ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Emerging Therapies in Melanoma

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H&O What are the current outcomes in melanoma, and how are the data evolving?

JW In the past, standard treatments for metastatic melanoma have included chemotherapy agents like dacarbazine or temozolomide. These agents produced median survival times of only 7 or 8 months. Another agent for metastatic melanoma that has been approved by the US Food and Drug Administration (FDA) is interleukin-2 (IL-2), but it has a response rate of only 10–15%. In *BRAF*-mutated melanoma, survival ranges from 12–16 months, depending on the clinical trial data. In 2012, with the approval of the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)–blocking antibody ipilimumab (Yervoy, Bristol-Myers Squibb) and the *BRAF* kinase inhibitor vemurafenib (Zelboraf, Hoffmann-La Roche), as well as other medicines under development, there is cause for hope that survival can be further improved. However, current survival in melanoma is a moving target, so it is difficult to approach this topic as a single category.

H&O What role does immunotherapy play in the treatment landscape?

JW Immunotherapy plays a very important role in the treatment landscape because it is the source of durable responses. It is a way to not only control the disease in the short term, but it is most emblematic of a means to durably control the disease. Although only a minority of patients benefit from immunotherapy, these benefits appear to last for a very long period of time.

H&O What were your recent findings regarding the abscopal effect?

JW The abscopal effect occurs when localized radiation therapy delivered to a single tumor in a patient with advanced-stage cancer leads to regression of tumors outside of the radiation field. Although it is a very rare phenomenon, it has been reported in several cancers, including kidney, melanoma, and lymphoma. Our research involved a single patient who was treated with radiation while also receiving ipilimumab. Although her disease was not growing quickly on maintenance ipilimumab, it was progressing. We irradiated 1 tumor that was causing her pain, and that tumor had a nice regression. However, a surprising observation was that lesions in areas not targeted by radiotherapy—right hilar lymphadenopathy and splenic lesions—had also regressed. Ten months later, computed tomography scans showed that the improvement persisted, with the continued presence of minimal disease. Essentially, this shows that we were able to stimulate a systemic immune response.

H&O What are the implications of these findings?

JW These findings have taught us a significant amount about the potential advantages of combining immunotherapy with other cancer treatment options, with a specific focus on radiation therapy. Furthermore, several clinical trials to prospectively validate this approach are under way in prostate cancer (NCT00861614) and melanoma (NCT01449279).

H&O What are some other promising agents?

JW In the September 29 online edition of the *New England Journal of Medicine*, Flaherty and associates reported the results of a phase I/II, multicenter, open-label study of the *BRAF* inhibitor dabrafenib combined with the *MEK* inhibitor trametinib in patients with metastatic melanoma and *BRAFV600* mutations (*BRAFV600* or *BRAFV600K*). The combination of dabrafenib and trametinib was shown to be safe in patients with *BRAF*-mutated metastatic melanoma. It also provided significant improvement in progression-free survival when compared with dabrafenib monotherapy.

In addition, drugs that target the programmed death-1 (PD-1) pathway hold considerable promise for the treatment of melanoma. The PD-1 inhibitor BMS-936558 has demonstrated efficacy as well as durable responses in heavily pretreated patients exhibiting non–small cell lung cancer, renal cell carcinoma, and melanoma.

Overall, I think that there is an evolving landscape of different treatment options that are showing early benefit for patients with melanoma, including some that directly target the tumor, like the *BRAF* and *MEK* inhibitors, and others that target the host immune response, like ipilimumab and the PD-1–blocking agents.

H&O What advances have been made in improving patient quality of life?

JW The general hope is that these treatments are relatively well tolerated, and the survival benefit that patients are able to achieve translates into an improvement in their quality of life. Ideally, treatment will result in not only extended overall survival, but as a result of better disease control, its associated symptoms will abate and patients will feel better.

H&O What are the biggest remaining challenges?

JW There are still patients who do not benefit from certain treatments like immunotherapy, and it is thus of critical importance to determine why some patients respond and others do not. We need options for those patients who do not have *BRAF* mutations. Specifically, those who have a *BRAF* mutation need effective, targeted therapies. Another remaining challenge is determining how to rationally combine targeted therapy with immunotherapy.

H&O What does the future hold?

JW The future is likely about combinations. We should utilize BRAF, MEK, and KIT inhibitors, which provide very rapid disease regressions in a significant number of patients whose tumors harbor those respective mutations, and we need to complement that with immunotherapies that will hopefully provide durability to those responses. Achieving disease control so that we can properly induce an immune response that will provide for long-lasting control of the cancer is key. Combinations should not be empiric, but rather rationally designed and properly investigated in clinical trials to ensure safety and optimal efficacy.

Suggested Readings

Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012 Sep 29. [Epub ahead of print]

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ClinicalTrials.gov. Study of immunotherapy to treat advanced prostate cancer. http://clinicaltrials.gov/show/NCT00861614. Identifier: NCT00861614.

ClinicalTrials.gov. Pilot ipilimumab in stage IV melanoma receiving palliative radiation therapy. http://clinicaltrials.gov/show/NCT01449279. Identifier: NCT01449279.

Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: releasing the restraints on anti-tumor immunity for patients with melanoma. *Cancer J*. 2012;18:153-159.

Postow MA, Callahan MK, Wolchok JD. The antitumor immunity of ipilimumab: (T-cell) memories to last a lifetime? *Clin Cancer Res*. 2012;18:1821-1823.