In the space of a few years, metastatic melanoma has been transformed from one of the most intractable cancer problems to one of the most promising areas in cancer therapy. With the approval of several new drugs and numerous ongoing trials, the field is building on the successful targeting of molecules within tumor cells and on the surface of immune cells to better control the disease. Targeting the MAP kinase pathway in melanomas that harbor a BRAF mutation has led to the dramatic resolution of tumors, often over a matter of weeks. At the same time, “checkpoint blockade” therapy has unleashed the power of the immune system to keep tumors in check, often for prolonged periods.

Yet challenges remain. For example, the responses of some patients to vemurafenib (Zelboraf™), which targets mutated BRAF, were so dramatic that they were reported on the front page of the *New York Times* and led to approval of the drug in 2011. However, the excitement has been tempered by the realization that these responses are seldom durable, and that the drug can paradoxically unleash other driver mutations resulting in keratoacanthoma-type squamous cell carcinomas and new melanomas. In this issue of *The Melanoma Letter*, Dr. Caroline Robert and colleagues discuss exciting ongoing trials with new MEK inhibitors designed to increase the extent and durability of responses and mitigate the risk of carcinogenesis. The recent approval of trametinib (Mekinist™) was the first salvo fired for MEK inhibition in melanoma management, and many other MEK therapies are being tested.

The identification of a mutation in exon 15 of the BRAF gene in 50-70 percent of melanomas was the catalyst for molecular classification. Since then, additional somatic mutations, most resulting in activation of either the MAPK (mitogen-activated-protein kinases) pathway or the PI3 kinase pathway, have been identified. Aberrant activation of the MAPK pathway occurs in more than 65 percent of melanomas.

**The Molecular Age**

The molecular classification of melanoma has played a key role in changing our approach to treatment of advanced disease. It is now a core part of diagnostic and therapeutic strategies. Melanoma is the cancer that carries the highest number of somatic mutations, with an average of 30 per Mb (megabase pair). Analysis of the spectrum of these mutations shows a clear enrichment for C->T or G->A transitions at pyrimidine dinucleotide sites, reinforcing the premise that damaging UV rays are a major melanoma risk factor.

Historically, metastatic melanoma has been one of the most treatment-refractory cancers. For decades, no drug demonstrated an overall survival (OS) benefit. However, recently the situation radically changed. Melanoma has emerged as a “model” tumor for which innovative therapeutic strategies have demonstrated significant efficacy. Two strategies, immunotherapy and targeted therapy, opened new treatment avenues, leading in 2011 to US and European approval of two landmark drugs: the anti-BRAF agent vemurafenib (Zelboraf™) and the anti-CTLA-4 monoclonal antibody ipilimumab (Yervoy™). This year, two additional targeted agents — another anti-BRAF drug, dabrafenib (Tafinlar™), and for the first time, an anti-MEK agent, trametinib (Mekinist™), were approved in the US. The MEK pathway represents a new complementary therapeutic target that could greatly expand opportunities for overcoming treatment resistance and lengthening lives.

**Anti-MEK Agents in Perspective**

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From the Editors

In the space of a few years, metastatic melanoma has been transformed from one of the most intractable cancer problems to one of the most promising areas in cancer therapy. With the approval of several new drugs and numerous ongoing trials, the field is building on the successful targeting of molecules within tumor cells and on the surface of immune cells to better control the disease. Targeting the MAP kinase pathway in melanomas that harbor a BRAF mutation has led to the dramatic resolution of tumors, often over a matter of weeks. At the same time, “checkpoint blockade” therapy has unleashed the power of the immune system to keep tumors in check, often for prolonged periods.

Yet challenges remain. For example, the responses of some patients to vemurafenib (Zelboraf™), which targets mutated BRAF, were so dramatic that they were reported on the front page of the *New York Times* and led to approval of the drug in 2011. However, the excitement has been tempered by the realization that these responses are seldom durable, and that the drug can paradoxically unleash other driver mutations resulting in keratoacanthoma-type squamous cell carcinomas and new melanomas. In this issue of *The Melanoma Letter*, Dr. Caroline Robert and colleagues discuss exciting ongoing trials with new MEK inhibitors designed to increase the extent and durability of responses and mitigate the risk of carcinogenesis. The recent approval of trametinib (Mekinist™) was the first salvo fired for MEK inhibition in melanoma management, and many other MEK therapies are being tested.

