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Trailblazing Melanoma Research At the 2017 ASCO Annual Meeting

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Next June, if you attend the American Society of Clinical Oncology's 2018 annual meeting, the biggest annual gathering of oncologists in the U.S., bring comfortable shoes. The McCormick Center in Chicago is so vast, you get all the daily aerobic exercise you need just walking briskly from one end to the other to attend any of hundreds of sessions and presentations.

Between June 1 and 6 this year, I rushed back and forth attending sessions involving melanoma and other skin cancers. In this issue of *The Melanoma Letter*, you'll find my distilled overview of key melanoma developments and research that emerged at the conference. We hope you will come away with new information that you and your patients can put to important use.

Several themes and trends were dominant throughout the conference.

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From the Editors

The Annual Meeting of the American Society of Clinical Oncology (ASCO), held in Chicago each June, brings together more than 40,000 physicians, researchers and other health professionals from over 100 countries to discuss state-of-the-art treatment modalities, new and experimental therapies and ongoing controversies in the field. The largest annual gathering of oncologists in the U.S., the meeting is also attended by scores of dermatologists, educators, members of the press and patient advocates. The attendees frequent lectures, seminars, oral presentations and poster presentations going on 10 or 11 hours a day. In their spare moments, they can explore an exhibitors' hall stretching over several acres.

This year, The Skin Cancer Foundation's scientific director and longtime executive editor of *The Melanoma Letter*, Mark Teich, attended the conference, going to skin cancer sessions on behalf of the Foundation, in hopes of obtaining insights into new and improved strategies on the horizon for melanoma patients. Often enough, his hopes were rewarded. In this issue of *The Melanoma Letter*, he shares highlights on the present and future of diagnostics and treatment for melanoma and other skin cancers.

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WE ARE IN THE IMMUNOTHERAPY ERA

Ever since the anti-CTLA-4 drug ipilimumab (Yervoy) was FDA-approved, making a huge splash at ASCO in 2011, checkpoint blockade immunotherapy has kept adding notches to its belt. With each passing year, more drugs in this category have been approved, each improving on the last. In fact, in the past year, checkpoint blockade therapy has become the unquestioned king of cancer treatment. It was *everywhere* at ASCO. Research presented at the conference introduced important new uses not just in melanoma, but in advanced squamous cell carcinoma, Merkel cell carcinoma and an ever-expanding list of non-skin-related metastatic or inoperable cancers, from lung, renal and bladder to head and neck cancers. Extending overall survival for unparalleled lengths of time in many stage III and IV patients, it is leading the wave of a treatment revolution that could one day provide the first bona fide cures for a wide range of advanced cancers.

Combination Therapies: Two (or More) Treatments Are Better than One

AIDS was a death sentence until scientists put together the right combination of drugs in a cocktail that could bring the disease to a standstill in most patients. Today, scientists are similarly looking for the right combination of drugs and strategies to grind advanced melanoma to a halt. Through decades of arduous and often heartbreaking trial and error, they have come to believe there is no single magic bullet, no miraculous monotherapy that will cure melanoma by itself. But by finding the right, synergistic drugs and methodologies to work in tandem, they have been able to keep delaying disease recurrence and extending the lives of patients further. Current frontline therapies for melanoma include the combination checkpoint blockade therapy nivolumab [Opdivo]-ipilimumab, approved in 2015, which has improved greatly upon ipilimumab monotherapy, and the targeted combination therapies dabrafenib-trametinib (Tafinlar-Mekinist) and vemurafenib-cobimetinib (Zelboraf-Cotellic), which have improved patients' prognosis beyond what vemurafenib alone ever did. Researchers are now looking not just for even more effective two-way combinations, but also *triple* combinations incorporating non-drug strategies such as radiation and adoptive T-cell transfer therapy, which may outdo the two-way combinations. The implicit hope is to put together the equivalent of the combo antiretroviral therapies that stopped AIDS from being a killer in most people.

Increased Treatment Options Bring Tougher Choices

Back in the 1990s, when Interleukin-2 (IL-2) was the only approved medicine for stage IV melanoma, extending life for at best about 4 percent of patients, physicians had nothing else to choose from except ineffective chemotherapies and unproven treatments in clinical trials. Today, after virtually no meaningful therapies had been approved in about two decades for advanced melanoma, a dozen were approved in the past six years. Physicians now can select from targeted monotherapies and combination therapies, intralesional therapies, checkpoint blockade monotherapies, combination nivolumab-ipilimumab, IL-2 and Interferon alfa-2b, as well as non-drug treatments such as adoptive T-cell transfer therapy or radiation. Plus, there are countless varieties of treatments in clinical trials (scores of which were presented

Checkpoint blockade therapy has become the unquestioned king of cancer treatment.

