

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Drugs in Development for Melanoma



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H&O What are the shortcomings of existing agents for melanoma?

KF All of the new melanoma agents approved by the US Food and Drug Administration (FDA) have been approved for use in overt metastatic disease, so a major shortcoming is the lack of treatments for the adjuvant therapy setting. Targeted molecular therapy and immunotherapy have been shown to work in metastatic disease, and if possible we would like to see data showing that they also work as adjuvant therapy.

Another problem is that despite the enormous progress over the past 5 or 6 years in developing new agents that substantially prolong life in metastatic disease, the majority of patients with metastatic melanoma still die of their disease. We are excited that some patients are surviving for several years and may continue to survive for even more years. This represents a dramatic improvement over where we were 5 years ago. Still, these patients are in the minority.

Finally, and this relates to the second problem, we see a high rate of resistance to melanoma treatments. Resistance can be either immediate or acquired, and it occurs with both targeted molecular therapy and immunotherapy.

H&O Which agents have been approved over the past 5 years?

KF In the area of targeted molecular therapy, we now have the BRAF inhibitors vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) and dabrafenib (Tafinlar, Novartis)

and the MEK inhibitor trametinib (Mekinist, Novartis). All 3 of these agents were approved as single-agent therapies for patients with *BRAF* mutations, who represent approximately half of all melanoma patients. And then in early 2014, the FDA approved the combination of dabrafenib and trametinib for these patients.

In the area of immunotherapy, we saw the approval of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody ipilimumab (Yervoy, Bristol-Myers Squibb) in 2011. After that came the approval of the programmed death 1 (PD-1) inhibitors pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol-Myers Squibb) in 2014. The FDA is likely to approve a combination of ipilimumab and nivolumab for previously untreated patients with metastatic melanoma. This combination was shown in the phase 3 CheckMate 067 study (Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma), which was published in the *New England Journal of Medicine* earlier this year, to produce significantly longer progression-free survival than ipilimumab alone. In a subset of patients with programmed death ligand 1 (PD-L1)-negative tumors, the combination was more effective than either ipilimumab or nivolumab alone. High-grade adverse events were more frequent with the combination than with single-agent therapy.

H&O What new chemotherapy agents for melanoma are being developed?

KF We have seen results from the most recent phase 3 clinical trial with nab-paclitaxel (Abraxane, Celgene),

the albumin-bound form of paclitaxel that already is FDA-approved for use in breast cancer, lung cancer, and pancreatic cancer. The CA033 study (a Trial of ABI-007 Versus Dacarbazine in Previously Untreated Patients With Metastatic Malignant Melanoma) found that progression-free survival in melanoma was better with nab-paclitaxel than with dacarbazine, which is the historical standard benchmark chemotherapy drug in melanoma. The study did not find a difference in overall survival, however, so it is not clear whether nab-paclitaxel should be considered the new standard for melanoma patients. That is the only real development in the past several years now in terms of traditional chemotherapy treatment.

H&O What new agents for melanoma are being developed in the area of immunotherapy?

KF The immune checkpoint inhibitors ipilimumab, pembrolizumab, and nivolumab are just the first few of a whole generation of antibody therapies that are directed to regulators of the immune system. These antibodies block inhibitory molecules on immune cells, particularly CD8+ effector T cells, allowing these cells to recognize and even eliminate tumors when maximally successful.

Many of the antibodies that are in development work by “blocking the brakes” on the immune system, like the agents that are already available, whereas others work by “pressing the gas pedal” on the immune system. Some of these antibodies are being studied as stand-alone treatments, and many are being studied in combination with backbone immunotherapies.

H&O What are some of the specific immunotherapy agents that are in trials right now?

KF Several agents are being studied in phase 1 trials that target inhibitory factors, specifically T-cell immunoglobulin and mucin protein 3 (TIM-3) and lymphocyte activation gene 3 (LAG-3). As for agents that target activating factors, the most notable ones are those targeting OX40, LX4, and 41-BD.

In addition, we have seen a resurgence of interest in antibodies that target CD40. That approach initially was developed in the late 2000s, prior to the emergence of CTLA-4 and PD-1 antibody therapy. Antibodies that target CD40 did show some promise in melanoma when used as single agents. Now, phase 1 studies are examining these agents in combination with backbone therapy.