Continued on page 2
BRAF Inhibitors

BRAF is a serine/threonine kinase belonging to the RAF family, which includes two additional enzymes, ARAF and CRAF (RAF1). BRAF is downstream of RAS proteins and upstream of MEK and ERK proteins on the MAPK pathway, which is involved in the response to transmembrane cellular growth factors. A recurrent gain-of-function V600E BRAF mutation is present in 50-70 percent of melanomas. Downstream from RAS and RAF proteins on the same MAPK pathway, the MEK1 and MEK2 proteins are found; encoded by the MAP2K1 and MAP2K2 genes, respectively, they harbor activating mutations in 8 percent of melanomas.

Vemurafenib was approved in 2011 as a first-line treatment for patients with unresectable or metastatic melanoma harboring the V600E BRAF mutation, based on a Phase III trial of 675 subjects in which patients receiving vemurafenib had significantly improved overall survival compared to those on dacarbazine, and median progression-free survival (PFS) of 5.3 months versus 1.6 months for those receiving dacarbazine. Vemurafenib patients produced a 48 percent objective response rate vs. 5 percent for dacarbazine. Responses became evident clinically as well as on PET scans within 1–2 weeks of initiating treatment. The most common adverse events were arthralgia, fatigue, and cutaneous manifestations such as rash, photosensitivity, and squamous cell carcinoma (SCC) of the keratoacanthoma type.

New BRAF inhibitors are being developed, and findings suggest comparable clinical efficacy. Dabrafenib was FDA-approved this year based on a Phase III clinical trial in which dabrafenib-treated patients with advanced metastatic or unresectable melanoma had 4.51 months of progression-free survival (PFS), versus 2.7 months PFS for chemotherapy patients. The dabrafenib patients had a 51 percent objective response rate, including good signs of efficacy in patients with brain metastases.

Dabrafenib may also have a better efficacy/toxicity profile than vemurafenib, with patients demonstrating almost no photosensitivity and fewer keratoacanthomas and SCCs (7 percent, versus 20-30 percent with vemurafenib).

However, there are two major concerns with all BRAF therapies thus far. The most challenging is the short median duration of clinical responses, with most patients relapsing 4 to 12 months after therapy is initiated. Various mechanisms of drug resistance have been described, most reflecting primary resistance present from the beginning and expressed over the course of treatment, likely due to clonal heterogeneity of the tumors. Numerous distinct resistance mechanisms that can reactivate the MAPK pathway or use other proliferation pathways have been identified.

The second downside of BRAF inhibitors is that, paradoxically, they can activate the MAPK pathway in cells devoid of BRAF mutation. This unwanted side effect probably requires an additional somatic event such as a UV-induced RAS mutation on the signaling pathway. Such an event could explain the appearance of squamous cell neoplasias as well as the new melanomas observed in patients receiving BRAF inhibitors. For this reason, the risk of internal cancer should not be overlooked, and patients should be closely monitored, especially with potential adjuvant use.

MEK Inhibitors

Trametinib

Potent inhibitors of MEK1 and MEK2 proteins downstream on the same MAPK pathway are also being developed [Figure 1]. The most advanced, trametinib, a non-allosteric cAMP (cyclic adenosine monophosphate) inhibitor, was recently FDA-approved for metastatic or unresectable melanoma patients whose tumors express BRAF V600E or V600K gene mutations. Approval was based on the randomized Phase III METRIC trial including 322 patients with advanced melanomas harboring such V600 mutations. Eligible patients previously treated with at most one line of therapy excluding BRAF or MEK inhibitors were randomly assigned to receive either trametinib orally b.i.d. or chemotherapy (dacarbazine or paclitaxel). Crossover to the trametinib arm was allowed for patients whose disease progressed in the chemotherapy arm. The primary endpoint was improved PFS, but the researchers also looked at response rate, safety, and overall survival.

A statistically significant improved PFS of 4.8 months was achieved in trametinib-treated patients compared to 1.5 months in the chemotherapy patients. More surprisingly, though 51 patients (47 percent) initially treated with chemotherapy crossed over to the trametinib arm, improved overall survival was noted — 6-month survival of 81 percent.
in the trametinib arm vs. 67 percent in the chemotherapy arm, with a 46 percent reduced risk of death in the trametinib patients. The objective response rate in the trametinib arm was 22 percent, versus 6 percent in the chemotherapy arm. The most common adverse events with trametinib were skin rashes, usually of a papulo-pustular type, with less than 8 percent at grade 3 or 4. Diarrhea, peripheral edema, and fatigue, though common, reached grade 3 or 4 in less than 6 percent of cases. Potential serious adverse events involving the retina or myocardia were rare and mostly reversible.

