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ASCO 2018: It's Personal

Expanding the Reach of Precision Medicine

For the third year in a row, I attended the annual meeting of the American Society of Clinical Oncology (ASCO), and for the second straight year we are dedicating an issue of *The Melanoma Letter* to what emerged as the most important trends in state-of-the-art medical practice and the most promising research into the prevention, detection and treatment of melanoma and other skin cancers. As a service for the busy medical professionals reading this, I have distilled what I think are the dozen most important developments from the many sessions I attended. The first two have to do with the conference itself and medical practice in general, then we touch on prevention, detection/diagnosis and treatment in turn.

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"CURE" IS NO LONGER A DIRTY WORD

Skin cancer specialists have always been guarded about their aims, speaking of their desire to give advanced patients more time to live and improve their remaining time. Now, they admit wanting it all for patients: full-blown cure and a normal life after cancer. "We are, in fact, curing patients right now…including those with metastatic cancer," said Norman E. Sharpless, MD, director of the National Cancer Institute, at the opening session. "Thanks to decades of progress in cancer science, now we have hope, we have options and, sometimes, we even have cures."

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IT'S PERSONAL

The key to achieving cures is increasing precision and personalization — treating patients as entire individuals, with their own genetic markers, tumor burdens, mutational status, life situations and psychology. Personalization was the watchword of this, the 54th annual meeting of ASCO, embodied in its theme, "Delivering Discoveries: Expanding the Reach of Precision Medicine." Physicians are fine-tuning strategies to the individual in multiple ways. Increasingly, they are seeking "big data" — more and better information from every useful venue, including interventional sources such as clinical trials and noninterventional sources ranging from registries, observational studies and patient self-reports to genetic and molecular test results. Every actionable bit of info like this can help patients live better and longer.

Next-Generation Sequencing (NGS)

One avenue to personalization is **next-generation genetic sequencing (NGS),** a contemporary form of high throughput DNA profiling that helps find somatically mutated genes to target treatments against.

Last year, the FDA approved the first NGS diagnostic test, the FoundationOne CDx, a "broad companion" test that detects genetic mutations in 324 genes and two genomic signatures in any solid tumor type, including melanoma. Every test result also

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shows MSI (microsatellite instability, the predisposition to mutation that results from impaired, abnormally functioning DNA mismatch repair) and TMB (tumor mutational burden, the number of mutations within a tumor genome, which many scientists now consider a marker for response to immunotherapy). Since the status of PD-L1 (programmed death-ligament 1), an immune checkpoint ligand, is also being widely investigated as a marker of immunotherapy responsiveness, PD-L1 immunohistochemistry testing can be ordered with the test.

Since FoundationOne CDX was approved, the Centers for Medicare & Medicaid Services has begun covering NGS-based diagnostic laboratory tests for patients with advanced cancer, and several other NGS tests have been developed.

Metastatic cancer patients who undergo molecular profiling can benefit in three ways: They could test positive for a rare but targetable mutation. The test could find markers of genetic syndromes or microsatellite instability to target. And the patient's profile might reveal therapies that *won't* work, so another course of therapy could start immediately, without wasting time and money.

Recently, the PD-1 immune checkpoint inhibitor pembrolizumab (Keytruda) was approved for treating every solid tumor that has mismatch repair or high microsatellite instability. NGS tests could help target intervention for any of these tumor types, since they are accurate screens for microsatellite instability.

However, only a small percentage of patients will have useful findings on NGS, and much remains to learn about who and when to test, as well as how to interpret findings. With new tests rapidly appearing and evolving, and no centralized overseeing body or standards, judging the various tests is difficult, noted Leonard B. Saltz, MD, Memorial Sloan Kettering Cancer Center. "It's easy for patients and families to build up expectations that far exceed what we can realistically hope to deliver yet," he concluded.

Reference:

Kuderer NM, Burton AK, Blau S, et al. Comparison of 2 commercially available next-generation sequencing platforms in oncology. *JAMA Oncol* 2017; 3(7): 996-998.

Finding Biomarkers

Hunting for **treatment biomarkers** that reveal which patients will benefit most from which treatments is another important aspect of personalization. Biomarkers can also often show treatment response, helping physicians know whether to stay with a treatment or switch.

To date, the targeted therapies have the most reliable marker: Melanoma patients who have the mutant BRAF gene are the only ones who can benefit from BRAF-targeted therapy. Patients with nonmutated, wild-type BRAF can't opt for it.

Immunotherapists are looking for much more precise markers. Today, even with the most successful checkpoint blockade therapies, at least 40 percent derive no benefits. While an unsuccessful treatment is tried, the cancer is advancing, and subsequent treatments are often less successful than if they were used initially. The perfect marker would allow starting with the ideal treatment.

Unfortunately, no validated predictive marker yet exists for melanoma. Overexpression of PD-L1, now a target of several immunotherapies, is recognized as the most common biomarker predicting patient response to anti-PD-1/PD-L1 therapy, and there are now four different commercial tests for PD-L1. However, not enough data exist to establish it as a truly predictive biomarker, and there's no consensus on how to use it: Patients with low or no expression of PD-L1 often benefit from anti-PD-L1 therapy as well as those who overexpress it.

Three other pretreatment markers being investigated are obesity, LDH (lactate dehydrogenase) and tumor burden. In general, nonobese patients with normal LDH and low-volume disease have better outcomes. However, this is true across

treatments and not necessarily predictive of a specific treatment's success.

