at this time. Other key questions regarding the value of virtual screening efforts include: (1) Do we always need to see patients in person for follow-up visits when we are now proficient in telemedicine? (2) Is telemedicine an option for our most at risk populations as many elderly and underserved patients do not have smartphones, tablets or computers in their home? (3) How do we reach these patients remotely? (4) Can we utilize mole image analysis apps to better evaluate pigmented skin lesions via telemedicine? (5) How do we validate, improve and prioritize the various apps that are available or in development?

Surgery and neoadjuvant therapy

In many hospitals around the country, as COVID-19 numbers spiked, elective surgeries were delayed or cancelled, including cancer surgeries. Concerns about the availability of adequate personal protective equipment and the risks of transmission to hospital personnel, especially anesthesia providers, led to moratoria on surgeries even in areas where coronavirus infection rates were relatively low. Surgical committees were formed to help prioritize cases as ORs slowly reopened, with some patients waiting weeks or months for surgery based on perceived relative urgencies.

The risks of surgical delays must be weighed against the risk of a patient acquiring COVID-19 infection in the hospital or early postoperative period, and against the impact of operating on a patient with occult or active COVID-19 infection. Available data suggest a substantial risk of mortality associated with general anesthesia during active COVID-19 infection and anecdotal evidence points to an increased risk of thrombotic events in the postoperative period as well. Thus, risks and benefits of delaying surgery must consider the prevalence of COVID-19 in a specific region, the availability of non-operative or preoperative therapy and the urgency of surgical intervention. Other factors impacting decision-making regarding cancer surgery are the nature of the procedure (general anesthesia vs. local/conscious sedation), the likelihood of requiring intensive care unit care and the type of facility (general acute care hospital, free-standing cancer center, ambulatory surgery facility not attached to a hospital).

The widespread delays in scheduling surgery for patients with melanoma forced many oncologists to consider neoadjuvant therapy for patients with advanced stage tumors (resectable clinical stage III and IV disease). However, this in turn led to the question of which neoadjuvant therapies could be safely administered without putting patients at increased risk of infections or other complications that would require them to seek urgent medical evaluation. Many patients did not want to leave their homes and most oncologists were concerned about administering immunotherapy without regular follow-up. A major concern surrounding neoadjuvant immunotherapy was the unknown and possible severe consequences of concomitant pneumonitis and COVID-19. Fortunately, additional studies have suggested that immunotherapy does not dramatically increase the risk for severe complications of COVID-19; thus, neoadjuvant immunotherapy may be considered as a valid option for patients, even in the COVID-19 era.

As a therapeutic modality without clear immunosuppressive or stimulatory properties, BRAF-targeted therapy was viewed as an acceptable alternative therapeutic approach even in the context of a concurrent COVID-19 infection (albeit in the absence of data). However, BRAF/MEK inhibitor therapy is known to be induce pyrexia and chills, which would complicate triaging of patients when evaluating for possible symptomatic SARS CoV-2 infection. Specific BRAF/MEK inhibitor combinations have different rates of pyrexia and chills, so choosing a regimen with a low incidence of pyrexia such as encorafenib plus binimetinib made sense despite the absence of data for that combination in the neoadjuvant setting.

Another concern with neoadjuvant therapy is uncertainty about the duration of preoperative treatment required. Virtually all melanoma neoadjuvant therapy clinical trials reported to date have utilized a relatively short duration of preoperative systemic therapy with surgery scheduled soon after the last dose of drug. While some single-institution experience had suggested that six months or more of preoperative treatment was feasible and safe, there was substantial concern that such prolonged preoperative treatment might compromise resectability. Broader experience has now shown that this fear was overblown, and prolonged preoperative treatment can allow patients the flexibility to wait until surgery could be scheduled in a safe environment.