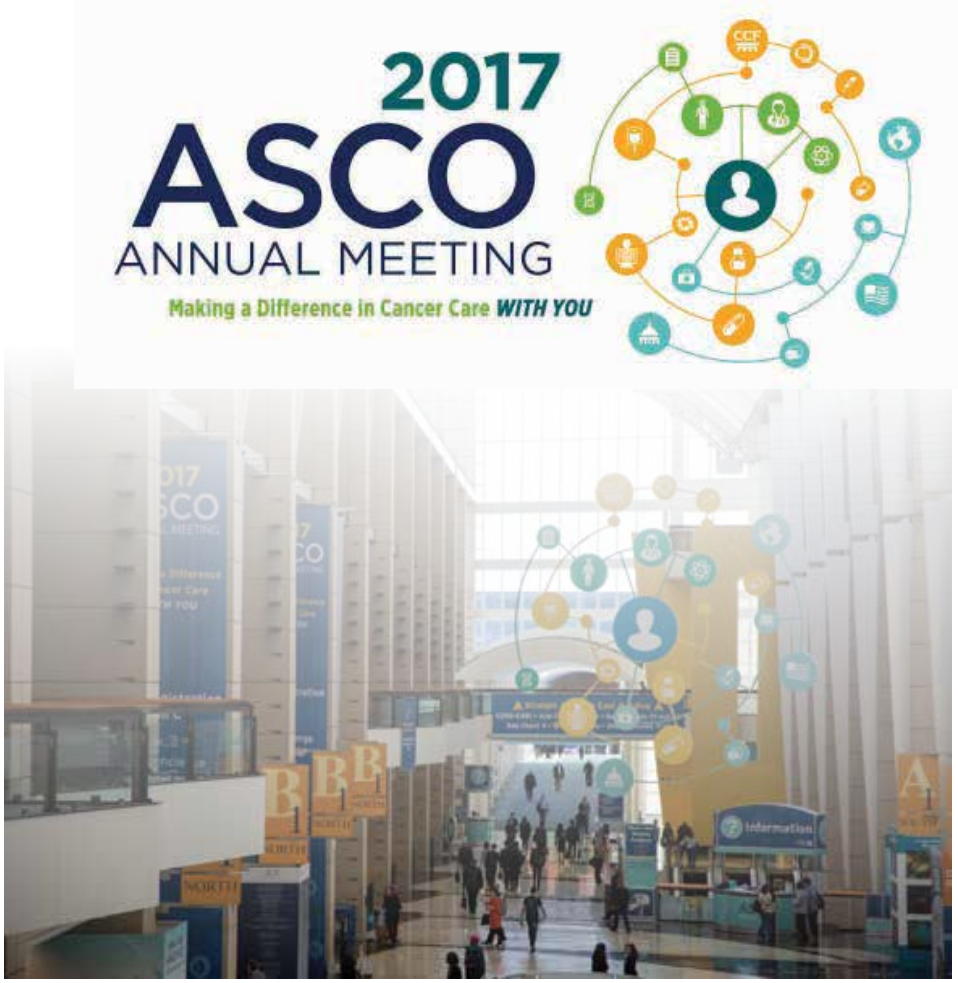
at ASCO). Ipilimumab, already approved for stage IV patients, was recently approved for high-risk stage II and stage III patients as well, instantly replacing Interferon alfa-2b as the frontline treatment. And for stage IV, physicians have at least narrowed frontline treatments down to the combination targeted therapies, anti-PD-1 checkpoint blockade monotherapies and combination nivolumab-ipilimumab. Most oncologists today would shorten that list to the anti-PD-1 checkpoint blockade therapies, but even then, deciding between the monotherapies pembrolizumab (Keytruda) and nivolumab or combination nivolumab-ipilimumab is a crucial, difficult choice.

Multiple studies appearing at ASCO confirmed that pembrolizumab or nivolumab alone are safer choices with excellent results, while the more toxic combo nivolumab-ipilimumab offers slightly better results, giving patients a bit better chance at long-term survival, but with a risk of far more debilitating, lingering side effects. Deciding between even these few possibilities can be agonizing decisions for doctors and patients. Sometimes it boils down to which patients seem healthy, young and strong enough to handle the combo therapy and could have a long potential lifespan ahead of them if the therapy works.

If the frontline treatment fails, deciding what to do next becomes even harder. I attended an interactive session led by Vern Sondak, MD (chair of the Department of Cutaneous Oncology at Moffitt Cancer Center), where I and dozens of doctors followed a patient's progress, voting for this or that treatment at various stages of her melanoma's advance, and it was astonishing to see these professionals making widely divergent treatment choices at every juncture for the same patient.

