Advances in Immunotherapy for Metastatic Melanoma

Part 1: The Pathogenesis of Melanoma
Part 2: Harnessing the Immune System
Part 3: Challenges of Immune Modulation
Part 4: On the Horizon

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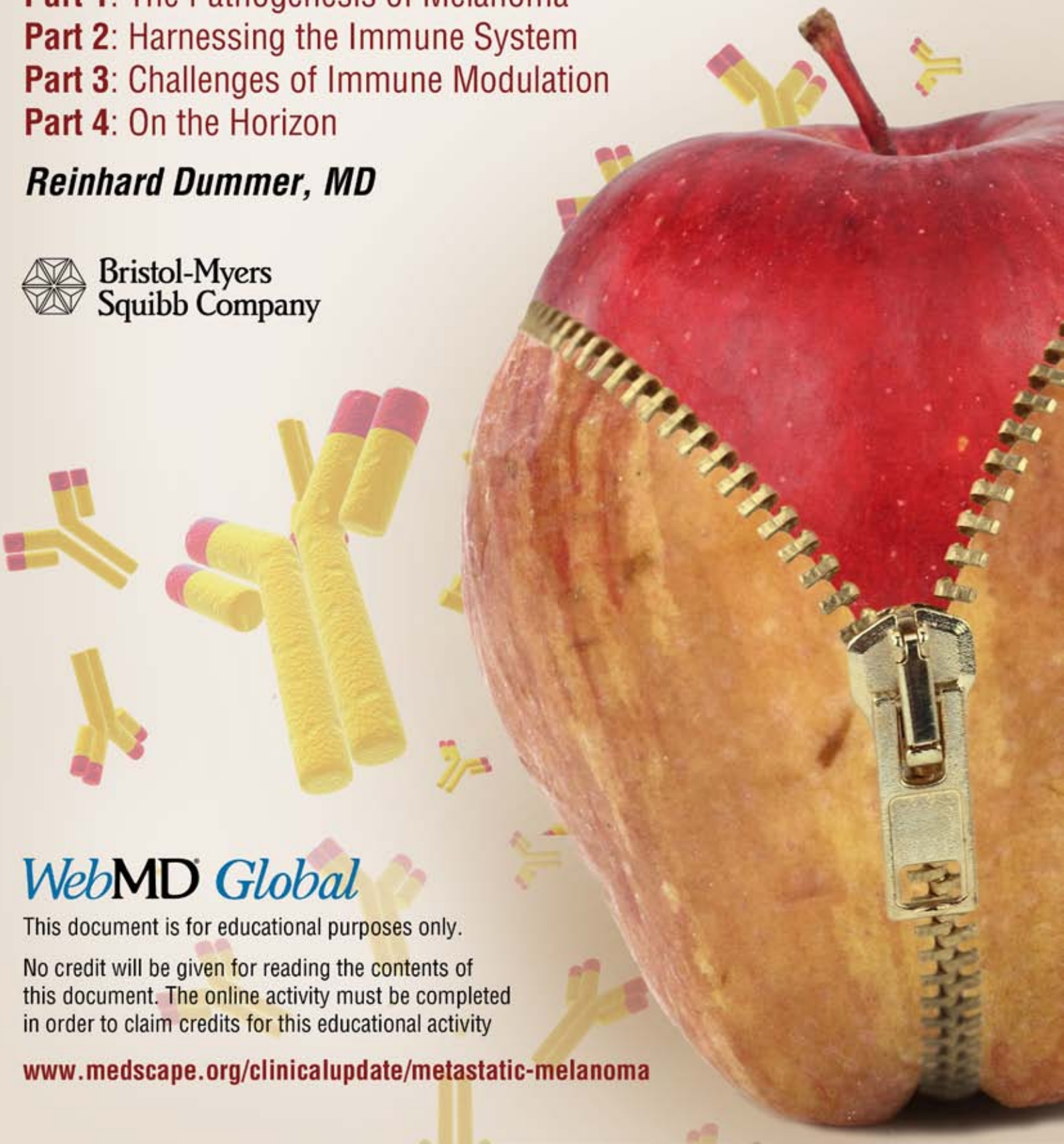

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This activity is intended for non-US physicians, specifically oncologists, dermatologists, oncology nurses, and other healthcare professionals involved in the diagnosis and treatment of patients with metastatic melanoma.

Goal

The goal of this activity is to provide foundational information on the role of the immune system in the pathogenesis of melanoma and its implications for clinical practice. Particular emphasis will be placed on recent research advances in the understanding of tumor immunology and recent advances in immunotherapeutic approaches to melanoma.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Explain the role of the immune system in the development of melanoma and the rationale for immunotherapy as a treatment for metastatic disease
2. Summarize clinical data on immunotherapeutic approaches for metastatic melanoma
3. Describe the kinetics of the response to CTLA-4 blockade and their implications for assessing clinical efficacy in patients with metastatic melanoma
4. Identify the unique immune-related adverse events associated with CTLA-4 blockade and other immunotherapy regimens

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INTRODUCTION

Metastatic melanoma is an aggressive and highly immunogenic malignancy that accounts for a relatively small proportion of all skin cancers, yet is responsible for the majority of skin cancer deaths. The prognosis for patients with stage IV (metastatic) melanoma has traditionally been bleak, with a median survival time of approximately 9 months, and 3-year survival rates of less than 15%.[1] In the recent EORTC 18032 multi-centre trial of temozolomide versus dacarbazine in stage IV melanoma (N=859), median overall survival was 9.1 months in temozolomide-treated patients and 9.4 months among patients who received dacarbazine.[2] The paucity of durable remissions in patients with metastatic disease was also illustrated in a 2010 analysis of long-term survival among patients treated at the British Columbia Cancer Agency between 1998 and 2006. During this period, only 11% of 397 patients treated with dacarbazine or temozolomide achieved durable remissions, defined as survival of 18 months or more after the date of first treatment.[3]