So what have we learned and what questions remain? Although neoadjuvant therapy research is ongoing to assess its true value, this approach is likely here to stay. In the current era, we must carefully integrate the risks and benefits of surgery and neoadjuvant therapy against the risks of COVID-19 when making decisions about deferring surgery. Questions still remain about the best preoperative therapy for patients with BRAF mutant melanoma, and what postoperative treatment should be delivered to patients who have a pathologic CR. But surgeons and oncologists should feel reassured that neoadjuvant therapy is a safe option and that preoperative treatment can continue for several months or longer if necessary.

Adjuvant therapy and treatment for unresectable metastatic melanoma

Adjuvant therapy—Most oncologists advocate for starting adjuvant therapy for high-risk melanoma within ninety days of surgery based on the pivotal trial designs. However, during times of high COVID-19 prevalence, adjuvant therapy may be deferred beyond 90 days post-

surgery to minimize the risk to the patient and to resource challenged healthcare systems. The availability of longer interval regimens for nivolumab (4 weeks) and pembrolizumab (6 weeks) has eased some of these concerns for both patients contemplating and in the midst of adjuvant therapy. Also, arguments for use of BRAF targeted therapy vs. immunotherapy in patients with BRAF mutant disease have been further accentuated by pandemic-related considerations of their distinct toxicity profiles and risks of hospital exposure. It is unknown how these delays in the initiation of therapy, changes in preferred treatment approaches, skipping doses of immunotherapy or skipping adjuvant therapy altogether will impact patient outcomes.

Metastatic disease therapy—It is also unclear how the pandemic has altered the therapeutic management of patients with metastatic melanoma. Here we list some pointed examples: (1) Are patients being treated more frequently with anti-PD-1 monotherapy rather than in combination with anti-CTLA-4 due to concerns about the increased toxicity? (2) Have oncologists migrated to longer intervals between anti-PD-1 treatments, such as the pembrolizumab Q6 week regimen? (3) Are patients with BRAF mutant melanoma treated more frequently with oral BRAF-targeted therapy to minimize visits to the cancer clinic or hospital infusion center? (4) How has telemedicine been used to assess treatment-related toxicities and minimize visits to the clinic? (5) What other avenues are being used to minimize clinic visits, such as using local laboratories for blood draws instead of the hospital or clinic? (6) Are patients being tested for COVID-19 before initiating therapy, and should asymptomatic patients be retested while on therapy? (7) If patients test positive for COVID-19, how is a decision made to resume therapy? (8) How long are oncologists and patients willing to wait to resume treatment? (9) When offices are reopened, to what extent are patient volumes restricted compared to pre-pandemic, and how have waiting rooms been reconfigured to support social/physical distancing?

Clinical trials

COVID-19 has had a dramatic impact on clinical trial conduct. Given patients' decreased willingness to come to clinics for scheduled visits and risk exposure, some trials have granted waivers for certain requirements such as biopsies and other procedures. Many trials have also permitted use of telemedicine visits or obtaining certain tests at facilities close to home instead of at the study site. For example, the National Cancer Institute (NCI) released a memorandum on guidance for their clinical trials affected by COVID-19, such as detailing what may constitute a minor deviation with regards to missed visits or biopsies (https://ctep.cancer.gov/investigatorResources/corona_virus_guidance.htm).

Increased allowance of telemedicine visits and off-site testing, if they remain an option in clinical trials in the post-COVID-19 era, may actually improve access and accrual to clinical trials. Many patients need to travel long distances to participate in clinical trials, which inevitably creates barriers to enrollment for patients who would otherwise be eligible and willing to participate. This can also lead to disparities in trial access, with patients who have the financial means and resources to take time off work and afford long travel better able to enroll in trials. The pandemic experience may support the paring down or making optional tests that are not critical for the study conduct and other measures such as enabling an

electronic and remote consent processes, mailing oral study medications or study kits to patients and utilizing closer off-site facilities for certain trial tests, exams or treatments that may provide long-lasting benefit in clinical trial access for our patients.

Unanswered questions remain, including: (1) What will be the long-term impact of the pandemic on collection of research-related tumor biopsies and blood on clinical research? (2) Will there be any long-term impact for patients previously infected with COVID on their immune system and ability to respond to immune checkpoint inhibitors? (3) Will suspension of clinical trials at many institutions hinder accrual momentum? (4) Will data supporting major clinical breakthroughs be delayed or compromised substantially due to the pandemic? (5) How will NCI-designated cancer centers in hard-hit areas be impacted when they apply for renewal of their Cancer Center Support Grant?

