This year, The Skin Cancer Foundation is celebrating its 40th birthday. It’s an important milestone for the Foundation, reflecting on four decades of invaluable work. Since its start in 1979, along with its many other endeavors, the SCF has championed revolutionary strategies for the prevention, detection, diagnosis and treatment of melanoma and other skin cancers that ultimately became state of the art.

The Melanoma Letter has been an important part of this effort since it was launched in 1982. It has given a forum to the world’s top clinicians and investigators to distill the key elements of their work for dermatologists and other medical professionals across the U.S. In 1992, when Donald Morton, MD, pioneered the sentinel node biopsy technique for the early detection of melanoma metastases to the lymph nodes, we worked closely with him to introduce it widely that year in our pages. We periodically reported the ongoing research on it, until it was proven to be tissue-saving and lifesaving — and embraced by most dermatologists and oncologists. We frequently wrote about dermoscopy, an early detection tool for melanoma, when many considered it a fringe technique, and today it is a mainstay in dermatologists’ offices. When John Kirkwood, MD, developed the first FDA-approved adjuvant treatment for high-risk stage II and III melanoma, we headlined the technique in The Melanoma Letter, and the SCF sent him on tour around the U.S. to discuss its impact. We presented...
early research on immunotherapies and targeted therapies that were later FDA-approved, and today they form the backbone of treatment for advanced melanoma, extending and saving the lives of patients whose cases once would have been hopeless.

Mark Teich, the SCF’s scientific director, has been with the Foundation for 27 of its 40 years, since 1992, and has been the staff editor of The Melanoma Letter ever since. We have worked with him as editor-in-chief and associate editor on this award-winning publication for more than two decades. So, we have certainly achieved continuity along with what we believe is a consistently high standard of new, accurate and vital information for you, our readers.

For the fourth straight year, Mark attended the American Society of Clinical Oncology’s annual meeting, and it has been a recent tradition in The Melanoma Letter for him to bring back findings from the front. This issue features Q&As that he did with two of the presenters, who happen to be leaders and icons of melanoma research, Jeffrey Weber, MD, PhD, and James P. Allison, PhD. We think you’ll find something fascinating and valuable in these interviews, which illuminate the state of the art and the future of treatment for advanced melanoma.

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The two dominant forms of treatment for advanced melanoma now are checkpoint blockade immunotherapy and BRAF-MEK targeted therapy. What are their relative strengths and drawbacks, and which would most physicians consider the frontline therapy today?

**Jeffrey Weber, MD, PhD:** If you look at the longest-term data with combination checkpoint blockade therapy, ipilimumab-nivolumab (Yervoy®-Opdivo®), there’s about 53 percent four-year overall survival (OS) now, and it looks like this plateaus. So we’re essentially going to cure about half of all patients on ipilimumab-nivolumab. Using the anti-PD-1 checkpoint blockades monotherapies, either pembrolizumab (Keytruda®) or nivolumab, you probably plateau at about 40 percent. So you gain about 10 percent with the combo, but with a tripling of toxicity.

With targeted therapy, if you look at the latest data at this year’s annual meeting, the results of the Combi-D and Combi-V trials of combination dabrafenib-trametinib (Tafinlar®-Mekinist®), it’s about 34 percent long-term survival. The second combination targeted therapy developed, vemurafenib-cobimetinib (Zelboraf®-Cotellic®), is probably going to have about the same results once the long-term studies are in, and the newest combo, encorafenib-binimetinib (Braftovi®-Mektovi®), may have slightly better results, but it will take some years for the long-term results to come in. To date, average OS with this combination has been 33.6 months.

So, do the math. Would you rather have a 34 percent plateau with BRAF-MEK targeted therapy at four years or a 40 to 50 percent plateau at four years with checkpoint blockade therapy? That’s why most people in the academic world now go with frontline checkpoint inhibition, usually combo ipi-nivo. We’ll save the targeted therapy for later.

Now, some patients are too ill to go on the combo checkpoint blockade therapy or have had an allograft transplant requiring immunosuppressants or have autoimmune disease, and those folks won’t go on checkpoint blockade; those folks will go on targeted therapy instead if they have mutant BRAF. But most, if they can, will choose to go on immunotherapy first, given the lower survival plateau of the targeted therapy.