Spontaneous regression of melanoma has been described in the medical literature since the mid 19th century, with a reported incidence as high as 15% in primary melanoma.[4] Spontaneous regression of metastatic melanoma is extremely rare -- occurring in fewer than 1 in 400 patients -- but 5-year survival in such patients has been estimated at 49%.[4] Examination of regressing primary melanoma lesions from such patients has revealed extensive lymphocytic infiltration and overexpression of helper T cells and inflammatory cytokines.[5-9] These phenomena have fueled investigations into the mechanisms by which host immune defenses combat melanoma, with the goal of developing treatments that can exploit or enhance such immune activity. This work has led to the identification of numerous antigens, peptides, and other tumor-specific molecules that can be recognized and
targeted by T and B immune responses.

In addition, recent discoveries regarding the pathogenesis of melanoma -- notably the immune regulatory mechanisms responsible for the recognition and control of transformed cells, and the genetic mutations associated with melanocyte transformation -- have helped researchers identify a range of new therapeutic targets for melanoma. As a result, clinicians now have access to several immunotherapeutic approaches that have the potential to produce durable responses in patients with metastatic melanoma, and to fundamentally change the treatment paradigm for this disease.

The Pathogenesis of Melanoma

Genetics

The precise sequence by which normal melanocytes become malignant is incompletely understood. Available evidence indicates that transformation is a multistep process in which progressive genetic alterations, including mutations, translocation and deletions and epigenetic alterations, derange the normal cycle of cell proliferation, differentiation, and death and increase susceptibility to the carcinogenic effects of ultraviolet radiation.[10,11]

Over the last decade, it has become clear that there are distinct genetic pathways involved in the development of melanoma at different sites and at different levels of sun exposure (Table 1).[12] Up to 60% of melanomas contain mutations in the gene encoding the serine-threonine protein kinase B-RAF (BRAF) -- a critical component of the growth-promoting mitogen-activated protein (MAP) kinase pathway -- and depend on MAP kinase signaling for their growth and survival.[13,14] Much smaller percentages of patients with melanoma have been found to have activating mutations in the human KIT, NRAS, GNA11, or GNAQ genes.[15-17]

Table 1. Genetic Mutations in Melanoma

Site of Melanoma	Frequency of Mutation				
	BRAF	GNA11	GNAQ	KIT	NRAS
Acral surfaces	15%			15%	15%
Mucosal surfaces	5%			20%	15%
Skin with chronic sun damage	10%			2%	10%
Skin without chronic sun damage	50%				20%
Uvea		25%	55%		

From Curtin JA, et al. *N Engl J Med.* 2005;353:2135-2147[12]; Curtin JA, et al. *J Clin Oncol*. 2006;24:4340-4346[17]; Sosman JA. ASCO. 2011:367-372[16]; Van Raamsdonk CD, et al. *N Engl J Med*. 2010;363:2191-2199.[15]

Immune Response to Transformed Melanocytes

Transformed melanocytes are known to acquire tumor-specific antigen peptides and tumor-associated antigens (TAA)[18] that can be presented to cytotoxic (CD8+) T cells by class I major histocompatibility complexes (MHC-1) on antigen-presenting cells (APC). Antigens expressed in normal and neoplastic melanocytes include gp100, MelanA/MART-I, MAGE-1, tyrosinase, and tyrosinase-related proteins.[19]

Binding of these antigens to the T-cell receptor (TCR) serves as the initial trigger for a cascade of events that culminates in T-cell activation and expansion, including binding of B7–1 and B7–2 to CD28 on the T-cell membrane, stimulation of the phosphatidylinositol 3′ kinase (PI3K)/ AKT pathway by activated CD28, and upregulation of transcription factor NF-kappaB and prosurvival signals such as Bcl-2 and Bcl-XL (Figure 1). In addition to antigenic changes, malignant transformation induces a process known as oncogenic stress, which activates several anti-oncogenic pathways, including increased susceptibility of tumor cells to lysis by immune effectors, and increased apoptotic cell death or senescence. [20,21]