While tumor burden is a negative treatment factor, tumor *mutational* burden, or TMB, may be a biomarker for success. A poster presentation at ASCO found that a strong immune checkpoint activating mutation (ICAM) exists in melanoma, identifiable through clinical sequencing assays. Tumors with a high mutational burden (ICAM-positive patients) are significantly more likely to respond to immune checkpoint therapy than ICAM-negative patients. Patients with fewer than 125 mutations showed significantly worse survival. Once refined and validated in prospective trials, ICAM threshold may be a useful biomarker of response to checkpoint blockade therapy that can prioritize patients likely to benefit.

Jennifer A. Wargo, MD, MMedSc, MD Anderson Cancer Center, said that while we don't yet have reliable pretreatment biomarkers to predict treatment response, we have useful markers to monitor response *during* treatment. Dr. Wargo described preclinical work that helped determine potential biomarkers of response in 53 melanoma patients who received ipilimumab. While initial pretreatment biopsies did not predict treatment response, the immune signatures in the biopsies obtained during treatment proved highly predictive of success or failure, helping to shape subsequent treatment. "These early-on treatment biomarkers can be valuable predictors until we learn to better identify pretreatment biomarkers," she said.

Dr. Wargo is investigating the gut microbiome as a potential biomarker, since studies suggest it affects patients' response to immunotherapy. She and her team collected oral and gut microbiome samples, both before and after patients had been treated with checkpoint blockade therapy. Microbiome sequencing and immune profiling found that patients who responded to anti-PD-1 therapy and had extended progression-free survival had much greater diversity of gut bacteria. Fecal samples from the patients then produced comparable results in rodents. A multidisciplinary team is now launching a clinical trial to study how treatment modifications affect the gut microbiome and whether fecal transplants can elicit better therapy response.

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Reference:

Cadley J, Simpson D, Ferguson R, et al. Mutation burden in conjunction with MAPK-pathway mutation status as a prognostic biomarker of overall melanoma survival. *J Clin Oncol* 2018; 36: (suppl; abstr 9584).

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ALL IN THE FAMILY

The United States Preventive Services Task Force has withheld recommending generalized total-body screening for skin cancer. Meanwhile, researchers are homing in on individuals and families at high risk of skin cancer who should be carefully screened for genetic mutation strains.

Skin cancer patients can help their families by convincing them to be tested for **germline (hereditary) mutations** that predispose them to skin cancer. These are gene changes in reproductive (germ) cells that get passed on, becoming incorporated into the DNA of every cell in the offspring's body. Knowing that the family has such a mutation can redouble the need for prevention and surveillance in at-risk individuals, improving their long-term survival chances.

"The goal of a commercial hereditary panel is to predict functional changes correlated with disease risk," noted Bryan P. Schneider, MD, Indiana University Melvin and Ben Simon Cancer Center. "Commercial laboratories have access to huge cohorts of families with and without disease, which allows for elegant segregation studies."

Somatic mutations, in contrast with germline mutations, are DNA alterations that occur *after* conception, such as those caused by ultraviolet radiation. Somatic mutations in the BRAF gene, for example, can occur anywhere in the body *except* the germ cells, thus cannot be passed on. These alterations can cause cancer or other diseases.

Oncologists now often advise patients with advanced cancers to get next-generation sequencing to identify somatic

"It's not your fault whether you have a germline mutation or not, and by not telling your family, you're leaving them at risk of a preventable disease."

mutations as potential drug targets, and these tests may uncover germline mutations as well. Unlike the somatic mutations, inherited ones cannot be targeted for treatment and can't help the patient. However, if a potential germline mutation is suspected, the patient can submit to germline testing, giving his/her family the gift of foreknowledge if genes are found predisposing to skin cancer.

Charité N. Ricker, MS, LGC, cancer genetics counselor, University of Southern California Keck School of Medicine, explained that obtaining consent for germline testing often requires extensive conversations. "Our discussion ranges from what genes to test, to what results can come from these analyses, to what the implications are if the test proves informative — the psychological impact on family members and what our preventive interventions can be."

Sometimes, when patients realize they have a germline cancer mutation, they don't want to burden their families with this knowledge, or feel tremendous guilt and are ashamed to tell them. "I explain, 'It's not your fault whether you have a germline mutation or not, and by not telling your family, you're leaving them at risk of a preventable disease.'"

Obviously, not all situations call for germline testing, and physicians have to use their clinical judgment. Some, in fact, consider germline testing unnecessary because high skin cancer risk factors, including familial skin cancer history, are usually obvious. But Dr. Ricker believes that genetic testing has been underutilized.

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BETTER BIOPSIES?

A profound goal for next-generation cancer diagnostics is learning earlier, fuller information about a patient's tumor through less invasive options. New strategies for tumor diagnosis are being explored, from liquid biopsy and breath biopsy to stool, urine and saliva tests.

"Tissue biopsy is invasive, and you have to be careful with it," said Patrick C. Ma, MD, West Virginia University Cancer Institute, at ASCO. "Even some primary tumors aren't that accessible." The primary tumor, he explained, is where you get your best, first chance to look at the tumor's "heterogeneity and evolution," how it's growing and what cancer cells it contains, all of which lead to different therapy responses. The more ways you can look at the primary tumor without causing destruction, the better. Tissue biopsy captures the tumor's evolution only up to when it's removed, and there's only so much testing you can do before there's inadequate tissue left to study.