Not all of these studies are looking specifically at melanoma, but several of them have either a complete or a heavy focus on melanoma. As we know, antibodies generally have shown the greatest effect in melanoma compared with other cancer types.

H&O What new agents for melanoma are being developed in the area of targeted molecular therapy?

KF We have laboratory and clinical evidence that MEK inhibitors, such as trametinib, can play a role in treating patients with melanoma that does not have a *BRAF* mutation. MEK inhibitors may have single-agent efficacy, and perhaps even more of a role as a backbone treatment in combination therapy.

Data from phase 2 clinical trials support the notion that MEK inhibitors are likely to play a role in treating some fraction of patients whose tumors have mutations in genes other than *BRAF*. The other most common gene mutations that we know about are those in *NRAF* and *NF1*. The vast majority of patients with colorectal cancer have a mutation in one of those 3 genes: *BRAF*, *NRAF*, or *NF1*.

We have preliminary data from clinical trials that support the idea that a MEK inhibitor may benefit patients, especially when given in combination with another agent. We hope to be able to achieve results with a combination of 2 targeted drugs, including a MEK inhibitor, that are just as good as what we have seen with single-agent *BRAF* inhibitor therapy.

H&O What other types of combination therapies are being studied?

KF We are likely to see a broad role for the combination of targeted molecular therapy and immunotherapy. Patients with a *BRAF* mutation would receive a *BRAF* inhibitor, and those without a *BRAF* mutation would receive a MEK inhibitor. A number of phase 1 melanoma-specific clinical trials are being conducted that combine targeted therapy with immunotherapy. Although it is still early, we have already seen clinical data emerge at the annual meeting of the American Society of Clinical Oncology (ASCO) and other venues that support the idea that this is a promising strategy.

One of the trials that captured special attention at the ASCO meeting was a study by Ribas and colleagues that is looking at a dabrafenib/trametinib backbone in combination with an experimental PD-L1 antibody called MEDI4736 for patients with *BRAF*-mutant melanoma. The trial also examined the use of trametinib plus MEDI4736 for patients with wild-type *BRAF*. Although this trial was focused on determining the correct regimen and dose, it also produced encouraging data on response to therapy—it may be that the use of combinations can boost efficacy.

H&O What additional agents are being developed for melanoma, such as vaccines?

KF Vaccines have long been studied for use in melanoma. Most of these vaccines target proteins that are known to be present on melanocytes, the precursor cells that can become melanoma. Other vaccines that target developmental fetal antigens also have been studied in the overt metastatic and adjuvant settings.

Although these vaccines have consistently failed to demonstrate meaningful benefit when used as stand-alone agents, we have scientific evidence to support the idea that they might produce a synergistic effect in combination with anti-CTLA-4 and anti-PD-1 agents. We have seen a resurgence of interest in the idea of using a vaccine to amplify or steer an immune response against the tumor, without magnifying the risk for autoimmune side effects.

Vaccines are being developed and investigated largely in academic centers with funding from the National Institutes of Health, as we have not seen as much focus on these from the pharmaceutical industry. When we look at some of the early trials that are being undertaken, however, we do see some early hints of proof of concept. Should these findings continue, they might open the floodgates in terms of further investigation in this area.

H&O What other agents are being developed for use in melanoma?

KF Researchers also are doing work in the area of cellular therapy, in which immune cells that are collected from patients are manipulated in the laboratory and then reinfused. Most of this work in melanoma has centered on adoptive T-cell therapy, which requires less engineering than chimeric antigen receptor (CAR) T-cell therapy.

Cellular therapy has been in clinical trial testing mode for more than 13 years, and the technology has continued to evolve over this time. We have known for years that responses and durable responses can be achieved with that approach. The question is whether continued advances in other areas leave a role for that approach, such as in patients who are not expected to respond to other immunotherapies, such as anti-PD-1 and anti-CTLA-4 therapies.

I believe that the way we are going to produce durable remissions in the majority of patients—and someday, the vast majority of patients—is to align subpopulations of patients with these different approaches. Many patients will likely require a combination approach that employs multiple modalities.

Suggested Readings

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