Biology/therapy

No vaccine for melanoma has been approved despite decades of research. The development of vaccines to SARS-CoV-2 has accelerated our knowledge of therapeutic vaccine development. COVID-19 vaccine development has enabled the comparison of vaccines developed by various approaches, such as CanSino (adenovirus AD5 vector), Oxford (adenovirus vector), Moderna and BioNTech/Pfizer (mRNA vector), Innovio (DNA electroporation), OncoSec (DNA electroporation +IL-12), as well as via peptides (Novavax), for generation of humoral and T cell responses directed against the SARS-CoV-2 spike protein. This knowledge may translate into the development of novel vaccines in melanoma and other cancers.

Cytokine release syndrome (CRS) can be a serious consequence of cytokine and checkpoint inhibitor immunotherapy for patients with melanoma and other cancers. CRS results in acute respiratory distress syndrome (ARDS) and occurs when the body mounts an extreme immune response, either due to enhanced activation by cancer immunotherapy or due to a superimposed viral infection. One of the key complications in patients during the current COVID-19 pandemic is a form of ARDS. Therefore, lessons previously learned in melanoma may inform treatment of COVID-19 and vice versa. Drugs targeted against cytokines or their production are currently in trials for both cancer and COVID-19. For example, catecholamines can increase cytokine (specifically IL-6) production by signaling through the alpha-1 adrenergic receptor (a1-AR). By targeting various steps and molecules in this process, researchers hope to overcome the initial steps of CRS. Prazosin is an a1-AR antagonist used to treat hypertension. A retrospective analysis of non-COVID-19 patients with ARDS on prazosin demonstrated that these patients had lower rates of requiring ventilator support. Efforts to move this drug into clinical trials for COVID-19 are underway. Another drug, tocilizumab, which inhibits IL-6 (one of the key cytokines involved in ARDS and which has been used to overcome CRS observed with CAR-T therapy), is also under investigation in COVID-19 patients. So far, limited results demonstrating safety and efficacy of this drug in COVID-19 patients have been published and several trials are underway, but off-protocol use of this drug has been widespread in some hospitals. Dexamethasone, commonly used for CRS-associated reactions, has proven to be an effective therapy for the inflammatory pneumonitis induced by COVID-19. Acalabrutinib, a BTK inhibitor, and

ruxolitinib, a JAK/Stat inhibitor, have also shown the ability to reduce CRS, prompting clinical trials in patients with COVID-19 with some early promising results. Finally, mesenchymal stem cells, which can be derived from the bone marrow, umbilical cord and placenta, are in clinical trials for the management of ARDS; however, their potency is unclear.

What have we learned? Just as we have applied lessons from treating CRS in patients receiving immunotherapy for melanoma and other cancers to managing complications in patients with COVID-19, we may learn from COVID-19 management how to better manage CRS in patients receiving cancer immunotherapy. We also hope to determine whether checkpoint blockade should be halted or discontinued in the event of acquiring a COVID-19 infection.

Psychosocial impact

COVID-19 has forced our patients to significantly curb the social interactions in their daily lives and has forced many patients into home confinement. This isolation has greatly increased their feelings of depression and hopelessness. If they do come into the oncology clinic, they are often not allowed to bring a visitor due to exposure risks. Having difficult discussions regarding disease progression or end-of-life issues with a patient who has no family or friends for support can cause extra psychological trauma and confusion for the patient and is often heart-wrenching for the care team. In addition, faces, which are the most expressive part of our bodies, are now covered by masks for both patients and caregivers. There are no smiles to be shared. No hugs for comfort or encouragement. Often, there are no social workers physically present to be able to come speak with someone in need.