In contrast, a relatively noninvasive molecular profiling test like liquid biopsy, from a simple blood draw, can be repeated without tissue destruction. (Several companies have liquid biopsies in the pipeline toward FDA approval that include solid tumors such as melanoma.) Thus, it can follow the natural course of the evolving tumor and how it reacts to therapy. You can also identify rare driver mutations or lack thereof, leading you to potentially effective drugs or to cancel ineffective ones, perhaps turning to a clinical trial.

With that increased precision, you can "ride out a targeted therapy until resistance is fully active," getting the fullest value of the therapy before switching to another.

These new comprehensive molecular profiling methods are also excellent at identifying sources of treatment resistance. Today, physicians seek answers to why cancers resist certain therapies from the start in certain patients, why resistance usually kicks in sooner or later and how to overcome it. "It's valuable to know, say, that if you are variant 7-negative, you will do well and continue responding to AR-targeted therapies, while if you are variant 7-positive, you will do poorly," said Peter Kuhn, PhD, University of Southern California. Gaining this knowledge has been made possible by the movement "away from bulk analysis over to single-cell analysis" of genes and proteins. With that increased precision, you can "ride out a targeted therapy until resistance is fully active," getting the fullest value of the therapy before switching to another.

Liquid biopsy is the furthest along of the non-tissue strategies, yet just one new part of the larger picture. "It is adding to the clinical context for the patient, but not meant to replace anything," said Dr. Kuhn. "For the full picture, the single cell work has to connect with the bulk work. It has to connect with the imaging data and the clinical data."

The heyday for these nontissue methods is in the future. We are still exploring what cancers they can prove most useful for, and tissue biopsy remains the gold standard. But as Dr. Ma put it, "the goalpost is moving, and every year there are more clinical applications and validations in this area."

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SLNB USE GAINS, CLND USE FADES

Two major studies on sentinel lymph node biopsy (SLNB) and completion lymph node dissection (CLND) have confirmed the overall survival (OS) value of the former in some patients and negated the OS benefits of the latter. Some ASCO presenters said flatly, "The CLND era is over." In reality, it's more complex than that, but based on those studies and modifications in the new eighth edition of the American Joint Committee on Cancer (AJCC) melanoma

staging guidelines, decision-making about when to use SLNB and CLND has changed.

CLND

It had been standard to perform SLNB for stage II melanomas at high risk of spreading to the regional lymph nodes, in the belief that metastases show up first in the sentinel nodes. If no metastases were found, the rest of the regional nodes were spared and the patient remained stage II. If mets *were* found, the patient was upstaged to stage III and CLND was performed, 1) to increase staging accuracy and aid in clinical decision-making; 2) to help prevent regional recurrence and reduce the risk of developing distant mets; and 3) to improve melanoma-specific survival (MSS) and OS compared with simple observation.

However, two multicenter randomized controlled trials (the 2016 German DeCOG-SLT trial and the long-awaited 2017 Multicenter Sentinel Lymphadenectomy Trial-II, or MSLT-II) proved to be "practice changing" for CLND. Neither trial demonstrated improved MSS or OS for patients with a positive SLNB who underwent immediate CLND, compared to those who merely underwent post-SLNB observation (the latter going on to CLND only if later examination with ultrasound found metastatic *nonsentinel* nodes).

Though the studies pointed to certain benefits, including a slightly higher disease-free survival rate and regional disease control rate, none of this increased OS. Joshua Mammen, MD, PhD, University of Kansas, explained that when you perform CLND, you usually find that only the sentinel nodes were cancerous. Thus, you're disfiguring the patient and risking serious complications like lymphedema with no overall survival benefit. The sentinel node biopsy would have been sufficient.

The rationale for CLND was a hypothetical orderly progression of skin cancer starting with the primary tumor and passing through the lymph nodes, with lymph as the incubator that sends metastases on to distant body parts and organs. If you interrupted that progression at the lymph nodes, you might stop melanoma from passing to distant sites. But it turns out that melanoma and other cancers sometimes jump from the primary to the lymph node basin and distant sites simultaneously. When that happens, CLND has no survival benefit.

Based on the new findings, automatic CLND is no longer the protocol after a positive sentinel node biopsy. "CLND and careful observation with ultrasound will now both be options for patients with low-risk micrometastatic disease," said Mark Faries, MD, John Wayne Cancer Institute, lead author of MSLT-II. "CLND can provide significant staging information beyond SLNB, but its downsides, including risk of lymphedema, may lead some patients to elect observation, while potentially having nonsentinel nodal mets might tip the scales for other patients toward additional treatment. CLND should be discussed and offered, depending upon the probability of non-SLN metastases, the morbidity of the procedure and the staging value of CLND on adjuvant systemic therapy or clinical trial enrollment."