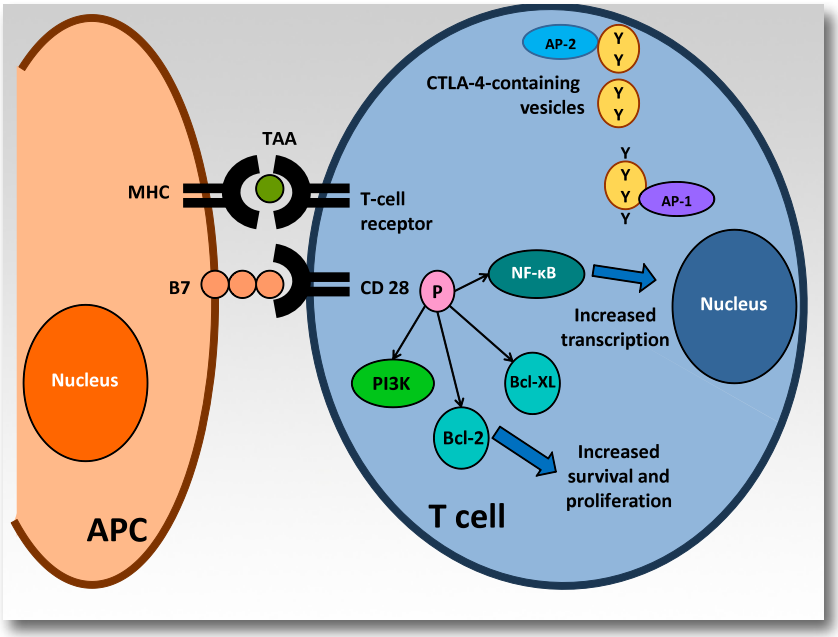

Figure 1. T-cell activation in melanoma. T-cell activation begins when TAA are bound to MHC molecules on the surface of an APC, leading to detection and binding of TAA by the TCR. Costimulatory signals -- notably, binding of CD28 on the T cell with B7 on the APC -- stimulate the PI3K/AKT pathway, upregulating numerous prosurvival pathways, including cytokine production and T-cell expansion.

AP = adapter protein complex; APC = antigen presenting cell; Bcl = B-cell lymphoma; CD = cluster of differentiation; CTLA = cytotoxic T lymphocyte-associated antigen; MHC = major histocompatibility complex; NF-κB = nuclear factor kappaB; PI3K = phosphatidylinositol 3′ kinase; TAA = tumor-associated antigens; TCR = T cell receptor

Adapted from Salama AKS, et al. *Clin Cancer Res*. 2011;17:4622–4628.[22]

As noted earlier, histologic examination of spontaneously regressing melanoma lesions has consistently found that clinical regression is associated with infiltration by T cells and melanophages,[5,6] and high levels of tumor infiltrating lymphocytes (TIL) are associated with better outcomes in patients receiving treatment for melanoma.[23] The fact that such tumor-specific immunity is present in such an aggressive and treatment-resistant malignancy has been one of the most troubling paradoxes in medicine.[24]

Immune Counter-Regulatory Pathways

As first reported by Gershon and Kondo in 1970,[25] T cells play a critical role not only in immune activation, but also in down-regulation of the immune response. Since this seminal discovery, research has shown that regulatory T cells (Tregs) are part of an intricate system of checkpoints that prevent autoimmune targeting of normal cells (Figure 2).[22,26-28]

Activation of T cells has been shown to induce the upregulation and cell-surface expression of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4),[29] which directly competes with CD28 to inhibit T-cell activation.[30] There is also evidence that CTLA-4 may alter T-cell motility and regulate the availability of cofactors required for TCR signaling.[29,31] Other regulatory molecules -- notably programmed death-1 (PD-1) -- further limit T-cell activation through inhibition of TCR-mediated signaling.[22] Binding of PD-1 to its ligand, PDL-1, also inhibits cytokine production.[32]

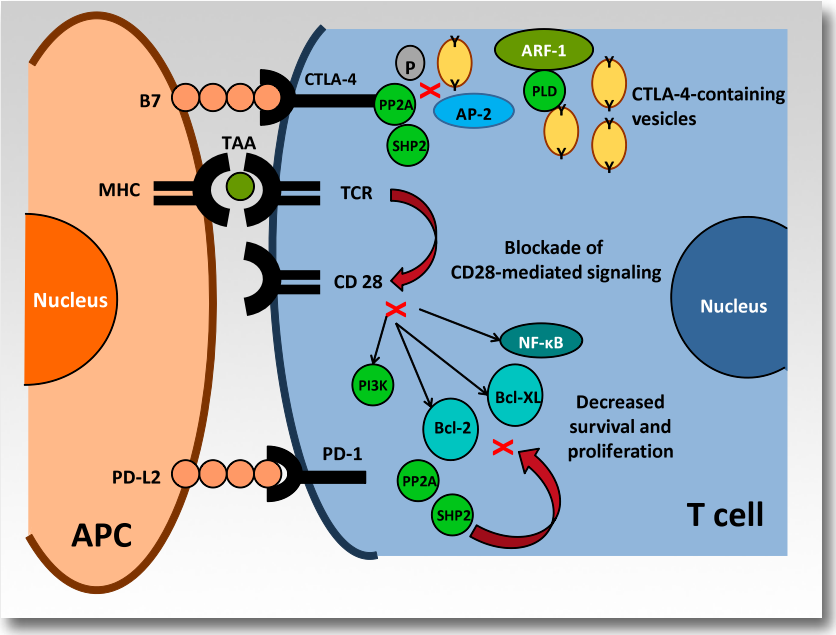

Figure 2. T-cell inactivation in melanoma. T-cell activation triggers a negative regulatory feedback mechanism that inhibits T-cell receptor signaling, IL-2 gene transcription, and T-cell proliferation. This negative regulation is characterized by upregulation of CTLA-4, which directly competes with CD28 for binding of B7 and may also have a negative effect on CD28 signaling. Other regulatory molecules, including PD-1, also limit T-cell activation and may inhibit TCR-mediated signaling.