In these instances, telemedicine has emerged as a life-saving measure. Patients can connect virtually with either a social worker or psychiatrist and meet face to face without masks and in the privacy of their own homes. They are able to make a personal connection, albeit virtually. A comprehensive review of telemedicine and quality of life in cancer patients demonstrated that a virtual connection was just as effective as an in person visit on cancer patient’s quality of life. But the most horrible impact of COVID-19 may well be on the terminally ill, including those with non-COVID illnesses such as advanced melanoma, in that they often die alone. Dying with your loved ones only allowed on a video screen is a previously unthinkable scenario and causes unfathomable grief.

Finally, the psychosocial impact of the pandemic on healthcare workers cannot be overlooked. Many physicians, including medical oncologists, have been pulled from regular duties and assigned clinical responsibilities in COVID-19 wards. By all accounts, the impact of dealing with this pandemic has been a huge psychological drain, and often physicians and nurses were the ones holding the aforementioned video screens or being the conduit of daily information from the patient to their family or friends. In addition, physicians and other healthcare workers tried to minimize and manage the risks posed to themselves and their families, and some watched in horror as their own colleagues succumbed to this disease. Younger physician-scientists also appropriately worry about the impact to their careers. Helping our colleagues to find avenues to regain lost time and funding in the research realm is imperative. Finally, acknowledging the stress and anxiety this pandemic has had on the

melanoma community, both patients and their healthcare team, is a first step in trying to achieve a critical balance of providing care while keeping safety an utmost priority.

RECOMMENDED READINGS (64–68)

KEY AREAS FOR FUTURE STUDY AS A CONSEQUENCE OF THE COVID-19 PANDEMIC: Table 5

CONCLUSIONS/THE PATH FORWARD

Our understanding of the biology and our success in managing melanoma has progressed greatly over the past half decade, with as many as 50% of patients with stage IV disease being anticipated to be long term survivors and up to half of those patients with high-risk stage III disease who were once destined to progress to stage IV disease being prevented from disease relapse. Simultaneous progress has been made in primary and secondary prevention with new technologies for melanoma detection and new policies for sun and ultraviolet light protection. This progress has been manifest by the remarkable overall decline in annual mortality in the US from melanoma.

However, such progress has created new disease states (e.g., immunotherapy and targeted therapy resistant disease), raised new questions, and exposed new challenges and opportunities for further research in order to continue this progress. Further, the recent pandemic has created new challenges to the dermatologist and medical and surgical oncologist alike, while it has also accelerated the development of novel technologies for melanoma detection and the relaxation of clinical trial procedures that may pay dividends in broadening the reach of melanoma research. Yet at the same time, the pandemic is putting further strains on both patients and caregivers and the careers of young investigators entering this field.

This updated MRF-sponsored State of the Science report highlights the many new questions, challenges and opportunities across the melanoma spectrum. We anticipate that over the next 5 years significant advances will be made in: non-invasive imaging complemented by artificial intelligence; our understanding of clinical dormancy and how to exploit it for better patient outcomes; developing rationally-based combinations of immune- and non-immune-based drugs and more sophisticated biomarkers to help determine the optimal combination and sequence for individual patients; the development of more representative animal models of melanoma that will better inform clinical trial designs; and learning how to combat metastatic melanoma at challenging sites such as the brain and leptomeninges. In this report we offer a roadmap for how research might proceed in order to sustain progress and ultimately reach our goal of preventing mortality and limiting morbidity from melanoma.