Trametinib was thus the first MEK inhibitor to demonstrate therapeutic benefit in a Phase III randomized trial.

Selumetinib
In a recent, randomized Phase II trial of 91 treatment-naive patients with metastatic BRAF-mutated melanoma, those receiving a combination of the MEK inhibitor selumetinib and dacarbazine demonstrated a trend towards a survival benefit, with a median OS of 13.9 months, vs. 10.5 months among patients receiving dacarbazine alone. More notably, patients receiving selumetinib plus dacarbazine had a significant PFS of 5.6 months, compared to just three months for the dacarbazine monotherapy patients. The safety profile of selumetinib and dacarbazine combined was consistent with that of each drug separately.

The Future: Combination Therapies
Trametinib is thus far approved only as a monotherapy, and it may be a welcome option as such for BRAF-mutated patients who cannot tolerate BRAF inhibitors. But it appears that the main use will be in combination with BRAF inhibitors. Initial results of an early three-arm Phase II randomized trial evaluating two doses of trametinib and dabrafenib in combination vs. dabrafenib monotherapy were recently published. Response rate and PFS were higher in the high-dose combination, with 76 percent objective responses in the combination arm versus 53 percent in the dabrafenib monotherapy arm, and a PFS of 9.4 months vs. 5.8 months for the monotherapy. The duration of response was also longer — 10.5 months in the combination group and 5.6 months in the dabrafenib arm. As preclinical studies had predicted, the paradoxical activation of the MAP kinase pathway during anti-BRAF monotherapy was much less frequently observed with the combination therapy. This was borne out by a much lower occurrence of SCCs and keratoacanthomas — just 7 percent of the patients undergoing combination therapy vs. 19 percent in patients receiving dabrafenib alone. Based on these convincing early results, GlaxoSmithKline has already filed for FDA approval of the two-drug combination, with final-stage Phase III data expected late this year.

Combination therapies using other MEK and BRAF inhibitors are now being tested against BRAF inhibitor monotherapy in several Phase III trials. One critical question is whether anti-MEK agents will be effective in patients who fail anti-BRAF monotherapy. Unfortunately, it seems that anti-MEK therapy alone will not be the answer; among 40 patients receiving trametinib after BRAF inhibitor resistance, the response rate was only 5 percent, with a median PFS of just 1.8 months.

We do not have statistically significant data concerning the efficacy of the BRAF/MEK inhibitor combination in patients resistant to BRAF inhibitors, but preliminary studies on a small population of patients have reported some responses and disease stabilization.

Conclusions
Although immense progress has recently been achieved in melanoma treatment, questions must be addressed. We do not yet know, for example, whether anti-MEK agents will have a significant role used alone, or if their use in combination with anti-BRAF agents will become the new standard of care for targeted therapy of BRAF-mutant melanoma. We also have to evaluate these and other drugs used sequentially.

Researchers fully understand that overcoming advanced melanoma will be a long, complex battle. Multiple mutations in melanoma lead to multiple disease pathways and many routes for the cancer cells to escape targeted drugs. Both intra-pathway and inter-pathway drug combinations will probably be met by secondary resistance, and in the near future, most patients will relapse. It will therefore be of fundamental importance to combine the targeted therapeutic strategies with immunotherapies.

Editor’s Note: This story originated with a presentation by Dr. Robert at The Skin Cancer Foundation’s 14th World Congress on Cancers of the Skin in Sao Paulo, Brazil.

References
From Discovery to Development: Blocking PD-1 and its Ligands

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On the heels of the recently approved anti-CTLA-4 drug ipilimumab, a new class of immune checkpoint therapies targeting the programmed death-1 (PD-1) receptor and its ligands is showing remarkable promise both as a monotherapy and in combination with other agents. Results from recent clinical trials hold the realistic hope of improved progression-free and overall survival for patients with advanced melanoma, with fewer toxicities to interfere with treatment.