AP-2 = adapter protein complex 2; APC = antigen-presenting cell; ARF-1 = ADP ribosylation factor-1; Bcl = B-cell lymphoma; CD = cluster of differentiation; CTLA = cytotoxic T lymphocyte-associated antigen; MHC = major histocompatibility complex; NF-κB = nuclear factor kappaB ; PD = programmed death; PD-L = programmed death ligand; PLD = phospholipase D; PI3K = phosphatidylinositol 3′ kinase; PP2A = protein phosphatase 2A; SHP = Src homology phosphatase; TAA = tumor-associated antigens; TCR = T-cell receptor

Adapted from Salama AKS, et al. *Clin Cancer Res.* 2011;17:4622–4628[22]

Cancer Immunoediting and Escape

In the 4 decades since the initial identification of Tregs and the counter-regulatory immune response, numerous studies have documented the presence of immune dysregulation in metastatic melanoma.[19] Both Tregs and immunosuppressive dendritic cells have been found to be significantly upregulated in patients with stage IV melanoma, and the presence of a high percentage of Tregs has been linked to shorter survival.[33,34] Melanoma cells have been shown to lose MHC-1 cell-surface molecules over the course of progression, thereby decreasing the recognition of malignant T cells by cytotoxic T cells, [35,36] whereas PD-1 expression in TILs in metastatic melanoma lesions is increased, with a corresponding decrease in effector cytokine production.[32]

Similar findings in preclinical models of melanoma and in other malignancies have led researchers to hypothesize that the immune system "not only protects the host against tumor formation but also shapes tumor immunogenicity."[37] This "cancer immunoediting theory" postulates that the balance between tumor cells and host resistance evolves through 3 distinct phases -- elimination, equilibrium, and escape (Figure 3) -- which ultimately enable some transformed melanocytes to evade im munosurveillance and progress to more advanced disease.

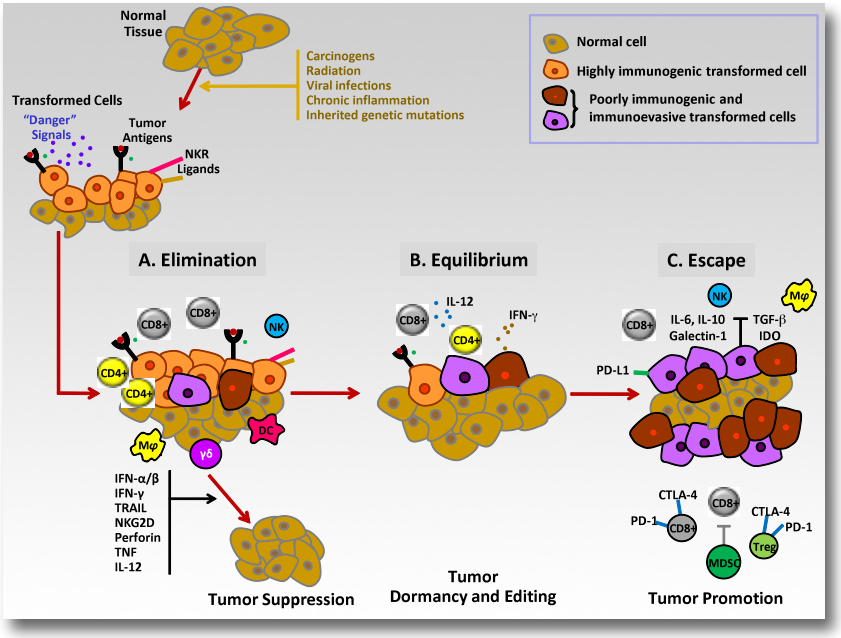

Figure 3. Cancer immunoediting. A. Elimination Phase: Innate and adaptive immune systems detect and destroy transformed cells in developing tumor (IFN-alfa/beta, IFN-gamma, IL-12, TNF, TRAIL, NKG2D, Perforin). B. Equilibrium Phase: Adaptive immune system keeps residual tumor cells in a dormant state by suppressing cell growth and sculpting the immunogenicity of tumor cells. C. Escape Phase: Tumor cells acquire the ability to evade immune recognition and destruction (eg, loss of antigens, induction of anti-apoptotic mechanism)

γδ = gamma-delta T cells; CD = cluster of differentiation; CTLA = cytotoxic T-lymphocyte-associated antigen; DC = dendritic cell; IDO = indolamine 2,3-dioxygenase; IFN = interferon; IL = interleukin; Mφ = macrophages; MDSC = myeloid-derived suppressor cells; NKG2D = natural killer group 2, member D; NKR = natural killer cell receptor; PD = programmed death; TCR = T cell receptor; TNF = tumor necrosis factor; TRAIL = TNF-related apoptosis-inducing ligand; Treg = regulatory T-cell

Adapted from Schreiber RD, et al. *Science.* 2011;331: 1565-1570.[37]

During the elimination phase, coordinated activation of the innate and adaptive immune systems protects the host from the developing tumor. During equilibrium, the adaptive immune system keeps tumor cell variants in a state of dormancy, but selection pressure may lead to antigen loss, defects in antigen processing, resistance to immune effector mechanisms, or alterations in the tumor microenvironment. The escape phase occurs when the accumulation of these changes enables tumor cells to circumvent immune recognition and destruction.[37]

Although immunoediting is generally thought to be sequential, it is possible that variations in the tumor microenvironment may cause tumor cells to enter the equilibrium or escape phase without going through earlier phases. In addition, there is evidence that immunoediting can occur at varying rates across multiple lesions within individual patients. A recent report documented all 3 phases of immune editing in a melanoma patient receiving CTLA-4 monotherapy, with each tumor at a discrete phase in the immunoediting process.[38] The importance of the tumor microenvironment in determining the course of melanoma progression was further illustrated in a 2008 preclinical study that demonstrated switching between invasive and proliferative cellular phenotypes during the course of disease progression, and suggested that the host immune responses may actually contribute to this switch via inflammation-induced hypoxia.[39]

Harnessing the Immune System

Nonspecific immunotherapies
The earliest immunotherapeutic approaches for melanoma focused on nonspecific stimulation of the immune system with the stimulatory cytokines interleukin-2 (IL-2) and interferon (IFN) alfa. Both agents produce durable responses in a small subset of patients, but are also associated with significant adverse effects.[40] Interferon alfa-2a and b are currently approved for the treatment of melanoma by the European Medicines Agency, while IL-2 and IFN alfa-2b are both approved for use in the United States.