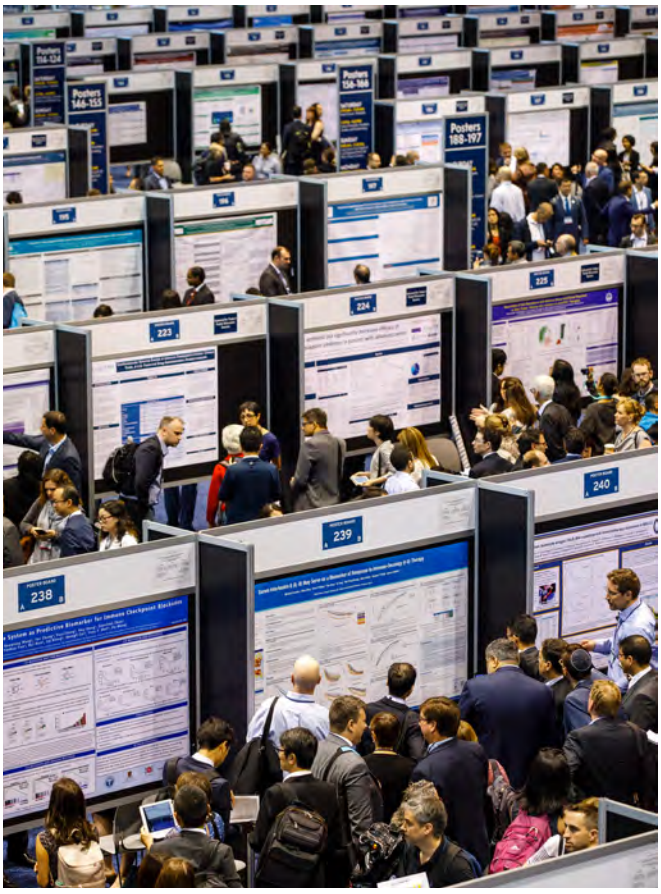
Dr. Faries added that since close observation requires regular ultrasound tests and tight coordination between various medical specialists, it might be possible only for patients living near a major medical center. "If close follow-up is not possible, the patient should probably go ahead with CLND," he said.

SLNB

CLND's loss of stature may be SLNB's gain. Though MSLT-II found no CLND OS benefit, an earlier trial, MSLT-1, found that SLNB did have an OS benefit in patients who had intermediate primary tumors 1.2 to 3.5 mm thick with positive sentinel nodes.

Research has shown that after a positive sentinel node is found, 80 to 90 percent of patients have negative CLND pathology. Thus, in those cases, SLNB itself may be accomplishing any OS benefit. Those first one or two nodes in the regional basin may indeed be serving as "sentinels," taking up any initial metastases, with no detectable mets going further in the basin. Thus, removing the sentinel nodes alone may often get the job done.

With the new AJCC guidelines, the technique's use may have broadened. Previously, SLNB was not recommended for patients with thin melanomas <1 mm in Breslow thickness (except when they were ulcerated or had a high mitotic rate), based on their low rate of metastasis. In the new guidelines, SLNB can also be considered for patients with T1b melanomas (0.8-1.0 mm Breslow thickness or <0.8 with ulceration), after discussing the risks and benefits with patients. This recommendation follows reports of slightly



The annual meeting brings together more than 40,000 oncology professionals from around the world to discuss state-of-the-art treatment modalities, new therapies and ongoing controversies in the field.

higher rates of metastases in patients with T1b lesions and of a better prognosis among patients with thin melanomas >.8 mm found to have negative SLNBs, versus those who do not undergo SLNB.

"Although only a small percentage of these patients have nodal mets, the *absolute number* of patients is substantial," said Dr. Faries. "The decision to perform SLNB is not cut and dried. It's vital for the clinician to be familiar with the benefits and risks, so patients can be fully informed."

SLNB is still not recommended for T1a melanomas — thin, nonulcerated melanomas >0.8 mm thick. Also, as of the eighth edition, mitotic rate will no longer be considered in staging or opting for SLNB, though still an important prognostic factor. This will help avoid overuse in patients with low likelihood of regional nodal disease.

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COMBOS ARE KEY

Scientists have learned that no single treatment for advanced skin cancers is a magic bullet. Despite major advances by individual targeted therapies and checkpoint blockade immunotherapies, they have not routinely brought cures, so they are now often second-line behind various combination therapies: combo targeted therapies, combo immunotherapies, combo targeted therapies/immunotherapies and all of the above, paired with other strategies such as radiation, chemotherapy and further surgery.

Combination BRAF-MEK-Targeted Therapy

Nothing is more exciting in clinical oncology than a new therapy with unprecedented results. One such therapy for patients with stage IV or unresectable melanoma is the oral targeted combination BRAF-MEK blocker encorafenib-binimetinib (Braftovi-Mektovi). It recently made a splash, being accepted for FDA review in the months leading up to ASCO, where its clinical trials were heralded. Then it received FDA approval in the weeks after.

This new combination joins vemurafenib-cobimetinib (Zelboraf-Cotellic) and dabrafenib-trametinib (Tafinlar-Mekinist) as approved targeted combination therapies for patients with the mutant BRAF gene. The combinations have replaced the individual BRAF blockers as frontline targeted therapies.

Encorafenib-binimetinib may be the best of the lot. Reinhold Dummer, MD, lead author of the clinical trials that led to FDA approval, asserted that its superior benefits in progression-free survival (PFS, the study's primary endpoint) instantly made it standard of care in targeted therapy. Median PFS for the new combo was more than twice as long as for vemurafenib, more than five months longer than for encorafenib alone, and longer than for either vemurafenib-cobimetinib or dabrafenib-trametinib (by a couple of months).

While overall survival results (a secondary endpoint of the study) are still maturing, median OS for the combo was 33.6 months versus 23.5 months with encorafenib alone, 16.9 months for vemurafenib alone and 24 months for the two previously existing targeted combos. After two years in the combo arm, 58 percent of patients were alive, and after three years, 47 percent were alive. Dr. Dummer explained these superior results. "Encorafenib is a BRAF blocker with target dissociation times far longer than for other BRAF inhibitors, which leads to sustained target inhibition, and binimetinib is a MEK inhibitor with a short half-life that makes dose modifications easier."