The Need for Better Biologic Markers (Biomarkers)

Even with checkpoint blockade's stunning success in melanoma compared with what came before, about 60 percent of all treated stage IV patients on that therapy die within five years. Many do not respond at all to the medicine. Researchers are desperately seeking to identify biologic markers in patients that will show who can benefit from this therapy, so that those who won't can start with other therapies and avoid losing valuable months as their disease worsens. In targeted therapy, the discovery of the defective BRAF gene gave scientists their first definitive marker, and it has been immensely helpful to know that only the 40 to 50 percent of advanced melanoma patients who have that defective gene can reap any benefits from targeted therapy. Ultimately, researchers want to pinpoint ever more specific markers that will both predict and improve the utility of a host of therapies.



Personalized, Precision Treatment

Gone are the days when oncologists fired this or that chemotherapy at a cancer, trying to destroy it and sometimes also massacring everything else in the chemo's path. In keeping with the quest for patients' meaningful biologic markers, cancer therapies today are increasingly being custom-designed for specific patients with specific cancers. Molecular profiling, mutational assays, next-generation whole-exome sequencing, new biopsy strategies that can pinpoint a tumor's genomic changes over time, and overall increasing knowledge of tumors' biological microenvironment are leading to development of tailored treatments targeting key molecules that allow particular cancers to flourish and metastasize. These strategies aim to give patients more bang for their buck — more precise, personalized treatment to eliminate their cancers while doing the least harm.

Managing Side Effects

All treatments for advanced melanoma come with side effects, some worse than others. Perhaps ironically, the targeted therapies actually cause extreme photosensitivity and squamous cell carcinomas, which are usually small and easily

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treatable. The checkpoint blockade immunotherapies, especially combination nivolumab-ipilimumab, can produce side effects ranging from mild, early onset rashes and pigment loss (vitiligo) to serious, sometimes life-threatening endocrine complications like damaged or destroyed pituitary and thyroid glands. In at least one way, these serious reactions, called immune-related adverse effects, or irAEs, are a positive, since they reveal that the therapy is working, powerfully kicking on the immune system. On average, the therapy results may be *better* for patients who have these problems. But the complications must be controlled, generally by steroids.

Fortunately, physicians are getting better at managing these patients, and very few die from the complications, though they may have to stay on steroids long-term to overcome the damage, keep inflammation down and control the immune system's overreactions. Some new research shows that with lesser, grade 1 and 2 side effects, physicians may be able to continue checkpoint blockade treatment — pembrolizumab or nivolumab monotherapy if not the combination therapy — even as patients remain on steroids. With grade 3 side effects, they will probably hold off on treatment until the symptoms abate, and with grade 4, they will probably stop the treatment for good. The good news is that these patients' immune systems have already been switched on, and the former treatment's beneficial effects may continue even though the treatment has been discontinued. A key precept that emerges from all this: It is essential for the physician and the patient to stay in close communication throughout the treatment, so that any side effects can start being managed immediately, with as little damage done as possible. This includes follow-up visits at least once every three to six months. An important study presented at ASCO this year found that patients who kept in close contact with their physicians had less damaging side effects and significantly more successful overall results.

As we explore some of the most exciting and significant work presented this year at ASCO in specific areas of melanoma research, these aforementioned themes and trends show up again and again.

DETECTION, DIAGNOSIS AND PROGNOSIS

The universal truth with melanoma and other skin cancers is that the earlier you find and treat them, the less damage they do, and the better the chances of survival. This is as true for recurrences as for primary tumors. At ASCO this year, researchers approached the quest for earlier detection of recurrences from myriad directions. In fact, "earlier" was just part of the equation: With the advent of new diagnostic technologies, the goal today is to glean as much information from a tumor as possible, dredging up whatever secrets it can reveal about its individual biology, genetic underpinnings and genomic alterations that will help in predicting its advance and attacking its vulnerabilities. The fuller this information is, the more precise the treatment plan can be, targeting therapies to specific tumor characteristics. Growing evidence shows that patients receiving such personalized "treatment matching" have better outcomes.

Sentinel Node Biopsy and Completion Lymph Node Dissection

To date, sentinel node biopsy (SLNB) remains the standard for detecting early melanoma metastasis in patients with high-risk primary tumors. Donald Morton, MD, introduced the tissue-sparing concept in 1992, which held that metastases draining from the primary tumor into the local lymph node basin would show up in the first one or more nodes (the sentinel nodes), so you could remove and microscopically examine just them, sparing the others. If the sentinel nodes proved negative for melanoma, you saved the cost, hassle, disfigurement and potential major complications of removing all the nodes. You had to remove and examine the rest of the nodes only if the sentinel nodes were positive.

The biggest debate has been whether SLNB and CLND actually extend life for anyone, and if not, whether they are justified at all.