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Table 1

Prevention and Early Detection Recommendations

1	Improve understanding of the role of vitamin D deficiency as well as various behavioral diagnoses (addictions, affective disorders, etc.) that may be associated with sun-seeking behavior.
2	Carry out long-term safety studies on sunscreen in a multidisciplinary fashion with representatives from dermatology, pharmacology, toxicology, public health, and behavioral science.
3	Encourage FDA to accelerate investigation and incorporation of superior UV filters from abroad, based on their worldwide safety and efficacy data.
4	Encourage public health messaging to include promotion of sunscreen use as part of other sun protective behaviors, including sun avoidance at peak UV times and use of sun protective clothing, hats, and eyewear.
5	Preferentially target early detection strategies to the populations at highest risk for fatal melanoma (e.g., middle-aged and older white men, and individuals of lower socioeconomic status).
6	Coordinate approaches to educate stakeholders on the dangers of UV radiation overexposure in support of legislative initiatives to restrict indoor tanning by minors at the state and national levels.
7	Develop and adopt a safe and effective oral chemopreventive drug as an alternative to sunscreens.
8	Create and facilitate cooperative international cohorts of individuals with germline mutations associated with melanoma risk to improve knowledge of phenotype, risk, and response to melanoma therapy.
9	Secure funding for dissemination and implementation science to assure that progress is made through cooperation across the entire spectrum of stakeholders including patients and patient advocates, primary care and melanoma specialists, laboratory scientists, public health and population scientists, and engineers.
10	Create standardized and secure imaging documentation, which represents a powerful opportunity to enhance serial skin self-examination and facilitate objective and accurate skin cancer screening by medical providers.
11	Require all AI platforms to perform prospective clinical testing and randomized controlled trials to assess their diagnostic capabilities vs. that of the health provider, and to demonstrate improved sensitivity, specificity and cost effectiveness before becoming part of routine clinical practice.
12	Promote the automated diagnosis of melanoma through effective integration of prospectively validated non-invasive diagnostic devices, including AI and augmented intelligence platforms, which will be paradigm-changing and may greatly enhance primary care-based diagnoses and prioritize patient referrals to dermatologists in rural areas with specialist shortage.
13	Promote the development, documentation, and implementation of formal survivorship plans for individuals treated with curative intent, which represents a critical approach to decrease associated morbidity and improve patient quality of life.

Table 2

Dormancy/Metastasis Recommendations

1	Develop more physiological animal models that recapitulate the complex and dynamic nature of human melanoma cells and their microenvironment, including, but not limited, to the stroma, the vasculature and the immune system.
2	Develop experimental systems that allow for systemic non-invasive imaging of tumor cell dormancy and awakening and define to what extent tumor cell fate is determined by anatomical location, aging and risk factors such as UV exposure.
3	Use cutting edge genomic and mechanistic analyses to dissect the underlying basis of the plasticity of human melanomas, namely “cellular states” that may be distinct in naïve vs. treated patients, particularly following neoadjuvant or adjuvant therapy.
4	Assess long-pending questions of tumor cell tropism and the competency for metastasis, with a focus on mechanisms that distinguish brain vs. extracranial metastases.
5	Place more emphasis on the study of non-cutaneous forms of melanoma (i.e., ocular and mucosal), which are lagging behind in the characterization of dormancy vs. awakening indicators.
6	Incorporate clinical biopsies at the time of surgery beyond the primary tumor to help inform about (pre)metastatic niches, including bone marrow and not just conventional sentinel lymph nodes.
7	Develop more sensitive imaging tools for the detection of micrometastases in tissues and disseminated cells in liquid biopsies.
8	Determine what and when to collect specimens for analyses in patients who have remained asymptomatic for years or after undergoing long-term treatment.
9	Employ liquid biopsies that follow tumor-associated material (e.g., cfDNA, exosomes), and also secreted factors whose accumulation accompanies, or ideally, precedes tumor cell awakening.
10	Encourage collaborative groups to integrate animal modelers and cell biologists with clinical experts and researchers in other fields to better address minimal residual disease and its reactivation in vivo.
11	Develop genetic and non-genetic mechanisms of adaptation, which ultimately may lead to hyper-progression with cross-resistance to targeted and immune-based therapies.