The new combo offers not only improved survival, but a better safety profile, Dr. Dummer added. The previous combinations have unique toxicities that can reduce their ability to deliver optimal treatment, including pyrexia and photosensitivity, whereas the new combo has so few major side effects that only 5 percent of patients had to discontinue the therapy, despite longer exposure.

Reference:

Dummer R, Ascierto PA, Gogas H, et al. Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs. vemurafenib (VEM) or enco in *BRAF*-mutant melanoma. Presented Monday, June 4, 2018. ASCO abstract 159079.

Immunotherapy Combinations

The variety of agents and strategies being tested in combination with the checkpoint blockade therapies is overwhelming. Alexander Eggermont, MD, PhD, Gustave Roussy cancer institute, said that more disease remissions than ever have been achieved in advanced melanoma in the past seven years with the anti-CTLA (ipilimumab) and anti-PD-1 (pembrolizumab and nivolumab) checkpoint blockade therapies along with T-VEC. The most successful of all these therapies, he said, has been the combo checkpoint blockade therapy nivolumab-ipilimumab.

However, it is by no means always successful. Dr. Eggermont noted that the majority of patients are still not living more than a few years. And because of its potentially serious immune-related adverse events (irAEs), it can be a toss-up deciding between the combo and the anti-PD-1 monotherapies, which have almost comparable survival benefits and a better toxicity profile. "Nivolumab and pembrolizumab monotherapy have been phenomenally successful in melanoma, and it will be difficult to show that combining anything with the anti-PD-1 drugs will be significantly better," he said.

He pointed to an array of recent experimental combination immunotherapies that have not panned out. "A lot more research needs to be done to obtain better insights into the optimal mechanisms and timing of combination therapies," he concluded.

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RADIATION: THE NEW IMMUNOTHERAPY?

One new tool in combination immunotherapy that *does* look extremely promising is radiotherapy. "Three years ago, we didn't know radiation therapy could prime the immune system for immunotherapy. Now we are more convinced," said Marka R. Crittenden, MD, PhD, Providence Cancer Center. Preclinical and early phase studies combining it with checkpoint blockade immunotherapy suggest that radiation may synergistically react

with the immunotherapies, boosting immune response in several ways: releasing and processing tumor antigens, upregulating cell death receptors, deleting regulatory T cells and activating other T cells for attack.

Like the intratumorally injectable immunotherapy T-VEC (talimogene laherparepvec), made from a noncommunicable herpes virus, radiation can produce both local effects, ridding the primary tumor microenvironment of remaining cancer cells through immune-related clearance, and *abscopal* bystander effects, where the radiation acts as a "de facto in situ vaccine," stimulating a systemic immune response that helps control *distant* disease.

"Radiation alone is a second-rate vaccine, but when added to immunotherapy, it modulates the tumor environment and makes it amenable to treatment. Patients who do not respond to radiation or checkpoint blockade therapy individually can do very well on the combination," said Dr. Crittenden. Even if patients don't respond systemically to the checkpoint blockade therapy, they often have excellent local responses, with enhanced disease control of the radiated tumors, Dr. Crittenden pointed out. "This shows us that part of why the radiation works is that the immune system helps to clear the last residual cells."

Reports show that people with stronger existing immunity respond better. But more preclinical research must be done to home in on optimal immunotherapy-radiation combinations and learn more about timing and optimal fractionation doses. "Now we are starting to look at immunotherapy combined with radiation in the *neoadjuvant* setting, before surgery, to see if we can lower the immunotherapy doses, reduce toxicity and sometimes even obviate the surgery," Dr. Crittenden concluded.

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SOME METASTASES ARE MORE STOPPABLE THAN OTHERS

One important new use of radiation is the treatment of oligometastases, limited metastatic tumors that travel from the primary tumor to one or two distant parts of the body. Even if these locales are, say, the heart and lungs, local ablative therapy such as radiation can be curative. Combining radiation with systemic therapy can be even more effective.

"In combination with immunotherapy, radiation acts as a powerful local cytotoxin, boosts immunity locally, drives T cells into tumors and seems to improve T-cell function directly," said Ralph Weichselbaum, MD, who won ASCO's 2018 Karnofsky Memorial Award (for individuals whose clinical research has changed the practice of clinical oncology). And, he explained, if you can treat and stop oligometastases, you may stop the cancer from spreading altogether.

Dr. Weichselbaum was a pioneer in oligometastasis and named the concept. Co-director of the Ludwig Cancer Center for Metastasis Research at the University of Chicago, he predicted that some patients will develop only limited metastatic disease, for which localized therapy could be curative, and his major work focused on using radiation. He then made discoveries in the changing basic mechanisms of signal transduction and gene expression following radiation treatment, which led to investigation of combination chemotherapy, immunotherapy and radiotherapy in the quest to cure oligometastases.

"Both laypeople and general physicians have generally regarded metastases as disseminated and incurable in most adult solid tumors, and it's true that metastases are usually treated with systemic agents that are *not* curative," said Dr. Weichselbaum. "But I hypothesized that metastasis represents a *spectrum* of disease, based on tumor burden — number of mets, organ affected and growth pace. Some patients might have just a few metastases that can be cured. And now, with the new developments in immuno-oncology, especially in advanced melanoma patients, I'm persuaded that over 50 percent are likely to be cured."

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TREATING BEYOND ADVERSE REACTIONS

One of the most impressive phenomena I observed at ASCO was how far clinicians have come in managing the dreaded immune-related adverse events (irAEs) that often accompany checkpoint blockade therapies, especially combination nivolumab-ipilimumab. Formerly, it was often one and done for these medicines: Once a high-grade irAE developed, you took the patient off the therapy forever and started steroids to quell the irAE. If the disease didn't start progressing, you might leave the patient off all treatments beyond the steroids, since the therapeutic effects of checkpoint blockade therapies often continue for months or years after treatment ends.