However, many experts have always considered SLNB/CLND a flawed technique. One fear has been the risk of false negatives — micrometastases skipping the sentinel nodes and going straight to other nodes or other parts of the body, leading to full-blown recurrences. In a study appearing at ASCO this year, Nedjat and colleagues retrospectively reviewed all patients with head and neck melanomas who underwent SLNB at Johannes Gutenberg University in Germany from 2010 to 2016, and found that of the 79.2 percent who had negative SLNBs, 13.1 percent had at least one metastasis in the regional cervical node within one year. They concluded that SLNB has a high rate of false-negative findings, but that the lower complication rates for patients with negative SLNBs versus traditional CLNDs still made the technique worthwhile. They recommended that patients with negative SLNBs continue to be monitored by frequent ultrasound tests or computed tomography.

The bigger debate has been whether SLNB and CLND actually extend life for anyone, and if not, whether they are justified at all. Morton himself launched

two long-running studies, the international Multicenter Selective Lymphadenectomy Trials I and II (MSLT-1 and MSLT-II), the first gauging the value of SLNB, the second focusing on the value of CLND after a positive SLNB. MSLT-1 ultimately found that SLNB does not significantly increase overall 10-year melanoma-specific survival compared to nodal observation, except in patients with intermediate primary tumors found to have nodal metastases. On average, it increases disease-free survival (length of time before recurrence) in all patients, as well as identifying patients with nodal metastases who might benefit from immediate complete lymphadenectomy.

Unfortunately, MSLT-II, published in *The New England Journal of Medicine* almost simultaneously with the ASCO conference, found that performing CLND after a positive SLNB does *not* extend patients' lives either. It does increase the rate of regional disease control (reduces recurrence in the lymph node basin), but the authors urged caution about interpreting this too favorably, since it apparently has no bearing on overall survival.

At Dr. Sondak's interactive session ("Clinical Problems in the Immunotherapy, Surgery and Radiation Therapy of Melanoma"), he presented the case of a patient with a newly diagnosed primary tumor large and concerning enough to merit SLNB: Three left inguinal sentinel nodes were biopsied, and two proved positive. Dr. Sondak then had us vote electronically on whether to perform immediate CLND, or observe the patient over time ("watch and wait") through clinical palpation and ultrasound to see if tumors showed up in other nodes, while undertaking other established therapies or clinical trials. While the majority of votes were cast for immediate CLND, many doctors opted for watch and wait and various treatment choices, reflecting some of the uncertainty that has always surrounded SLNB and CLND.

Dr. Sondak said that, even if they have no overall survival benefit, there are several good reasons for these techniques, including their ability to pinpoint staging and help assign patients to clinical trials. For the moment, he noted, CLND after a positive SLNB remains standard of care for intermediate and high-risk melanomas. The new American Joint Committee on Cancer (AJCC) staging system guidelines on melanoma will go into effect at the start of the year, and as in the current system, the paired techniques will still be recommended for primary melanomas with certain high-risk characteristics. But the debate is far from over.

[Editor's note: Mark Faries, MD, lead author of the recent MSLT-II study, will be exploring all sides of the debate and discussing the study, its implications and the future of SLNB and CLND in the next issue of The Melanoma Letter.*]*

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Liquid Biopsy and Genetic Sequencing

The uncertainties with sentinel node biopsy have left researchers searching for less invasive, more definitive methods for establishing metastasis and metastatic risk. Liquid biopsy, one approach coming into its own across many cancer types, is increasingly used to help physicians understand a primary tumor's genomics and molecular biology to help guide treatment. The technique looks at circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA), bits of key genetic material in the blood. A simple blood test, it is much less invasive (as well as cheaper and less risky) than a standard tissue needle biopsy. Unlike tissue biopsy, it can easily be repeated in the course of therapy. While a needle biopsy yields information only about the initial tumor, liquid biopsy enables doctors to track the cancer's molecular changes to see if the situation is worsening or if the patient is responding to treatment. At an ASCO poster sesssion this year, Clouthier, et al. reported on their plan to use liquid biopsy to show how metastatic melanoma, head and neck squamous cell carcinoma and other cancer patients are responding to pembrolizumab immunotherapy.

Standard biopsy looks at just one site, but individual cancers can have a wide array of genomic changes and mutations, in different areas of the tumor as well as in different organs where the cancer has metastasized. Liquid biopsy allows physicians to see a much wider range of changes in the circulating blood. "Monitoring multiple mutations improves detection sensitivity compared to targeting individual loci, has predictive value and can be applied to all melanoma patients," concluded Wan, et al. in a study at ASCO of ctDNA taken from both the plasma and urine of BRAF-mutant metastatic melanoma patients.

This important information can help make predictions on survival or actually improve those survival chances. For example, it may reveal recurrences and resistance or other problems earlier than with traditional markers by giving a "real-time snapshot of tumor burden," and this might allow doctors to revise the prognosis and treatment plan accordingly. In one study appearing at ASCO this year, Berciano-Guerrero, et al. used liquid biopsy and gene expression profiling to reveal that two metastatic melanoma patients were having delayed, or "non immediate" allergic reactions (niAR) to combination targeted BRAF therapies; they immediately halted the targeted therapies and started steroid therapy to overcome the allergic reactions.