Interferon Alfa
Although the antineoplastic activity of IFN-alfa is well established, its mechanism of action remains incompletely understood.[41] It is thought that IFN alfa renders malignant cells more antigenic due to its effects on the expression of a range MHC antigens and APCs. This theory is supported by research studies that have shown increased lymphocytic infiltration of melanoma lesions in treated patients with metastatic disease.[42]

The value of IFN alfa in the treatment of melanoma was first demonstrated in the Eastern Cooperative Oncology Group trial 1684 (ECOG1684), which investigated the effect of high-dose IFN alfa (HDI) in 287 patients with high-risk (stage IIB or III) melanoma. High-dose IFN alfa was found to extend median disease-free and overall survival by approximately 1 year, with 5-year disease-free and overall survival rates of 37% and 46%, respectively.[41] Subsequent trials have yielded more equivocal results with regard to overall survival.[42]

A 2007 meta-analysis of data from 13 clinical trials of IFN alfa at various doses found that treatment was associated with statistically significant benefits in both event-free survival (CI: 0.81-0.93, $P = .00006$) and overall survival (CI: 0.84-0.97, $P = .008$), with no significant differences between dosing regimens. The authors concluded that this translated to an absolute survival benefit of approximately 3% (CI: 1%-5%) at 5 years.[43] A more recent meta-analysis of data from 14 randomized controlled clinical trials conducted between 1990 and 2008 found that treatment with IFN alfa was associated with an 11% decrease in risk of death ($P = .002$) and an 18% decrease in risk of disease progression ($P < .001$). Notably, there was no significant improvement in overall survival observed in trials that only enrolled patients with stage III disease. [42]

Interleukin-2
Interleukin-2 is a T cell growth factor that stimulates T-cell proliferation and function, triggers the release of cytokines (eg, IFN-gamma, tumor necrosis factor), and enhances natural killer cell proliferation and cytotoxic activity.[40] Long-term follow-up data on 270 patients treated with high-dose bolus IL-2 in 8 clinical trials between 1985 and 1993 indicate that IL-2 can produce durable treatment responses in patients with metastatic melanoma. Ten percent of patients survived for more than 5 years following treatment, including 12 patients who were continuously disease-free. As of 2004, median survival for the entire group was 11.4 months. These data suggest that high-dose IL-2 may be able to effect a cure in some patients with metastatic melanoma.[46]

The potential benefits of IL-2 therapy must be weighed against the significant dose- and treatment-limiting toxicities associated with its use. In the 8 trials mentioned above, 2.2% of patients died from treatment-related toxicities. The most severe toxicities resembled the clinical manifestations of septic shock, including hypotension, ventricular tachycardia, and respiratory failure.[47] As a result, administration of IL-2 is limited to highly experienced clinicians at well-established treatment centers, and is generally recommended only for select patients with excellent organ function.[46]

Researchers have explored many different options to maximize the effect of IL-2 while limiting toxicity, including combining IL-2 and cytotoxic chemotherapy[48,49] with or without the addition of maintenance IL-2,[50] as well as combining IL-2 and melanoma vaccines.[51] Many of these approaches have improved outcomes in selected groups of patients, but the adverse effect profile of IL-2-based therapy remains significant, prompting researchers to investigate new avenues in immunotherapy for the treatment of metastatic melanoma.

Specific Immunotherapies
Vaccines
Development of an effective melanoma vaccine has been a therapeutic goal for decades, but has met with limited success.[52] At present, the United States National Institutes of Health clinical trials database lists more than 200 clinical trials of melanoma vaccines that are underway or in development. Many of these vaccines target recognized melanoma antigens, including gp100 and MAGE.

Although no vaccine has yet demonstrated a statistically significant impact on overall survival, promising results have recently been reported. A phase 2 trial of intratumoral administration of an oncolytic herpes simplex virus vector encoding granulocyte monocyte colony stimulating factor (GM-CSF) vaccine yielded a 26% overall response rate in patients with metastatic disease (N = 50). Of note, 92% of responses were maintained for between 7 and 31 months, and overall survival at 2 years post-treatment was 52%. [53] A 2008 summary of 4 phase 2 trials of a DNA plasmid vaccine containing a combination of HLA-B7 and chimpanzee beta-2-microglobulin reported systemic and local responses in patients with metastatic melanoma, with an overall response rate of 8.9%.[54]

Most recently, a phase 3 comparison of high-dose IL-2 plus the gp100:209-217(210M)-peptide vaccine versus high-dose IL-2 alone in patients with metastatic melanoma (N = 185) found that the combination therapy produced a significantly greater overall clinical response (16% vs. 6%; *P* = .03). In addition, patients receiving IL-2 plus gp100 experienced longer progression-free survival (2.2 months [95% CI: 1.7-3.9] vs 1.6 months [95% CI: 1.5 - 1.8; *P* = .008]). Median overall survival was also longer in the vaccine plus IL-2 group than in the IL-2-only group (17.8 months; 95% CI: 11.9-25.8 vs. 11.1 months; 95% CI: 8.7-16.3), although the difference did not achieve statistical significance (*P* = .06).[55]