Now, however, physicians can often do a balancing act with adverse reactions to keep a therapy going. "If you catch them early enough, most irAEs can be managed," said Jeffrey Weber, MD, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health. But if the symptoms are serious, he acknowledged, it can become an intricate process, based on how bad the symptoms are, how strong the patient is and how well the drug has been working, among other factors.

Dr. Weber described three different tacks with three patients. In one patient on pembrolizumab who developed irAEs, he held off on the drug until he abated all symptoms with prednisone, then reinstituted pembrolizumab. With a patient on combo nivolumab-ipilumumab who developed severe irAEs, he did a careful

differential diagnosis to make sure something *else* wasn't causing the symptoms, then discontinued the immunotherapy permanently because her symptoms were so serious. He put her on permanent hormone replacement therapy. (All checkpoint blockade patients should be warned in advance that hormone replacement therapy may end up being necessary, Dr. Weber advises.)

In the third case, Dr. Weber was treating a young Merkel cell carcinoma patient with the anti-PD-L1 checkpoint blocker avelumab. He discontinued the drug because the patient developed hepatitis, but as soon as steroids abated the symptoms, the patient immediately developed diabetes. "You always have to stay alert, because as soon as one symptom resolves, another can start, even long after the therapy ends," he said. Amazingly, once the patient's blood sugar was controlled with insulin therapy, Dr. Weber put him back on the immunotherapy. "He'd been doing so well on the therapy, and even though he was going to need lifelong insulin therapy, there was no further damage we could do, so we resumed the avelumab."

Scientists are now researching better ways of quelling or preventing irAEs that won't dampen tumor immunity or necessitate stopping treatment. Perhaps steroids could be administered in a more refined, limited way; perhaps certain cytokines or other molecules driving the irAEs that aren't so important for antitumor immunity could be targeted, and you could block just those molecules without using blanket steroid therapy.

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WHEN DO YOU USE WHAT?

With so many effective therapies for advanced skin cancers, it's often difficult deciding which to use first. Do you start with a checkpoint blockade monotherapy? Combination nivolumab-ipilimumab? A combination targeted therapy like encorafenib-binimetinib? And if that initial treatment fails, then what? Researchers are seeking not just ideal treatments, but the ideal therapeutic sequence.

"You have to always stay alert, because as soon as one symptom resolves, another can start, even long after the therapy ends."

While the checkpoint monotherapies and combination nivolumab-ipilimumab are considered frontline for stage IV melanoma today because of their durable benefits, choosing between them can come down to several considerations. The doctor might not want to saddle a young patient with the potentially permanent damage caused by irAEs on nivolumab-ipilimumab, and an older, sicker patient might not be able to handle them. If a patient is overwhelmed by tumors, it might be advisable to start instead with a targeted combination therapy, which can produce faster results and reduce tumor burden more quickly. Then, you might switch to a checkpoint blockade therapy for more lasting benefits, even before resistance kicks in on the targeted therapy.

If the patient starts with checkpoint blockade therapy, the physician needs patience, since the benefits can take time to develop. Georgina V. Long, MD, PhD, Melanoma Institute Australia, said that you can be fooled into believing the disease is progressing, when it's really just "pseudoprogressing" because of the delayed treatment benefits. You have to hang in there.

Even with the checkpoint blockade therapies' more durable benefits in responding patients, about 30 percent start progressing in one to three years. If a new, limited metastasis (like an oligometastasis) shows up, says Dr. Long, you might continue the drug if overall it is leading to improved outcomes, and just add a complementary therapy. For one thing, if a patient on nivolumab or pembrolizumab monotherapy starts progressing, you can always consider adding ipilimumab to make it a combination checkpoint blockade therapy. It may lead to more virulent irAEs but stop the progression. Or, you can try a complementary therapy like T-VEC or radiation directly on the tumors to shrink them, allowing the checkpoint blockade therapy to work more effectively.

Dr. Long also said that when patients complete the two-year course of treatment on an anti-PD-1 therapy and later start "reprogressing," it's possible to re-challenge them with the therapy. In her pembrolizumab program, after a median 20.5 months post-treatment, 18 of 103 patients started progressing again. Eight were rechallenged with pembrolizumab. Half started responding again, their tumors shrinking, and three developed stable disease. Only one kept progressing.

Melanoma patients on checkpoint blockade therapy who begin reprogressing can also switch to BRAF-targeted therapies if they have the mutant BRAF gene. Research is ongoing to determine what works better as the second-line therapy — the targeted therapies or checkpoint blockade therapies.

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WHY WAIT FOR STAGE IV? TREAT AT STAGE III

Checkpoint blockade immunotherapies and targeted therapies are not only being paired with other therapies, but being given earlier. In the past year, nivolumab and dabrafenib-trametinib were approved as adjuvants for stage III, in the hope that earlier administration will better prevent recurrence and distant metastasis. Other adjuvants are in the wings. Experimentally, some are even being tried as neoadjuvants, preceding surgery, to enhance surgery benefits and sometimes even obviate surgery. But with all these new possibilities, which therapy do you use first?

Adjuvant Therapy

In 2015, ipilimumab was approved as a stage III adjuvant, the first melanoma adjuvant to increase overall survival as

well as recurrence-free survival. And just last year, nivolumab was approved as a stage III adjuvant, based on research showing it delayed recurrence longer than ipilimumab, with far less serious side effects. It instantly became the frontline adjuvant therapy.