The Pathway: PD-1 and its Ligands

Adaptive responses mediated by T and B lymphocytes play a critical role in antitumor immunity. The activity of the adaptive immune system is governed by tightly regulated molecular pathways that either promote or inhibit the full activation of immune cells. When a specific T or B cell receptor recognizes a target antigen, “immune checkpoints” that dampen immune activation are engaged. Ordinarily, these inhibitory pathways terminate immune cell activation at the appropriate time, preventing collateral damage to normal tissues. However, human cancers can commande these pathways, down-regulating antitumor immune activity and allowing unrestrained tumor growth.

The first immune checkpoint therapeutically targeted was cytotoxic T-lymphocyte antigen 4 (CTLA-4). After CTLA-4 blockade was shown to enhance antitumor immunity in preclinical studies, monoclonal antibodies (mAbs) blocking human CTLA-4 were developed, and a decade of clinical testing ensued. These trials culminated in FDA approval of ipilimumab (Yervoy™, Bristol-Myers Squibb, Princeton, NJ) in 2011 for the treatment of patients with metastatic melanoma.

A mechanistically similar though functionally distinct pathway that plays a central role in immune inhibition is comprised of PD-1 (CD279) and its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-1 is an inhibitory receptor expressed on activated T and B cells; its interaction with its primary ligand, PD-L1, inhibits the proliferation and survival of T cells. Like studies of murine anti-CTLA-4 that showed antitumor activity, preclinical studies of anti-PD-1’s effect on the PD-1/PD-L1 pathway also demonstrated its role in tumor immunosuppression.

Just as the antitumor properties of anti-CTLA-4 and anti-PD-1 were predicted by their corresponding preclinical models, so too were their side effect profiles. Whereas CTLA-4 genetic knockout mice die at 3-4 weeks of age from massive multi-organ lymphocytic infiltration and tissue destruction, PD-1 knockout mice develop late-onset strain- and organ-specific autoimmunity. These observations are consistent with the distinct expression patterns of the ligands.

Table 1: Agents Targeting PD-1 and its Ligands in Clinical Trials for Melanoma Patients

*Detailed information available at http://www.clinicaltrials.gov
for CTLA-4 and PD-1. The ligands for CTLA-4 (B7.1 and B7.2) are expressed ubiquitously on antigen-presenting cells such as monocytes and dendritic cells; in contrast, PD-L1 is expressed primarily in peripheral tissues (including tumor deposits), so a less global immunological effect would be expected from PD-1 pathway blockade. Although adverse events with potential immune-related etiologies have been observed for both anti-CTLA-4 and anti-PD-1, a lower rate of grade 3 or 4 adverse events during prolonged drug administration was encountered with PD-1 pathway blockade.

**Antibodies Blocking PD-1 and its Ligands**

Several agents that block the interaction of PD-1 and its ligands are currently being evaluated in clinical trials [Table 1]. The drug that has undergone the most extensive clinical testing is nivolumab (BMS-936558/MDX-1106/ONO-4538), a fully human IgG4-blocking mAb specific for human PD-1. An initial glimpse of its tolerability and clinical activity was seen in a first-in-human, Phase I, intermittent-dose, dose-escalation trial involving 39 patients. In this study, drug-related toxicities were manageable, and clinical activity was observed in patients with advanced treatment-refractory melanoma, renal cell carcinoma (RCC), colorectal cancer (CRC), and non-small cell lung cancer (NSCLC). The durability of tumor responses was demonstrated in a follow-up evaluation of three patients who experienced objective tumor regressions. Two patients, one with CRC and one with RCC, achieved complete responses, which were ongoing at last evaluation (three and five years, respectively). A melanoma patient experienced a partial response, which lasted 16 months after drug discontinuation. Following tumor progression, a partial response was again achieved with nivolumab re-induction.13

More recently, nivolumab was tested in a second Phase I trial with cohort expansion, intravenously administered biweekly to some 300 patients with treatment-refractory solid malignancies.14 Drug-related adverse events of special interest (i.e., immune-related events) occurred in about 45 percent of patients, though only 6 percent were grade 3 or 4. Three deaths associated with pneumonitis occurred, in two patients with NSCLC and one with CRC. Objective responses (PR or CR, by RECIST) to nivolumab were observed in 31 percent of patients with melanoma, 17 percent with NSCLC, and 29 percent with RCC. As in the first-in-human trial, responses were durable: among 65 responding patients, 42 responses (65 percent) lasted ≥1 year. Stable disease lasting ≥24 weeks was observed in 7 percent, 10 percent, and 27 percent of patients with melanoma, NSCLC and RCC, respectively. [Figure 1]. Among 27 responding patients who discontinued treatment for reasons other than progression, 19 (70%) maintained responses off-drug for ≥4 months. These findings demonstrate the potential for immune checkpoint blockade therapy to reset the equilibrium between tumor and host in favor of the immune system, leading to long-term, immune-based disease control. Median overall survival for melanoma patients receiving nivolumab therapy was 16.8 months.