**Mark Teich:** In what other situations would you go with targeted BRAF-MEK therapy first?

**JW:** The advantage with targeted therapy in the metastatic mode is that you get rapid regression in someone symptomatic with rapidly growing disease. This advantage disappears in someone with brain metastases, where combination ipilimumab-nivolumab is probably going to be more beneficial. Although no one has done a head-to-head study, the data for those with central nervous system (CNS) disease look much better giving combination ipilimumab-nivolumab, even for those with mutant BRAF, then following with targeted therapy after treatment failure or after side effects of the initial therapy become too serious.
With respect to adjuvant therapy, in the first year after treatment there's 88 percent relapse-free survival (RFS) with combination dabrafenib-trametinib (the one BRAF-MEK targeted therapy approved for adjuvant therapy), which is better than with pembrolizumab in the Keynote 045 study, with a similar patient population. So, it looks like there's a bump in the first year with the targeted therapy, but then things come down, so the big question is whether the pembrolizumab and nivolumab adjuvant studies will have a higher plateau at four and five years in RFS and OS. [Combination ipilimumab-nivolumab therapy has not been approved yet as an adjuvant therapy.] We don't know. There's not enough follow-up yet, but we'll find out. A study is underway, and so far, two years and three years after treatment starts, targeted and checkpoint inhibition adjuvant therapy look similar. The question is, will that hold up over time?

Another advantage of targeted dabrafenib-trametinib therapy in the adjuvant setting is that, unlike the approved frontline checkpoint blockade therapy adjuvants (nivolumab or pembrolizumab), it doesn't risk irreversible side effects such as endocrinopathies and diabetes. Although total toxicity is higher for the targeted therapies, the irreversible toxicity is lower. So if, for example, I see a patient, especially a young person, with a low-risk stage IIIA tumor, with good data for BRAF-MEK but not so much data for nivolumab or pembrolizumab, I might be tempted to go with frontline targeted adjuvant therapy rather than immunoadjuvant therapy.

However, because of the distant metastatic data showing a better plateau with immunotherapy, most academicians prefer adjuvant immunotherapy for their first choice rather than targeted therapy. To be honest, that's not directly backed up, because adjuvant trials haven't covered comparable patient populations, and they don't have the same follow-up. That's more of a gut feeling rather than a data-driven decision. But most of my colleagues who give adjuvant therapy will go with nivolumab or pembrolizumab first rather than combination dabrafenib-trametinib targeted therapy in the adjuvant setting.

**MT:** Since there's not long enough follow-up with the adjuvant therapies approved in the past couple of years [nivolumab, dabrafenib-trametinib and now pembrolizumab] to prove a long-term overall survival advantage, why risk the side effects from all of them?

**JW:** That's not an unreasonable question, except that recurrence-free survival tends to go hand in hand with overall survival. If you look at the combi-AD study (a randomized, double-blind phase 3 adjuvant trial of combination dabrafenib-trametinib versus two placebos), the RFS and OS benefits pretty much went in lockstep. For most adjuvant therapies, when you see an RFS advantage, it usually converts ultimately to overall survival advantage. In our treatment, that may be a little different. Let's say you get adjuvant nivolumab alone, and if that fails, you can go on targeted combo therapy if you're BRAF-mutated, so there's an inherent crossover. Survival falls out as a useful marker. If you're on ipilimumab and you fail, you can also get nivolumab, and if you're on nivolumab and you fail, you can get ipilimumab. That obviates the survival endpoint, and you can only use RFS as your endpoint. But a truly virtuous treatment will probably show an OS advantage, not as big in OS as you did in RFS, but you may well see that advantage. That's going to take another year of follow-up at least.

**MT:** Since combination ipilimumab-nivolumab has the highest survival rates in the metastatic setting, what are its chances of being approved soon in the adjuvant setting?

**JW:** A trial testing combo ipilimumab-nivolumab in the adjuvant setting finished its accrual, and we should know in 2020 or 2021 whether that's a positive study. The difference between nivolumab monotherapy and ipilimumab-nivolumab is probably not going to be as big as the difference that was found between pembrolizumab versus placebo, say, in the study that got adjuvant pembrolizumab approved. I think we're going to need longer follow-up with enough events to see a difference, but my gut says there will be an RFS and OS

"Do the math. Would you rather have a 34 percent plateau with BRAF-MEK targeted therapy at four years or a 40 to 50 percent plateau at four years with checkpoint blockade therapy?"
advantage with ipilimumab-nivolumab over nivolumab alone, just as there is in the metastatic setting. We’ll see how that plays out.