Adoptive Cell Transfer Therapy

Adoptive cell transfer therapy (ACT) utilizes expanded autologous TILs to attack and destroy melanoma tumor cells in vivo. The approach was first investigated in the late 1980s, when researchers at the US National Cancer Institute demonstrated that expanded TIL in combination with high-dose IL-2 could induce regression in poorly immunogenic murine tumor models.[56]

Unlike stimulatory cytokines or vaccines, ACT utilizes cells that have demonstrated a high level of antigen recognition and antitumor activity in the patient receiving treatment. Tumor-infiltrating lymphocytes can be derived from resected tumors or peripheral blood mononuclear cells, and can be genetically engineered to increase expression of TCR (Figure 4).[57] The cells can also be activated during the ex vivo expansion phase to help overcome immunosuppressive aspects of the tumor microenvironment, while lymphodepletion and administration of high-dose IL-2 can further suppress negative regulatory factors such as Tregs.[58]

ACT is an extremely effective form of immunotherapy. Objective regression of metastatic lesions has been documented in up to 72% of treated patients, while up to 40% have shown durable complete responses.[46,59] This response looks promising but must be confirmed in phase 3 clinical trials because the procedure is biased for patients in perfect general condition. In addition, at present this complex and demanding treatment is available at only a few centers worldwide.[45,58]

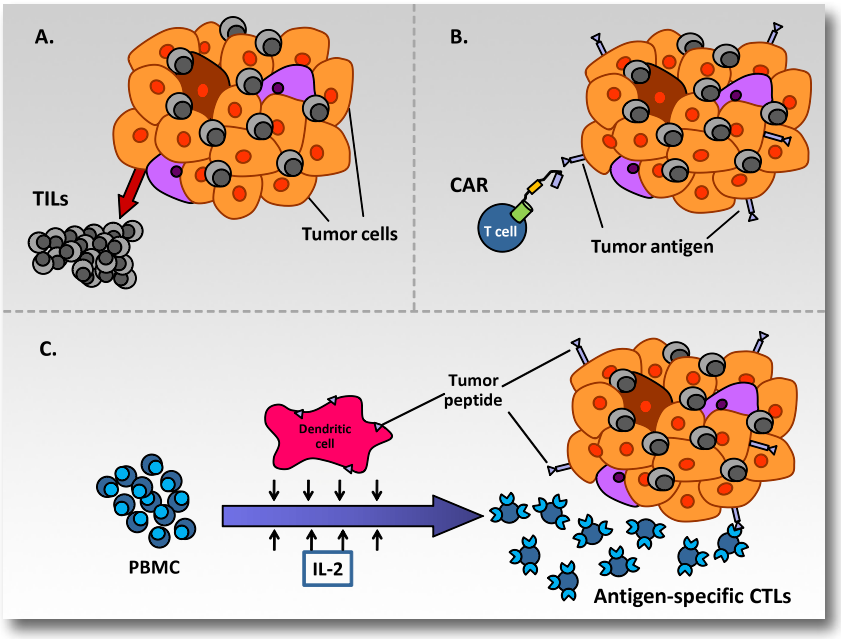

Figure 4. Adoptive cell transfer therapy approaches. A. TILs are harvested from tumor cells and cultured for subsequent infusion into the patient. B. PBMCs are genetically modified with a CAR or TCR specific for an antigen expressed by tumor cells. C. PBMCs are stimulated with peptides derived from a tumor antigen expressed on an APC to generate T-cell clones that recognize tumor antigens.

APC = antigen-presenting cell; CAR = chimeric antigen receptor; CTL = cytotoxic T lymphocyte; IL-2 = interleukin 2; PBMC = peripheral blood mononuclear cell; TCR = T-cell receptor; TIL = tumor-infiltrating lymphocyte

Adapted from: Heslop H. *Clin Cancer Res*. 2011;17:4189-4191.

Blocking Negative Regulators

The identification of the negative regulatory molecule CTLA-4 prompted intense interest in the therapeutic potential of blocking this molecule to enhance tumor-directed immune activation in patients with melanoma. The fully human IgG2 monoclonal antibody tremelimumab yielded promising results during phase 1 testing that included 29 patients with measurable melanoma: 2 patients in this group experienced a complete response and an additional 2 showed partial responses. In each of these cases, duration of response exceeded 2 years.[60] A subsequent phase 3 study (N = 655) of tremelimumab vs dacarbazine or temozolomide was closed for futility when interim analysis showed no significant survival advantage in the tremelimumab arm.[61]

In August 2010, Hodi and colleagues published the results of the first clinical trial in which a therapeutic agent showed a significant survival advantage in the treatment of stage IV metastatic melanoma. The multinational phase 3 study of the fully human IgG 1 monoclonal antibody ipilimumab enrolled 676 patients with unresectable metastatic melanoma (stage III or IV) who had received prior treatment. Median overall survival was 10.0 months among patients who received ipilimumab plus a glycoprotein vaccine (gp100), compared with 6.4 months among patients receiving gp100 alone. Median overall survival with ipilimumab alone was 10.1 months (Figure 5). No difference in overall survival was detected between the ipilimumab groups.[62]

More recently, a phase 3 trial comparing ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m^2) with dacarbazine (850 mg/m^2) in 502 patients with previously untreated metastatic melanoma yielded similarly positive results. Median overall survival was 11.2 months in the group receiving ipilimumab plus dacarbazine vs 9.1 months in the group receiving dacarbazine plus placebo. Higher survival rates were observed in the ipilimumab-dacarbazine group at 1 year (47.3% vs 36.3%), 2 years (28.5% vs 17.9%), and 3 years (20.8% vs 12.2%), with a hazard ratio for death of 0.72 ($P < .001$; Figure 5).[63]