The technique is especially useful when the patient's health or the tumor location (such as the pancreas or lungs) makes a tissue biopsy unsafe or untenable, and when inadequate regular biopsy tissue remains for mutation testing after the pathology test. Since treatment lowers ctDNA concentrations, researchers may

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use techniques like next-generation gene sequencing or individualized gene sequencing, which, through amplification or hybridization, maximize the number of mutations targeted per patient for observation; they allow higher-sensitivity monitoring of melanoma patients on therapy. In their study appearing at ASCO, Moehrmann and colleagues used next-gen sequencing, liquid biopsy and two kinds of PCR analysis to test the plasma of patients with progressing advanced melanomas and other cancers for BRAF V600, KRAS and EGFR mutations. Assaying plasma cfDNA from exosomal nucleic acid (exoNA) from living cells, they detected 39 of 41 mutations present in tumor tissue with 100 percent specificity, much better than the clinical findings from tissue biopsy or PCR testing of plasma cfDNA. It even allowed them to see that having high mutation allele frequency was a marker for shorter survival: Patients with high mutation allele frequency (MAF) had shorter median survival than patients with low MAF.

Liquid biopsy testing is not intended to replace traditional tumor biopsy testing. Thorough pathological assessment of the tumor tissue will remain critical to establish an accurate initial diagnosis. Once the diagnosis is established, ctDNA blood tests could be used for genomic analyses during treatment, for example to show genomic changes that might suggest a different treatment. The technique might also be a valid alternative when tumor biopsy is not possible.

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Gene Expression Profiling

Gene expression profiling (GEP), another attempt to enhance or outdo sentinel node biopsy (SLNB), can measure the activity or expression of many, sometimes thousands, of genes at once to produce a comprehensive picture of cellular function. It can help establish the threat of metastasis by showing whether and how fast specific cells are dividing, and how cells are reacting to treatment. Techniques like gene sequencing and DNA microarray technology help generate sufficient genetic and molecular information to build and analyze the gene profile.

One company, DecisionDX-Melanoma, has patented a well-known 31-gene expression profile that has proven to provide data beyond what SLNB can show. Studies have demonstrated that recurrence predictions based on DecisionDX-Melanoma's GEP are more accurate than SLNB-based predictions. A high percentage of recurrent melanoma patients showing up as high-risk on the company's gene profile have been SLNB-negative, and a far lower percentage of patients registering as low-risk based on the GEP recur compared with those who have negative SLNBs.

The annual meeting brings together more than 30,000 oncology professionals from around the world to discuss state-of-the-art treatment modalities, new therapies and ongoing controversies in the field.

However, *combining* the assessments of GEP and SLNB produces the most accurate recurrence predictions of all, identifying as high as *88 percent* of recurrences. These combined predictions can provide valuable prognostic information, significantly enhancing identification of high-risk melanoma patients and helping to guide surveillance decisions and enrollment of patients into clinical trials.

At ASCO this year, studies employed GEP profiles for a wide range of purposes in melanoma patients, from predicting responses and toxicity with anti-PD-1 therapy and combined CTLA-4/PD-1 blockade treatment to showing why V600K BRAF-mutant metastatic melanoma patients have inferior response and shorter survival with BRAF- and MEK-directed therapies than V600E-mutant patients do.

ADVANCES IN TREATMENT

Immunotherapies

Based on the astounding progress made with immunotherapy and targeted therapy in the past six years, it was not a shock to hear several presenters at ASCO predict something akin to a cure for advanced melanoma in the near future. Until 2011, the only FDA-approved treatments for these patients were the immunotherapies Interferon alfa-2b, which extended recurrence-free but not overall survival for high-risk stage II and stage III patients, and Interleukin-2, which extended overall survival in only about 4 to 6 percent of stage IV patients. In 2011, the approvals of the checkpoint blockade immunotherapy ipilimumab and the targeted therapy vemurafenib pushed the number up to about 20 percent five-year survival. The subsequent approvals of the anti-PD-1 checkpoint blockade immunotherapies pembrolizumab and nivolumab in 2014 brought that to 30 percent or higher, and combination ipilimumab-nivolumab has since reached heights of up to 40 percent.

These are meteoric improvements, but there is obviously further to go. Checkpoint blockade research — in fact, the whole burgeoning field of immuno-oncology — is heading down a wide variety of paths to take things the rest of the way, with new agents and combinations being tested and approved frequently. Some 250 presentations appeared at ASCO this year just involving checkpoint inhibitors. Some looked into why checkpoint blockade doesn't work well for 60 percent of patients, and why resistance eventually sets in for so many; others sought markers to predict which patients would thrive on which therapies; yet others combined checkpoint blockade therapies with other immunotherapies, targeted therapies or altogether different therapies such as radiation or chemotherapy. Many researchers and presenters explored the choice of secondary therapies when initial immunotherapies fail, the best sequence of therapies, ongoing versus intermittent therapy regimens and when, if ever, to return to therapies that have previously failed. Some explored the best ways to manage and reduce irAES and other side effects of therapy, for example, by altering drug doses, and when it makes sense to continue with, delay or discontinue a therapy after side effects begin. Some highlights:

Checkpoint blockade research is heading down a wide variety of paths, with new agents and combinations being tested and approved frequently.