MT: In the past, most people with distant metastases died within months. With these vastly improved survival rates from targeted therapy and checkpoint blockade therapy, why do the 2019 data from the American Cancer Society’s respected Cancer Facts and Figures still show only 23 percent average five-year survival for these patients?

JW: The survival figures always lag a year or two behind in the tumor registry. The death total is more important, and deaths are going down significantly, down to 7,230 this year from 9,320 last year (a 22 percent reduction). It’s probably going to keep dropping even more. That’s the key.

MT: Considering that combo ipilimumab-nivolumab has triple the risk of serious side effects, wouldn’t a lot of patients choose the far safer monotherapies, either nivolumab or pembrolizumab, even if 10 percent more patients have long-term survival with the combo? How do patients make this choice, and how do you advise them?

JW: Yes, the monotherapies are significantly less toxic, but it’s all in how you present it, and whether or not you show you’re enthusiastic about the combo and say you would choose it yourself. If you show hesitation for the combo checkpoint blockade, then patients mostly won’t stick with it.

Frankly, if I were a patient, and you told me I had a 6 percent higher chance of increased survival, hell, I want to live longer, so give me the toxic stuff, as long as you can reverse most of the toxicity. As we learn, we are able to reverse more and more of the toxicity, though still not all.

Now, if someone is not willing to risk the toxicity, or is older or more fragile, we’ll put them on a single-agent monotherapy, but usually paired with something else, an investigational drug, usually with low toxicity.

MT: One of the key things investigators have been looking into recently is optimal sequencing of these therapies. Does starting with combo ipilimumab-nivolumab, then when it fails or becomes intolerable moving to targeted therapy, work best, or does starting with targeted therapy and then moving to immunotherapy?

JW: There are two trials testing this, but they are difficult to accrue. Michael B. Atkins, MD, leader of one of those studies, has been very frustrated. His Intergroup Trial is an active 300-to 400-patient randomized study, but recruitment is taking a long time, since most patients want immunotherapy frontline.

They see the data from the COMBI-D and COMBI-V studies, and they want immunotherapy. They don’t want the targeted therapy, because dabrafenib-trametinib in the metastatic setting has a lower plateau of survival. I think they’re finally getting decent accrual, and though it’s taking a long time, that trial will eventually tell the story.

MT: One bit of exciting news this year appears to be some of the early findings with neoadjuvant therapy, which is adjuvant therapy given to high-risk melanoma patients before tumor surgery rather than after. Is it true that early success with neoadjuvant therapy appears to be a marker for durable treatment success?

JW: Yes, if I had to venture a guess, I’d say that’s exactly true — there’s a lot of excitement around neoadjuvant therapy, though it’s not yet standard of care. And it appears that it can distinguish early on those who would benefit from adjuvant therapy versus those who would not. In his trial presented at ASCO this year, Alexander M. Menzies, MD, showed that patients who have a pathologic complete response (PCR) to neoadjuvant therapy do better over time than those who don’t. But keep in mind, when Alex showed that compilation of data, he’d had probably about 100 patients with no relapse. However, the median follow-up was only 10 months, so who knows what’s going to happen after 20 or 30 months? That’s why you need to do a clinical randomized trial where you take patients who had complete responses to neoadjuvant therapy, and either treat or don’t treat them with adjuvant therapy after surgery. That would be a trial worth doing.

MT: All the drugs now being used as frontline adjuvant therapies for stage III melanoma — nivolumab, dabrafenib-trametinib and now pembrolizumab — had to gain specific approvals in the adjuvant setting after already being approved for stage IV. Will they also have to gain separate approvals in the neoadjuvant setting?

JW: I don’t think anyone is going to go for registration. They’re already approved drugs. I think the U.S. Intergroup will do a study of pembrolizumab neoadjuvant therapy versus no neoadjuvant therapy followed by pembrolizumab adjuvant therapy after surgery and a complete lymph node dissection. If that result is positive, it will be practice-changing, and it will get into the compendium and probably the National Comprehensive Cancer Network Guidelines, but I doubt they’ll go for an FDA approval. The therapy will just enter common practice. You don’t need a registration for every possible treatment.
In 2018, James P. Allison, PhD, won the Nobel Prize in Physiology or Medicine for his lifetime of contributions to the treatment of advanced cancer patients. His discovery of the CTLA-4 immune checkpoint led to the development of the anti-CTLA-4 drug ipilimumab (Yervoy®), the first FDA-approved checkpoint blockade therapy. Today, the drug combination pairing ipilimumab with another checkpoint blockade drug, the anti-PD-1 agent nivolumab (Opdivo®), has produced longer survival for advanced melanoma patients and many other cancer patients than any other treatment in history.