The importance of the interaction between PD-1 and its ligands in cancer immunosuppression is further supported by results from a multicenter, Phase I study from Brahmer and colleagues, demonstrating that PD-L1 blockade also has antitumor effects.15 Escalating doses of BMS-936559, a fully human mAb blocking PD-L1, were administered to 207 patients with melanoma, NSCLC, RCC, CRC, or ovarian, pancreatic, gastric, or breast cancer. Grade 3 or 4 drug-related toxicities occurred in 9 percent of patients, with no drug-related deaths. Overall, 9 of 52 melanoma patients (17 percent) experienced an objective response, five of which lasted ≥1 year. An additional 14 melanoma patients (27 percent) experienced stable disease that lasted ≥24 weeks. Objective responses and prolonged stable disease were also observed in patients with NSCLC, RCC, and ovarian cancer. Newer antibodies blocking PD-L1 are in the early stages of clinical testing and have demonstrated tolerable safety profiles as well as antitumor activity [Table 1]. Together, these studies suggest that blocking the PD-1/PD-L1 pathway may become a significant component of the future management of patients with metastatic melanoma and other solid malignancies, some of which were not considered responsive to immunotherapy until recently.

**Research in Progress: Optimizing Immune Checkpoint Therapy**

Current clinical studies centered on optimizing immune checkpoint modulation are generally focused on three

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**Figure 1:** Response of metastatic melanoma to anti-PD-1 (nivolumab, BMS-936558) administered at 1mg/kg every two weeks. Shown is the percentage change in the sum of the longest diameters of lesions from baseline. Immune-related patterns of response are demonstrated, including long-term stable disease and an overall reduction in tumor burden despite the appearance of new lesions. (From Topalian, et al, Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *New Engl J Med* 366; 2443-54. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission.)
Blocking PD-1, from page 5

broad areas: 1) the development of combinatorial therapeutic approaches [Table 2]; 2) the identification of biomarkers that predict and/or evaluate response to therapy; and 3) the implementation of immune-related clinical response criteria that may be more appropriate than conventional metrics for evaluating outcomes to therapy with anti-PD-1 and similar agents.

Combinatorial approaches

Preclinical models that combine immune checkpoint-blocking drugs with other agents have shown synergistic effects against tumor growth. These data suggest that combinatorial therapies might not only increase the percentage of treatment responders with the tumor types we have mentioned, but could also expand the spectrum of malignancies for which immunotherapy may be effective. For instance, one therapeutic strategy combines anti-PD-1 with blockade of additional immune checkpoints that may serve as dominant or co-dominant regulators of immune cell activation. Matsuzaki and colleagues demonstrated that human tumor-derived CD8+ T cells expressed both PD-1 and another immune inhibitory molecule, lymphocyte activation gene-3 (LAG-3). While blockade of either molecule alone was ineffective at restoring T cell function in vitro, combined application of mAbs blocking PD-1 and LAG-3 successfully bolstered T cell proliferation and cytokine production, consistent with findings from animal tumor models.18,19

Combinatorial strategies have also demonstrated success in the clinic. A recent trial from Wolchok and colleagues demonstrated a 40 percent objective response rate among 52 patients with melanoma who received ipilimumab and nivolumab concurrently.20 Other agents being tested in combination with immune checkpoint inhibitors include targeted drugs such as selective BRAF inhibitors, immune-based agents such as vaccines and cytokines, and chemotherapy drugs [Table 2].

Identifying molecular markers

Another active area of research is the evaluation of molecular markers predicting clinical response to PD-1 pathway blockade, such as the expression of PD-L1 in pretreatment tumor biopsies. Preliminary evidence of a correlation between tumor cell surface PD-L1 expression and the likelihood of response to anti-PD-1 therapy was observed in both the first-in-human trial12 and the larger Phase I trial14 of nivolumab. In the latter study, among a subset of 42 patients whose pre-treatment tumors were tested, 25 patients had specimens expressing PD-L1. Of those 25, 11 patients (44 percent) experienced an objective response to PD-1 blockade. Among the 17 patients whose tumors were PD-L1 negative, there were no responders.