Anti-PD-1 monotherapy

Both pembrolizumab and nivolumab monotherapy had impressive results across countless studies, with findings significantly stronger than for ipilimumab, and almost as strong as those for combination nivolumab-ipilumab, with much less severe side effects. Patients on these monotherapies have a much better chance of finishing their therapy regimens. In one phase 3 study presented on June 4 by Caroline Robert, MD, for example, pembrolizumab showed much greater safety and durability than ipilimumab in patients previously untreated with ipilimumab. With median follow-up of almost 34 months, overall response rates were 42 percent for pembro patients versus only 16 percent for ipi patients, OS rates were 50 percent versus 39 percent, and 68 percent versus 58 percent had responses lasting greater than or equal to 30 months. Nine months after completing treatment, 98 percent of the pembro patients were alive, and at 10 months, their risk for disease progression or death was only 9 percent.

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Immunotherapy for Brain Metastases

Compared with primary lung, breast, renal or colorectal cancer, melanoma has the highest propensity to metastasize to the brain: Over one-third of patients with metastatic melanoma eventually develop a clinically apparent brain metastasis, a major cause of death in advanced melanoma patients. Since the blood-brain barrier has been considered an impediment to treatment, historically most of these patients have been excluded from clinical trials. However, it turns out these brain metastases are often small, asymptomatic and circumscribed, and if

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you catch them when small, checkpoint blockade therapies can eliminate almost all of them. Jimmy Carter, for one, was safely treated with pembrolizumab and remains in complete remission.

The Checkmate 204 Trial, presented at ASCO 2017, showed that combination checkpoint blockade therapies could be almost as successful at eliminating intracranial metastases as extracranial metastases. Physicians administered a combination of 1 mg/kg nivolumab and 3 mg/kg ipilimumab three weeks at a time to patients with melanoma and at least one metastatic brain lesion, then followed with 3 mg/kg of nivolumab monotherapy every two weeks until disease progression or toxicity. The primary endpoint was intracranial (IC) clinical benefit rate (including objective overall response rate and stable disease, SD, for over six months), which proved substantial: ORR was 60 percent, with a surprisingly comparable objective intracranial ORR of 56 percent (21 percent complete responses). Adding in SD, the IC clinical benefit rate largely matched extracranial responses. The progression-free survival rate for those with IC metastases exceeded 65 percent after six months, with median PFS not yet reached, and only 4 percent of the 75 patients had to stop therapy due to adverse side effects. "The favorable safety and efficacy of this treatment may represent a new paradigm for patients with asymptomatic melanoma brain mets, and could change practice to avoid or delay whole brain radiotherapy or stereotactic brain therapy," said lead author Hussein Tawbi, MD.

A key question to resolve is what therapy sequences work best. Should you start with BRAF-targeted therapy, checkpoint blockade or another therapy? If that first therapy fails, what therapy should be tried next? This is a tremendously important question with both brain and non-brain metastases. If, for example, physicians know patients have less success with checkpoint blockade therapy after failing BRAF inhibitor therapy, should they try checkpoint blockade therapy first, even if patients have mutant BRAF?

The Australian Anti-PD-1 Brain Collaboration (ABC), led by Georgina V. Long, PhD, looked at this question and others, in a prospective, randomized phase 2 study comparing nivolumab monotherapy against combination nivolumab-ipilimumab in melanoma patients with asymptomatic or symptomatic brain metastases, some of whom had prior local or targeted therapy and some of whom hadn't.

Based on a median follow-up of 16.4 months, both nivolumab monotherapy and the combo therapy were active against melanoma brain metastases. However, patients with asymptomatic brain metastases who had not previously received local therapy had a more favorable response to combo nivolumab-ipilimumab than to nivolumab alone, with fairly comparable intracranial and extracranial ORR and PFS. The nivolumab monotherapy patients had far lower intracranial ORR and PFS. And patients who had previously failed local therapy had an especially poor response and PFS with the monotherapy.

However, combo patients whose disease previously progressed on BRAF inhibitor therapy also had poorer responses to therapy. The better antitumor activity among treatment-naive patients who had not progressed on a BRAF or MEK inhibitor, and their lower response if they *had* progressed on a BRAF or MEK inhibitor, suggested how targeted agents and immunotherapies may need to be sequenced for brain metastases in the future. "The combination of nivolumab and ipilimumab has high activity in melanoma brain metastases, and may be considered for up-front therapy," Dr. Long concluded.