In this year’s ASCO annual meeting, Dr. Allison offered a presentation on why some patients don’t respond to checkpoint blockade immunotherapy and what further investigation needs to be done for these patients. Mark Teich interviewed Dr. Allison about the most important trends in research for the future treatment of advanced melanoma.
JA: Well, I have to admit that I’m not entirely unbiased. Of course, since the PD-1 checkpoint was discovered and the anti-PD-1 drugs and anti-PD-L1 drugs were developed, they are much safer drugs than ipilimumab; the adverse events are similar, but they’re less frequent with the anti-PD-1 therapies. And other types of drugs have been developed that are even safer, but they work very differently and they remain to be proven effective.

Despite all the new drugs being tested and new checkpoints explored, it’s the combination of ipilimumab and nivolumab that has had the best possible results to date. Nivolumab and the other approved anti-PD-1 drug pembrolizumab (Keytruda®) have had very good results as monotherapies, and if you place their characteristics side by side against ipilimumab, it obviously favors the anti-PD-1 therapies. But it’s combination ipilimumab-nivolumab that has the greatest durability and appears to be saving the most lives. It has had the greatest success of any two-way combination therapy. Furthermore, algorithms have been developed that are becoming increasingly successful in dealing with the adverse events, as long as you pay close attention as treatment goes on; so more and more, the combination is prevailing.

Another important thing about ipilimumab is that it’s given only four times in the course of therapy, and that’s the end of it. The 10-year follow-ups on ipilimumab as monotherapy are just appearing now, and they show that after just those four treatments, 20 percent of patients are alive 10 years after you stop therapy, essentially cured. The anti-PD-1 drugs, on the other hand, are given every two weeks for a long time, until progression or until the side effects are too bad. That appears to be important, because the T cells are getting exhausted and you have to present the antigen again.

When you put anti-CTLA-4 and anti-PD-1 together, the number of T cells actually decreases from what you had in monotherapy, but the nonexhausted cells go way up. These nonexhausted cells get activated, and you’ve lost the exhausted cells. We’re not clear why, but you’re reversing the exhausted state. You’re radically changing the mechanism of action, and exhausted cells are no longer important. It’s an epigenetic change in the cells. You’re teasing out the nonexhausted T cells, and they may never get exhausted. The combination is key; by targeting multiple checkpoints, you can get durable remission.

To me, the 10-year results on ipilimumab are perhaps the most exciting news at the ASCO annual meeting this year, because they probably mean that all the approved checkpoint drugs will plateau, going 10 years and beyond, and patients who respond for that length of time are essentially cured. The 20 percent of patients responding at the four-year mark after treatment with ipilimumab are still responding 10 years and longer, and while the anti-PD-1 drugs haven’t been around long enough for 10-year results, the same will probably be true with the anti-PD-1 monotherapies as well as combination ipilimumab-nivolumab, meaning that 50 to 60 percent of patients on the combination will be cured. The combination has an additive response rate. So far, the responses with the combo therapy are holding at about four and a half years, and the chances are they’ll be holding at 10 and beyond in most patients. I think we can consider many of these patients cured.

MT: How can we get durable responses in more than 50 to 60 percent of patients?

JA: That’s the goal, to get the percentage as high as we can. With the basic standard of care now leading to about a 50 to 60 percent durable response, and with new combinations and other checkpoints being explored, we want to get as close to 100 percent as we can. We’ll be combining the new agents with those we already have. That’s the focus now, adding third or fourth drugs to the combinations we already have.

MT: Which of these new agents holds the most promise?