Posters and sessions at ASCO abounded with the possibilities. Dabrafenib-trametinib had been approved as an adjuvant shortly before the meeting, and now pembrolizumab took center stage with results from its phase 3 KEYNOTE-054 adjuvant trial, demonstrating 43 percent reduction in risk of recurrence or death versus placebo. Pembrolizumab has since been accepted for FDA review as a stage III adjuvant.

It's now open to debate whether BRAF-mutant patients should use checkpoint blockade therapy or targeted therapy as the frontline adjuvant. Two physicians literally debated the question at ASCO. Ragini Reiney Kudchadkar, MD, chair, Winship Cancer Institute, Emory University, claimed that the phase 3 OS/PFS data on dabrafenib-trametinib challenged the dogma that targeted therapies always lead to resistance and progression while immunotherapy leads to durable survival. "Also, the data show that permanent toxicities from BRAF-MEK inhibition rarely occur. As we use more treatments in the adjuvant setting, hopefully we're curing more people to live a long time, making quality of life more of an issue. Permanent toxicities have more relevance than ever. Given all that, seemingly everyone should be giving patients targeted adjuvant therapy."

Olivier Michielin, MD, PhD, University Hospital Lausanne, espoused the traditional view that checkpoint blockade should come first. Once you pass the 14 to 18-month mark, checkpoint blockade therapy shows more durable survival, he said, especially once treatment has ended. He also maintained that the toxicities for anti-PD-1 monotherapies are not demonstrably worse than for targeted therapies.

In the end, the physicians decided that both therapies were now good frontline options, depending on the patient's situation. For example, if adverse events were the bigger concern, if, say, the patient lived far from the treatment center and wasn't readily available for steroid treatment, dabrafenib-trametinib might be the better option. In a fit patient, with no situation such as living remotely, nivolumab remained the institutional first choice. Up the road, they said, finding biomarkers for treatment success will help physicians make such choices.

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Researchers have also begun exploring combo adjuvant nivolumab-ipilimumab, in the belief that its superior OS results for stage IV patients will carry over to the adjuvant setting. But its greater toxicity would carry over as well, Dr. Kudchadkar pointed out.

Neoadjuvant Therapy

Neoadjuvant melanoma therapy is new, but it's already a crowded landscape. BRAF-MEK-targeted therapies, checkpoint blockade therapies, intralesional/oncolytic therapies and even isolated limb infusion/perfusion are being tested. A study of neoadjuvant pembrolizumab has already produced a preliminary durable complete response (CR) in some patients. A major advantage of neoadjuvant therapy is that it allows physicians to assess response with disease still present and more antitumor antigens at their disposal. It can also mitigate the need for surgery.

But there are potential drawbacks, explained Alexander Christopher Jonathan Van Akkooi, MD, PhD, Netherlands Cancer Institute. If it doesn't work, it may produce a treatment effect/host response that makes surgical resection more difficult or even impossible. It may jump-start progression. If complications arise, it may affect patient compliance and attrition. And lingering toxicity may disqualify the patient from future treatment, including clinical trial eligibility.

Scientists are also looking into combination nivolumab-ipilimumab as a melanoma neoadjuvant. In the phase 1b OpACIN trial comparing neoadjuvant versus adjuvant combo nivolumab-ipilimumab, the neoadjuvant regimen proved superior. After a median follow-up of 24 months, none of the responders in the neoadjuvant arm had relapsed, while four of 10 patients in the adjuvant arm had relapsed. The irAEs were high in both arms, however. A phase 2 trial is being enrolled to identify an optimal dosing scheme to reduce irAEs and optimize benefits.

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CSCC AND MCC: WHAT'S ON THE HORIZON

Significant advances being made in both advanced cutaneous squamous cell carcinoma (CSCC) and advanced Merkel cell carcinoma (MCC) also generated excitement at ASCO.

Advanced CSCC

To date, only 30 percent of unresectable cutaneous SCC patients respond to current therapies, and no life-extending therapies have been approved. However, checkpoint blockade immunotherapies are changing the field.

The therapy currently knocking at the door is cemiplimab, a PD-1 checkpoint inhibitor that received a Breakthrough Therapy designation from the FDA in September 2017 and is now under priority review as a treatment for metastatic cutaneous SCC or locally advanced, unresectable SCC. The target date for the FDA's decision is October 28, 2018, based on both phase 2 data (in which over 46 percent of patients responded to the drug) and two phase 1 expansion cohorts. Updated results from the clinical trials were presented at the annual meeting. In the phase 2 study, out of 59 patients, 47.5 percent responded to the drug, including 24 partial responders and four complete

From the Editors

For the third year in a row, the scientific director of The Skin Cancer Foundation, Mark Teich, attended the Annual Meeting of the American Society of Clinical Oncology (ASCO) on behalf of *The Melanoma Letter* readership. For the many of you who did not have the privilege of being there in person, in this issue Mark walks you through what it was like to attend the meeting, rushing from session to session trying to glean the most important ongoing and anticipated developments in the field of melanoma.

The largest annual gathering of oncologists in the U.S., the meeting draws more than 40,000 physicians, researchers, other health professionals and patient advocates from over 100 countries who come to learn about state-of-the-art diagnostics, prevention and treatment modalities, newly approved and experimental therapies, and ongoing controversies in the field. The attendees participate in lectures, seminars, oral presentations and poster presentations going on 10 or 11 hours a day, and in their spare moments, can explore an exhibitors' hall stretching over several acres.