Georgina V. Long, PhD, speaks during Immunotherapy, Surgery, and Radiation Therapy of Melanoma session.

Based on these two studies, the blood-brain barrier no longer seems such a daunting obstacle, and combo checkpoint inhibitors appear to offer the greatest potential of any treatment to date as a frontline therapy for brain metastases. Finding the right complementary and secondary treatment strategies could be key to one day achieving cures. Combination targeted therapies, which have had a bit of early success in the frontline setting with brain metastases (*see our Targeted Therapy section*), could be a vital part of the mix, especially in the second-line setting.

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Checkpoint Blockade Treatment Beyond Progression

Since the targeted and checkpoint blockade boom began, patients have largely stayed on a given therapy until the regimen is completed, until disease progression or until side effects/toxicities become dangerous or intolerable. However, doctors are finding they may sometimes continue a medicine safely and effectively even beyond disease progression, or come back to it later, perhaps after other therapy has lowered the disease burden, making the tumor more responsive.

In a multicenter, international retrospective analysis presented at ASCO this year, again directed by Dr. Long, her team

reviewed the findings of phase 3 clinical trials on 85 previously treatment-naïve advanced melanoma patients whose disease progressed on nivolumab, as measured by RECIST (Response Evaluation Criteria in Solid Tumors) standards. They observed that the patients not only were able to continue taking nivolumab safely after progression, but that the drug provided benefits despite the progression; 28 percent of the patients had a target lesion reduction of greater than 30 percent as many as six weeks after progression, with no new or unexpected adverse events.

Checkpoint inhibitor responses have always danced to their own drummer: When ipilimumab was first being tested, doctors thought it was not working, because the response patterns were so slow. Eventually the effects kicked in, making up for the slow responses with durable, often sweeping effects. Similarly unpredictable, lagging response patterns may come into play here, with tumor reduction sometimes occurring *after* disease progression.

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Checkpoint Blockade for Advanced Cutaneous SCC

Along with countless studies on checkpoint blockade treatment for head and neck squamous cell carcinoma, the meeting featured a notable study of a new checkpoint blockade therapy for *cutaneous* SCC (CSCC) that had impressive, if early, safety and efficacy findings. The phase 1 trial tested a fully human anti-PD-1 monoclonal antibody dubbed REGN2810 on 26 patients with unresectable, locally advanced or metastatic CSCC. To date, there has been no standard of care for these patients. Since UV damage causes most mutations in CSCC just as in melanoma, these tumors might logically respond to PD-1 checkpoint blockade.

The patients all received 3 mg/kg REGN2810 by IV infusion every two weeks for up to 48 weeks, with biopsies taken at baseline, on day 29 and, if possible, at progression. The most common treatment-related adverse event was fatigue, but one patient had a rash, one had arthralgia and one had elevated enzymes suggestive of liver injury. The overall response rate (ORR) and disease control rate, respectively, were 52 percent (12/23) and 70 percent (16/23), including patients with stable disease. Median PFS and OS have not been reached, and only one patient has experienced progressive disease during treatment after initial response. In short, the well-tolerated treatment is the first ever to produce significant antitumor activity in patients with advanced CSCC. This potentially pivotal trial is still enrolling patients.

Reference

- Papadopoulos KP, Owonikoko TK, Johnson ML, et al. REGN: a fully human anti-PD-1 monoclonal antibody for patients with unresectable, locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC)—initial safety and efficacy from expansion cohorts (ECs) of phase 1 study. *J Clin Oncol* 2017; 35. ASCO Abstract 2503.

Triple Combination Therapy for Merkel Cell Carcinoma (MCC)

It was just a little poster presentation that appeared June 5 at ASCO, but it was impressive. It described the successful results of a very small, four-patient study from Fred Hutchison University and the University of Washington in Seattle, combining the recently FDA-approved checkpoint inhibitor avelumab (Bavencio) with two other treatments (autologous T-cell transfer therapy and either radiation or the immunotherapy interferon). Three out of the four stage IV metastatic MCC patients treated with this experimental combination were in complete remission following the treatment.

In the autologous T-cell transfer therapy, the researchers extracted T cells for the Merkel cell polyomavirus (MCPyV), which recognized the MCC from the patient's blood. Eighty percent of MCCs are caused by MCPyV oncoproteins, and abundant MCPyV-specific tumor-infiltrating lymphocytes are associated with good MCC outcomes. The researchers multiplied these T cells in the lab and reinjected them into the patient to boost their attack on the MCC cells. When they added the avelumab, it appeared to kick the enhanced T cells into high gear.