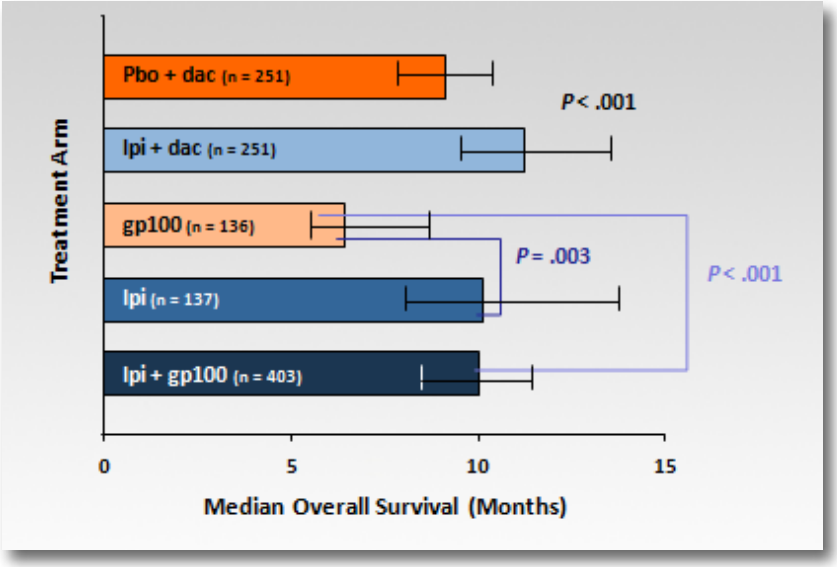

Figure 5. Overall survival in ipilimumab phase 3 trial. Median overall survival in the ipilimumab plus gp100 group was 10.0 months (95% confidence interval [CI]: 8.5-11.5), vs 6.4 months (95% CI: 5.5-8.7) in the gp100-alone group (HR for death, 0.68; $P < .001$). Median overall survival in the ipilimumab alone group was 10.1 months (95% CI: 8.0-13.8) (HR for death with ipilimumab alone vs gp100 alone, 0.66; $P = .003$).

IPI = ipilimumab; Dac = dacarbazine; Pbo = placebo

From Robert C, et al. *N Engl J Med.* 2011;364:2517-2526; Hodi FS, et al. *N Engl J Med.* 2010;363:711–723.[62,63]

On the basis of these trials, ipilimumab has been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of unresectable or metastatic melanoma (3 mg/kg every 3 weeks for a total of 4 doses).

1. A 58-year-old man with unresectable stage IV melanoma, whose disease progressed on first-line systemic therapy, is started on ipilimumab. Which of the following choices describes the mechanism of action of ipilimumab?

- Inhibition of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)
- Inhibition of B-RAF (BRAF)
- Polyclonal B-cell activation
- T-cell lymphokine activity
- Active immunization via antigen-presenting cells

Challenges of Immune Modulation

Managing Immune-Related Adverse Effects

The adverse effect profiles of immunotherapeutic agents are markedly different from those seen with traditional cytotoxic chemotherapies. Many patients who demonstrate a clinical response to immunotherapy will also demonstrate adverse effects consistent with an autoimmune activation. The intensity of these immune-related adverse effects (IRAEs) varies depending on each agent's kinetic profile and may or may not correlate with clinical benefit.[64,65]

A spectrum of IRAEs has been observed with anti-CTLA-4 antibodies, including inflammatory and autoimmune disorders such as colitis and dermatitis, and a range of endocrinopathies. A pooled analysis of adverse events from 14 clinical trials of ipilimumab (N = 1498) found that diarrhea, rash, and pruritus were the most frequently experienced adverse events (Table 2). Inflammatory gastrointestinal AEs (colitis, enterocolitis) were experienced by 32.5% of patients, 3 cases of which (0.2%) were fatal.[66]

Because the majority of AEs experienced during CTLA-4 blockade are autoimmune in nature, treatment should consist of immunosuppressive therapy. Several treatment algorithms are now available for the management of IRAEs during treatment with CTLA-4 antibody therapy,[67] and a recent analysis of the efficacy of treatment guidance on diarrhea and colitis across ipilimumab studies found that compliance with these guidelines led to faster resolution of symptoms.[68]

Table 2. Adverse Events in Pooled Ipilimumab Trials*

Adverse Event†	Any Grade n (%)	Grade 3/4 n (%)	Grade 5‡ n (%)
Diarrhea	554 (37)	104 (6.9)	0 (0)
Rash	498 (33.2)	37 (2.5)	0 (0)
Pruritus	412 (27.6)	6 (0.4)	0 (0)
Colitis	120 (8)	74 (4.9)	1 (< 0.1)
Abnormal hepatic function	74 (4.9)	17 (1.1)	1 (< 0.1)
Peripheral sensory neuropathy	67 (4.5)	6 (0.4)	0 (0)
Hypopituitarism	40 (2.7)	31 (2.1)	0 (0)
Hypothyroidism	27 (1.8)	2 (0.1)	0 (0)
Enterocolitis	18 (1.2)	9 (0.6)	0 (0)

N = 1498; * reported in ≥ 1% of patients; † all causes; ‡ grade 5 = death

From Ibrahim RA, et al. *J Clin Oncol.* 2011;29(Suppl):Abstr 8583.[66]

2. A patient with unresectable stage IV melanoma who is receiving second-line therapy with ipilimumab develops grade 3 diarrhea during the course of treatment. She has mild abdominal pain, but has no fever and denies blood in her stool. She is otherwise doing well and has not exhibited any other adverse reactions. Which one of the following represents the best treatment option for the management of the patient's adverse event?