Table 3

Targeted Therapy Recommendations

1	Optimize targeted therapies in mutant BRAF melanoma patients using combinations of BRAF and MEK inhibitors by: comparing the currently available drugs; assessing the timepoint when to safely terminate treatment in long-term responders; treating biologically early primary melanomas in the adjuvant and neoadjuvant settings; combining BRAF and MEK inhibitors with other signaling inhibitors for maximal killing of (all) malignant cells.
2	Optimize combinations of targeted therapy with anti-PD-1 immune therapy, including sequence, dose and combination.
3	Develop 2nd- and 3rd-line therapies for patients with acquired resistance to BRAF/MEK inhibitors.
4	Develop strategies for rapid assessment of resistance to more specifically target drivers of resistance through more extensive collection of tissues from pre-, on-, and post-therapy samples.
5	Develop new approaches to target additional drivers in cutaneous (non-acral and acral) melanoma including NRAS, CDK4/6, PI3K/AKT, MDM2/P53, IDH1, KIT and NTRK fusions, or in ocular melanoma RhoGTPase, BET, and YAP.
6	Determine how heterogeneity can be overcome for therapy by assessing the extend of heterogeneity in tumors pre-, on-, and post-therapy through single cell RNA and protein expression analyses; these studies should also be done in combination with immune therapy and, under experimental settings, with barcoded tumors to better understand how diverse our treatment strategies have to be to target all ‘persisters’.
7	Develop in immune competent mice with either murine or human immune cells new models of resistance to better understand the role of immune cells in resistance to targeted therapies and to better overcome resistance to both types of therapies.
8	Create research collaborations for clinical trials of targeted therapy approaches that might only apply to a minority of patients.
9	Encourage participation in Combo-MATCH Precision Medicine Cancer Trials at NCI, which may help to accelerate access to patients.

Table 4

Immunotherapy Recommendations

1	Promote research to better understand and further define the mechanisms of primary and secondary resistance to combination drug development and rational clinical study design.
2	Identify the optimal means of turning cold tumors into hot tumors.
3	Identify steroid sparing approaches for treating patients with symptomatic brain metastases and/or LMD.
4	Explore the merits of extending adjuvant anti-PD1 therapy into earlier stages of disease (e.g., Stage IIB and IIC).
5	Develop biomarkers to identify patients with high risk melanoma who are at risk of relapse, have disease that is sensitive to immunotherapy, and/or at risk of serious immune-related adverse events (e.g., DM or myocarditis) to improve the therapeutic index of adjuvant therapy.
6	Define the future role of surgery in patients receiving IO therapy by identifying mechanisms of immune escape to guide systemic IO therapy and then potential salvage resection of isolated residual non-responsive disease.
7	Determine the optimal length of IO therapy in the metastatic and adjuvant setting and identifying non-invasive markers to guide treatment cessation in order to minimize clinical, personal/emotional and financial toxicity.
8	Optimize the use of the neoadjuvant approach to guide combination therapy development and early identification of resistant disease requiring alternative therapy.
9	Develop immunotherapy strategies for treating melanoma patients with prior immune-related adverse events associated with prior immunotherapy or pre-existing autoimmune disease.
10	Create clinical research collaborations and incentives to sustain clinical trial accrual to facilitate continued improvements in outcomes for patients with melanoma.

Table 5

Key Areas for Future Study as a Consequence of the COVID-19 Pandemic

1	Determine how to maximize the utility of telemedicine for routine follow up visits and skin exams.
2	Determine how AI can be employed to better assess atypical moles during a telemedicine visit.
3	Define which patients are the best candidates for neoadjuvant therapy, which are the most effective neoadjuvant therapies (especially for patients with BRAF mutant tumors), and how long treatment can be safely extended prior to surgery; identify potential situations where surgery could be avoided altogether.
4	Develop approaches to utilize telemedicine to effectively monitor and assess IO/targeted therapy toxicity.
5	Determine when therapy can be resumed after SARS CoV-2 infection.
6	Assess if the delay in clinical trial enrollment or the omission of certain research procedures will affect the approval of effective therapies.
7	Explore whether our experiences during the pandemic can lead to changes in trial design and conduct that facilitates accrual of underserved populations.
8	Assess if CRS management can be streamlined based on the COVID experience.
9	Evaluate the long-term psychological impact of the COVID distancing requirements on patients, families and practitioners.
10	Assess if there are long-term consequences of COVID infection on the immune system that may influence the response of future patients to immune checkpoint inhibitors.