As successful as checkpoint blockade therapies have been, none have had lifesaving results as convincing as these. Three out of four patients going into complete remission is unheard of with metastatic MCC, a rare, aggressive endocrine skin cancer most often fatal for patients with advanced disease. Avelumab, a PD-L1 blocker (programmed death ligand-1, or PD-L1, is the ligand

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that links with PD-1 to block T cells in the body), was the first drug ever to extend survival in metastatic MCC patients. However, half of patients do not respond, suggesting a lack of adequate MCPyV-specific T cells and/or tumor evasion due to reduced HLA expression caused by the MCC. By expanding the MCPyV-specific T cells through adoptive transfer, and by upregulating HLA expression through radiation or interferon, the researchers produced a triple combination therapy that was more effective than any of the therapies alone.

A previous study of four patients combining the T-cell transfer therapy with radiation or interferon, but not including avelumab, was not as successful, with disease progressing in three of the patients, two of whom have since died.

Reference

- Paulson KG, Perdicchio M, Kulikauskas R, et al. Augmentation of adoptive T-cell therapy for Merkel cell carcinoma with avelumab. *J Clin Oncol* 2017; 35 (suppl; abstr 3044). ASCO 2017 abstract 3044, presented at poster session June 5, 2017.

Targeted Therapies

The developments in targeted melanoma therapy have not been as earthshaking in the past year as with the immunotherapies, and the anti-PD-1 and combo checkpoint blockade therapies have become further established as frontline therapies in the majority of stage IV patients. However, studies have further validated the two FDA-approved BRAF-MEK combination therapies vemurafenib-cobimetinib and dabrafenib-trametinib over the monotherapies vemurafenib and dabrafenib. Jeffrey Weber, MD, at NYU Langone Medical Center, presented findings at ASCO from the longest-term follow-up ever of a randomized trial on combination dabrafenib-trametinib, showing that more than one-fourth of treated patients with advanced BRAF V600-mutant melanoma remained alive at five years. In the subgroup of patients with normal baseline lactate dehydrogenase (elevated LDH levels are a marker for a poor prognosis) and fewer than three organ sites with metastases, *half* remained alive at 5 years. "Long-term survival is achievable with dabrafenib-trametinib in patients with BRAF V600-mutant metastatic melanoma, particularly those with favorable baseline factors," Dr. Weber reported.

One phase 2 study presented at ASCO, the COMBI-MB trial, even showed for the first time that combo dabrafenib-trametinib, like certain checkpoint blockade therapies, could produce significant responses across the blood-brain barrier in melanoma patients with brain metastases. Combo dabrafenib-trametinib administered to BRAF V600-mutant melanoma patients with brain metastases produced a median intracranial response rate (IRR) of 58 percent, an almost identical overall response rate of 58 percent, median PFS of about six months and six-month OS of about 79 percent. While the IRR and other figures were promising, the responses were less durable than for patients without brain metastases, and less durable than achieved in the checkpoint blockade studies.

While the findings on the combination targeted therapies are encouraging, Paul Chapman, MD, of Memorial Sloan Kettering, said at an educational session on June 5 that over all, the combos have been "a little better, not a lot better" than the monotherapies. "Perhaps 10 to 20 percent of patients go on for a long time," he said, "but most people eventually have disease progression."

For that reason, studies of new targeted monotherapies and combination therapies have been progressing toward FDA approval, including those directed at new parts of the mitogen-activated protein kinase (MAPK) cascade, the pathway that transmits signals for melanoma to grow and metastasize. The hope is that just as adding MEK blockers to BRAF blockers lengthened patients' survival, blocking other parts of the MAPK pathway such as NRAS will improve survival further for many patients.

Perhaps the most important and complex area of focus with the targeted therapies, says Dr. Chapman, one of the leaders in the development of the targeted therapies, is the quest to pinpoint and ultimately conquer the resistance mechanisms that eventually make them stop working. "We're learning a lot about these mechanisms," Dr. Chapman noted. "There are basically two types. First, there is the RAS-dependent type that relies on RAS to be activated, due either to an activating receptor-tyrosine kinase, or just an activating mutation in NRAS." When RAF activation happens, he says, it leads to dimerization of RAF kinases — two similar RAF kinases link together to form a molecular complex — and this dimer complex is resistant to the current RAF inhibitors. "This is a very common way that tumors escape our treatments," Dr. Chapman said. The other way is through a RAF-independent mechanism downstream of RAF, such as an activating mutation in MEK. "We're working on ways of overcoming these resistance mechanisms, like developing RAF inhibitors that can inhibit dimers, or adding MEK inhibitors, or doing these drug interventions on a different schedule that can avoid the resistance mechanisms altogether."

References

- Long GV, Eroglu Z, Infante JR, et al. Five-year overall survival (OS) update from a phase II, open-label trial of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600–mutant unresectable or metastatic melanoma (MM), Presented at ASCO June 4, 2017.
- Davies MA, Robert C, Long GV. A phase II study of combination dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600–mutant (mut) melanoma brain metastases (MBM). Presented at ASCO June 4, 2017.

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