- Octreotide
- Metronidazole
- Rifaximin
- Systemic corticosteroids
- Loperamide

Assessing Treatment Response

The mechanism of action of immunotherapies -- coupled with the inherent differences in the immune systems among individuals -- can lead to wide variations in the timing and nature of treatment response. Immune infiltration of primary and metastatic lesion can take weeks to months, and may be characterized by transient increases in tumor mass that can lead to premature treatment cessation if clinicians are not aware of the unique response patterns seen with immunotherapeutic regimens.[69]

For example, treatment with ipilimumab has been associated with 4 distinct response patterns: (1) response in baseline lesions; (2) a slow, steady decline in tumor burden; (3) an initial increase in tumor burden followed by a positive response; and (4) appearance of new lesions followed by a response in both new and baseline lesions.[69,70] Response Evaluation Criteria in Solid Tumors (RECIST) or modified World Health Organization criteria would define such transient increases in tumor burden as progressive disease and treatment failure.

Wolchok and colleagues have proposed immune related response criteria (irRC) to be utilized when evaluating treatment response in patients receiving immune therapy for solid tumors (Table 3).[69] Although there is not, as yet, a consensus on these criteria, they serve as a useful counterpoint to RECIST and WHO guidelines.

Table 3. Response Criteria: Immune-Related Response Criteria (irRC) vs World Health Organization (WHO)

Treatment Response	irRC Criteria	WHO Criteria
Progressive disease	At least 25% increase in tumor burden* compared with nadir (at any single point) in 2 consecutive observations at least 4 weeks apart	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single point)
Partial response	≥ 50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart	≥ 50% decrease in SPD of all index lesions compared with baseline in 2 observations at least 4 weeks apart, in absence of new lesions or unequivocal progression of non-index lesions
Complete response	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
Stable disease	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions

*Tumor burden = index and measurable new lesions

SPD = sum of the products of the 2 largest perpendicular diameters

From Wolchok JD, et al. *Clin Cancer Res.* 2009;15:7412-7420.[69]

3. After receiving 2 doses of ipilimumab (3 mg/kg) every 3 weeks, no treatment response is apparent and there is no shrinkage in tumor size. What would be your next step in the treatment of this patient's disease?

- Discontinue ipilimumab
- Continue ipilimumab at the same dose for 2 more cycles
- Continue ipilimumab at the same dose for 2 more cycles and add carboplatin/paclitaxel
- Increase the dose of ipilimumab and continue for 2 more cycles

Predicting Treatment Response

Despite the promising results that have been documented with new immunotherapeutic techniques such as CTLA-4 blockade and ACT, durable treatment responses have been observed in a relatively small proportion of treated patients. At present there are no markers that can be used to predict which patients will respond to immunotherapy. Evaluation of pre- and post-dosing biopsy specimens in 19 patients enrolled in a tremelimumab trial found that intratumoral infiltration of activated T lymphocytes was not predictive of clinical response, despite highly significant infiltration of lesions by CD8+ cells.[71]

To date, only baseline C reactive protein (CRP) levels ≤ 1.5 times the upper limit of normal have been found to have any predictive value in one patient population. In the tremelimumab phase 3 trial, patients with low CRP showed a significant survival benefit from tremelimumab compared with chemotherapy. Whether this finding can be reproduced in other patient populations is questionable.

On the Horizon

This is an exciting time for the treatment of melanoma. In addition to the recent US approval of ipilimumab, results of the phase 3 BRAF Inhibitor in Melanoma (BRIM-3) trial confirmed that the BRAF inhibitor vemurafenib can reduce the risk of death in the first 6 months after diagnosis of metastatic stage IV disease by 63% in previously untreated patients with metastatic melanoma with the BRAF V600E mutation.[72]

In a recent preclinical study, inhibition of the MAPK pathway with a selective BRAF V600E inhibitor was found to increase expression of melanoma-differentiating antigens and enhance antigen-specific recognition by cytotoxic T-lymphocytes -- indicating that the combination of BRAF inhibition and immunotherapy may yield a more effective response than either approach alone.[73] Other researchers have noted that targeted drugs such as vemurafenib may serve as immunosensitizers for immune treatment.[74] Similarly, the proteasome inhibitor bortezomib as recently been shown to sensitize melanoma cells for antigen-specific T cell attack during ACT.[75] Other reports show that inhibition of RAS/ Raf signaling results in the loss of melanocytic differentiation antigens in the context of phenotype switching.[76]

The advent of effective immunotherapies may soon lead to a range of new combination therapies designed to exploit the diverse mechanisms of action of available agents. For example, chemotherapeutic agents, which have traditionally had little effect on metastatic melanoma (such as cyclophosphamide and 5-fluorouracil), may be able to enhance the expression of tumor cell antigens or increase the susceptibility of tumor cells to lysis by immune effectors, thereby enhancing the efficacy of immune therapies.[77,78]

Conclusions

Recent clinical trial results have provided clear evidence that immune interventions may increase tumor recognition and elimination and induce durable treatment responses. Further research is needed to clarify the pathways involved in the immune response to melanoma and to further refine immunotherapeutic approaches and identify predictors of response that will enable us to optimize the choice of treatment for each individual patient. In the future, combination therapies with current and emerging agents -- not only immune therapies but targeted agents and cytotoxic chemotherapy -- may permit us to exploit multiple pathways and alter the immunoediting that allows tumor cells to circumvent immune defenses, which ultimately will translate into improved survival for patients with metastatic disease.

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