Mark attended sessions exploring new and improved strategies for melanoma and other skin cancers. Some of the most exciting developments he encountered this year were the practice-changing modifications made in sentinel node biopsy, complete lymph node dissection and staging, the revolution in adjuvant and neoadjuvant therapy and the giant steps forward in personalized, precision medicine. In this issue of *The Melanoma Letter*, he shares the highlights and dominant themes.

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responders. Some patients who had failed other therapies had CRs, including one patient with metastases to the brain. Only three responders went on to progressive disease.

Physicians speaking at an advanced CSCC session believed that the drug would soon be approved and become the new standard of care. Their biggest concerns were how to manage adverse events, what would be the second-line therapy once patients developed resistance and what the drug could be combined with to improve performance. Nikhil Khushalani, MD, vice-chair of cutaneous oncology at Moffitt Cancer Center, said that a major advantage in treatment of advanced SCC, which generally results from cumulative UV damage, is its high mutational load, which keeps increasing as we age. The higher the mutational burden, the higher the potential response to anti-PD-1 therapies.

Merkel Cell Carcinoma

Though avelumab (Bavencio) was the first checkpoint blocker FDA-approved for advanced MCC, pembrolizumab has been studied for the disease longer and is moving toward FDA approval. At ASCO, lead author Paul Nghiem, MD, University of Washington, presented findings from the expanded phase 2 trial of frontline pembrolizumab. Out of 49 patients, overall response rate (ORR) was 50 percent, 52 percent for those with the MCC polyomavirus. The OS rate at 18 months was 68 percent, versus 30 percent for historical chemotherapy data. Dr. Nghiem noted that these results represented the longest observation to date of patients with advanced MCC receiving frontline anti-PD-1 therapy, and that the study demonstrated durable tumor control, a favorable OS rate and a manageable safety profile.

"With avelumab approved and the success with pembrolizumab and nivolumab (a new trial of adjuvant nivolumab for MCC has had positive early results), the field has been turned on its head," he said. "Patients can do great regardless of their polyomavirus status. Treatment ends within 24 months, and most patients are doing well after discontinuation, with strikingly better durable response than chemo ever achieved. If patients get past the first year, they have a good chance of staying disease-free. The follow-up isn't long enough yet, but I say cures are possible."

Suzanne Topalian, MD, director of the Bloomberg/Kimmel Institute for Cancer Immunotherapy, presented results of the multicenter phase 1/2 nivolumab neoadjuvant trial on patients with advanced, resectable MCC, the first trial ever of an anti-PD-1 therapy as a neoadjuvant for MCC.

Eighty percent of patients reviewed after treatment had tumor regression, and 65 percent had a major pathologic response after surgery, including many CRs. Twelve months after treatment, only two patients had relapsed, and in some, the treatment obviated the need for more extensive surgery. "This needs more testing," Dr. Topalian concluded, "but the results are very promising."

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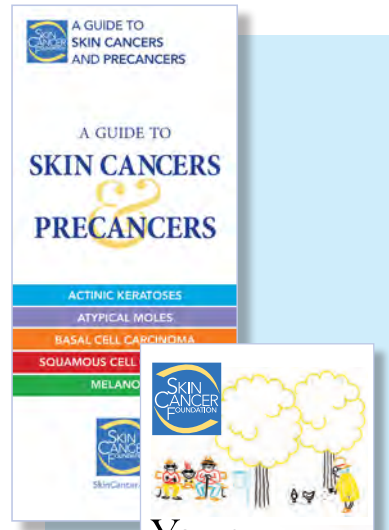

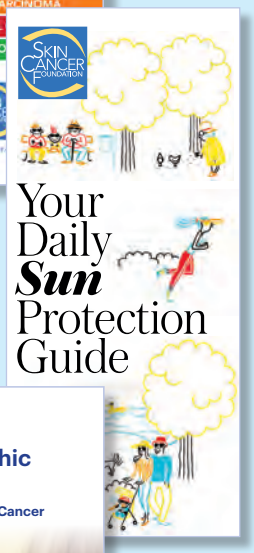

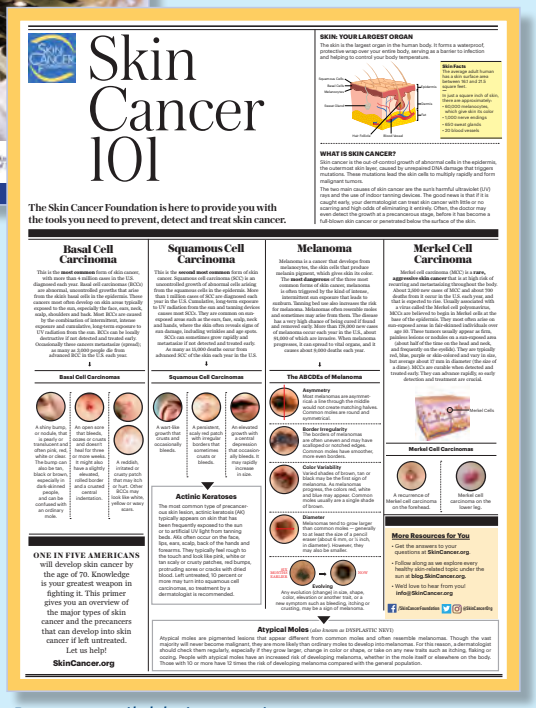

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