JA: There are a lot of candidates. But the goals have shifted: We’re no longer looking for a single agent home run as we always did in the past; we’re beginning to realize the importance of just adding 5 to 10 percent here and 5 to 10 percent there to the response rate, without toxicities. A
key factor we learned along the way is this: When patients didn't respond to ipilimumab, one of the reasons was that there are multiple checkpoints. So, for example, many who didn't respond to ipilimumab then responded to the anti-PD-1 therapies, which blocked a different checkpoint. There are also a lot of other reasons patients may not respond, but this is a very fundamental reason. The more checkpoints you uncover and block, the more T cells you have to fight the tumor. And one simple way you keep increasing durability of response is by putting these checkpoint blockers together. I think checkpoint combinations are going to become the standard of care for almost everything. Melanoma treatment is leading the way, but it's going to be the same sort of situation with other cancers, for example, kidney cancer, where the response rates are still under 50 percent.

**MT:** When you say that checkpoint combos are going to be the standard of care, are you talking specifically about ipilimumab combined with anti-PD-1 and other checkpoint blockers, or entirely different checkpoint combos?

**JA:** I think that combos of anti-CTLA-4 with anti-PD-1 drugs, with new agents added to them, are going to be the key. People disagree on the number of checkpoints out there — it depends on how you define checkpoints — but given the data to date with melanoma and other cancers, those are the two most important ones. There are others that may play another role, depending on the type of cancer, but those are the two most important in melanoma. For example, one relatively new molecule called VISTA, which is PD-1-like, is a newly discovered checkpoint present in a lot in patients with gastric cancer, but not so much in melanoma. So I think what we're trying to do, rather than just find new blockbuster checkpoints, is find ones in different tissues and just add antibodies to block those. You might have a cocktail of an anti-PD-1 drug and an anti-VISTA drug, or another drug blocking a different checkpoint, to get better and better response rates.

There are also many other agents out there and other checkpoints, but they're still in testing and not widely adopted yet. I also think that combining the checkpoint blockade therapies with BRAF-MEK therapies may end up a pretty amazing combination. It's just possible that these drugs can inhibit melanoma cells during their proliferation phase, but we'll have to design a strategy, figure out some different way of combining them or sequencing them than we have now, since now they interfere with one another in some ways. We need to make sure these additive therapies enhance rather than impede the immune response. Also, there's some liver toxicity now.

It's similar with other techniques being combined with immunotherapy, including radiation and chemotherapy, which are already proving very promising. What's happened is that people who do radiation therapy and/or some form of chemotherapy are now realizing that you don't have to kill every last tumor cell in the patient, you just have to kill enough to cause inflammation, which kicks on the immune system, and the immune system may take out the rest of the cancer. You just need to find the right dosage and means of administration of whatever it is so that it keeps toxicity down and enhances rather than impedes the immune response. With radiation, for example, you may kill a bunch of tumor cells, and then you come back a week later to kill some more, and immune cells are already priming T cells where the tumor was, or let's say where it still is. Its size has been reduced, and then you do another bolt of radiation, and you kill more tumor cells, but you're also killing the immune cells there. So, it's just a matter of figuring out how to do it in a way that it works against just the tumor and not against the immune system. There are pretty interesting results coming out of radiation therapy, and they're taking a careful look at what it does to the immune system.

**MT:** Will we ever assemble combinations that will achieve a 100 percent response?

**JA:** Well, with melanoma we're already getting near 60 percent, which isn't 100, but it's a lot better than 5 percent or whatever it was when we started. I would like to think of 100 percent as the goal, but there can be a limit to how many drugs you combine. You can't necessarily put 13 different things together. So I think there will be some limitations.

One thing that bothers me is that there are so many possibilities with so many combinations, so many diverse trials being run, and they're repetitive, and many aren't adding anything new. Even worse, there are some pivotal trials with, say, 100 or more patients, which is a lot, and some aren't being controlled well enough to leave a meaningful trail. In my opinion, if you do a trial with any kind of cancer right now, with any kind of treatment, and you don't do biopsies, it's just a waste. Whether something meaningful happens clinically or not, you can learn from it — you can learn from what doesn't work as well as what does work. You need to be looking for any changes in the tumors. We run a big lab at MD Anderson called Immunotherapy Platform, and that's one of our goals. On every trial we're involved in, we're looking at every clinical signal, every potential biomarker of success or failure, every change that occurs with therapy that might indicate if we're going in the right direction. And it's been useful so far.

**MT:** How long do you think we are from going the rest of the way, close to 100 percent responders?

**JA:** You just keep adding things to the mix, and you keep trying. I'd like to think of it as a 10-year plan.