While these findings require further exploration in Phase II and III trials, defining molecular markers of response is important. It not only allows more selective drug administration, but provides a basis for rational development of combination therapies based on PD-1 pathway blockade. For example, tumor biopsies obtained from 15 melanoma patients pre- and post-BRAF inhibitor therapy demonstrated a significant increase in tumor-infiltrating lymphocytes after treatment, which correlated with tumor regression and decreased tumor metabolic activity. These findings suggest that an immune response may play a role in the anti-melanoma activity of selective BRAF inhibitors, which could be augmented by the addition of an immune checkpoint inhibitor such as anti-PD-1.21

**Table 2: Combinatorial Treatment Trials Using Anti-PD-1/PD-L1 Agents for Patients with Melanoma**

<table>
<thead>
<tr>
<th>Anti-PD-1/PD-L1 agent</th>
<th>Combination agent</th>
<th>Eligibility*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab/ BMS-936558/ MDX-1106/ ONO-4538 Anti-PD-1</td>
<td>Multipurpose melanoma vaccine</td>
<td>Resected or unresectable stage III/IV melanoma (adjuvant or therapeutic trials). Results from the latter trial show an overall response rate of 25 percent, including in patients whose disease was refractory to ipilimumab.27</td>
</tr>
<tr>
<td></td>
<td>Anti-killer inhibitory receptor (KIR) antibody (BMS-986015)</td>
<td>Advanced solid tumors will be included during dose escalation, followed by cohort expansion in subjects with melanoma and other selected solid tumors.</td>
</tr>
<tr>
<td></td>
<td>Interleukin-21 (BMS-982470)</td>
<td>Initially, advanced solid tumors will be included. During the subsequent cohort expansion phase, tumor types will be restricted to RCC and NSCLC.</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab (anti-CTLA-4)</td>
<td>Phase III trial, first-line treatment for unresectable stage III/IV melanoma, comparing combination therapy against either drug alone</td>
</tr>
<tr>
<td>MPDL3280A/ RG7446 Anti-PD-L1</td>
<td>Vemurafenib (selective BRAF inhibitor)</td>
<td>Previously untreated BRAF V600-mutation-positive metastatic melanoma</td>
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<tr>
<td></td>
<td>Bevacizumab (angiogenesis inhibitor) or bevacizumab plus chemotherapy</td>
<td>Advanced solid tumors including melanoma</td>
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</tbody>
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*Detailed information available at http://www.clinicaltrials.gov
with nivolumab. Similar response patterns were observed in trials of ipilimumab, where the overall survival rates of patients with advanced melanoma exceeded the objective response rate. The response characteristics associated with immune checkpoint-blocking drugs present challenges for clinicians and regulators in accurately assessing clinical benefit as well as appropriate treatment management.

Looking Forward: From Clinical Trials to Community Practice

Twenty-four years passed between the cloning of the gene encoding CTLA-4 and FDA approval of ipilimumab for melanoma therapy. In the interval, the identification of the ligands for CTLA-4; the demonstration of mechanism of action in preclinical models; the observation that anti-CTLA-4 therapy could mediate tumor regression in early-phase clinical trials; and the demonstration of overall survival benefit in randomized Phase III clinical trials occurred. If anti-PD-1 therapy follows a similar timeline, approval of a drug blocking the PD-1 pathway might be expected within the next few years.

Early evidence of the clinical activity of anti-PD-1 and anti-PD-L1 has caused a paradigm shift in the way we treat melanoma, and will likely change our approach to the treatment of other tumor types as well. Given the durability of responses to checkpoint blockade therapy and the ability of these agents to reorient the adaptive immune system away from tolerance and toward immune attack, the continued application of these therapies brings us ever closer to harnessing the immune system’s potential against cancer.

References

Enclosed is your new issue of the Melanoma Letter

SkinCancer.org

February 7 – February 14, 2014

La Habana

Dr. Perry Robins invites you to join him for an informative and enjoyable meeting of The International Dermatology Exchange Program of The Skin Cancer Foundation at the Hotel Nacional in Havana, Cuba.

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PRICE PER PERSON FROM MIAMI: Double occupancy: $3,850, Single occupancy: $4,300

DEADLINES August 25, 2013: all forms and deposit payment of $750.

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