ARTICLE TITLE: Recent Developments in the Medical and Surgical Treatment of Melanoma

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2. Describe current surgical management of primary lesions, regional lymph nodes, and metastases in patients with melanoma.

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Recent Developments in the Medical and Surgical Treatment of Melanoma

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Increasing knowledge of the biology of melanoma has led to significant advances in drug development to fight this disease. Surgery is the primary treatment for localized disease and is an integral part of management in patients with more advanced disease. The last decade has become the era of targeted therapy in melanoma and has revolutionized the treatment of this disease. Since 2011, 4 new agents have been approved for the treatment of patients with metastatic melanoma: ipilimumab, vemurafenib, dabrafenib, and trametinib. Several new agents are currently in phase 3 trials with hopes of even more agents being approved for this once “untreatable” disease. How to integrate surgical options with more effective systemic therapies has become a new challenge for physicians. This review will provide an update on current surgical options, highlight the pathway to the development of the newly approved agents, and further discuss new treatments that are on the horizon. CA Cancer J Clin 2014;64:171-185. © 2014 American Cancer Society.

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Introduction
Melanoma is one of the most aggressive forms of skin cancer and the fifth most common cancer in the United States, with the incidence rising rapidly over the last few decades. In 2014, there will be approximately 76,100 new cases of invasive melanoma diagnosed in the United States and 9710 deaths from the disease. Melanoma is more common in white individuals than other racial and ethnic groups, and in males than females. The median age at the time of diagnosis is 61 years. The delay-adjusted incidence rate for invasive cutaneous melanoma increased by an average of 4.6% annually from 1975 through 1985, and by an average of 2.7% from 1986 through 2010. Over the past decade, the identification of novel gene mutations involved in the pathogenesis of melanoma as well as the discovery of key immune regulatory checkpoints has led to the approval of multiple targeted agents in metastatic melanoma. Through these discoveries, melanoma has emerged as a heterogeneous disorder comprising biologically unique diseases with specific targets.

Pathogenesis and Risk Factors of Melanoma
The pathogenesis of melanoma, as well as other types of skin cancer such as basal cell and squamous cell carcinomas, is thought to be mediated in part by DNA damage caused by exposure to ultraviolet (UV) radiation. This process was demonstrated in vivo when animals exposed to UV radiation developed cutaneous melanoma. Melanomas arise from melanocytes, which synthesize melanin, a pigment that protects the skin from harmful UV photons. There are 2 types of melanin: eumelanin, which produces a brownish-black pigment and pheomelanin, which produces a reddish-yellow pigment. There is evidence that increasing exposure to UV radiation from the sun and other sources is linked to the disease.

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increasing incidence of melanoma.\textsuperscript{5,6} Phenotypic features characterized by decreased amounts of melanin production such as fair skin, red hair, and light eye color are associated with an increased risk of melanoma. Other risk factors include atypical nevi, number of nevi, childhood sunburn exposure, personal and/or family history of melanoma or nonmelanoma skin cancers, immunosuppression, and xerosis.\textsuperscript{7} The prevention of melanoma based on alteration of these risk factors is prudent. Use of sunscreen to decrease UV exposure of the skin as well as close monitoring of nevi by both a dermatologist and by patients themselves are active methods of prevention and screening. Screening and prevention of melanoma is an active area of research.

A landmark study by Curtin et al\textsuperscript{5} hypothesized that the biologic behavior of melanoma varied based on the degree of UV exposure. In their study, they found significant differences in the rates of mutations based on the anatomic site of the primary melanoma. For example, lower rates of BRAF mutations were observed in melanomas of the upper respiratory or anogenital regions not directly exposed to UV radiation, whereas higher rates of BRAF mutations were noted in melanomas occurring on the trunk, which are associated with intermittent UV exposure. Melanoma is now distinguished by not only pathologic phenotype but also by molecular phenotype. This additional categorization has changed the way we view melanoma and guides the treatment of this disease.

**Staging of Melanoma**

The stage of a melanoma is based on tumor thickness and the involvement of lymph nodes and/or any other organs. The American Joint Commission on Cancer TNM staging system is the most common staging system used for melanoma. To appropriately stage melanoma, a biopsy is recommended to assess the depth of invasion of the tumor, mitotic rate, and the presence or absence of ulceration. These factors are important for both staging and prognostication.\textsuperscript{6} Breslow depth is considered one of the most important prognostic indicators, with patients with melanomas measuring less than 1 mm in depth having excellent (90% or greater) 5-year survival and those whose tumors measure greater than 4 mm having a more guarded prognosis (5-year survival rate of 50%). Stage III disease is defined by lymph node involvement, with stage IIIA being only microscopic involvement of a limited number of lymph nodes and stage IIIC representing multiple lymph node involvement and macroscopic disease.\textsuperscript{6} Baseline imaging is recommended if lymph node involvement is suspected clinically or if confirmed by biopsy, but may also be warranted based on clinical signs or symptoms. Stage IV disease represents distant lymph node involvement, as well as lung or any visceral involvement. Readers should refer to the National Comprehensive Cancer Network (NCCN) guidelines (nccn.org) for detailed information on the TNM staging of melanoma.\textsuperscript{8}

**Oncogenic Drivers of Melanoma**

In the past decade, a number of oncogenic drivers have been identified in the pathophysiology of melanoma, including \textit{BRAF}, neuroblastoma rat sarcoma (\textit{NRAS}), \textit{KIT}, and \textit{GNAQ} (guanine nucleotide–binding protein \textit{G} subunit alpha). As a result, melanoma is now being defined by its molecular aberrations. In the following sections, the biology and targeted therapies associated with each molecular alteration will be discussed in detail.

**BRAF**

**Biology**

Mutations in \textit{BRAF} result in constitutive activation of downstream signaling in the mitogen-activated protein kinase (MAPK) pathway leading to cell proliferation and the prevention of apoptosis.

Mutations in \textit{BRAF} were first discovered in 2002 through whole-genome screening conducted by Davies et al.\textsuperscript{9} A \textit{BRAF} somatic missense mutation was detected in 66% of patients with malignant melanoma, 80% of whom had a single substitution of glutamic acid (E) for valine (V) in codon 600. \textit{BRAF} V600E mutations are most commonly noted in melanomas originating from sun-exposed skin sites.\textsuperscript{10} \textit{BRAF} mutations occur more commonly in younger patients. An older patient whose tumor harbors a mutation in this gene more commonly harbors alternate mutations such as V600K or V600R.

**BRAF Inhibition**

There are a number of BRAF inhibitors that have been studied in melanoma. Sorafenib was the first known BRAF inhibitor, but unfortunately preclinical studies did not show significant responses in patients with melanoma regardless of the presence of \textit{BRAF} mutations.\textsuperscript{11,12} This is likely due to the lack of specificity of sorafenib to BRAF. More potent and specific inhibitors of BRAF were later developed, including vemurafenib and dabrafenib. These drugs have shown efficacy in \textit{BRAF}-mutant cells but not against cells with wild-type \textit{BRAF}.

The treatment of melanoma was revolutionized when a phase 1/2 clinical trial by Flaherty et al\textsuperscript{16} demonstrated a clinical benefit with vemurafenib at a dose of 960 mg orally twice daily in 80% of patients with stage IV \textit{BRAF} V600E-mutant melanoma. Until this time, no trial in metastatic melanoma had ever reported a response rate to this degree. Future trials demonstrated that these responses also led to a survival benefit both in the treatment-naive and treatment-refractory settings. A multicenter phase 2 study (BrAf In Melanoma: BRIM-2) documented benefit in treatment-
refractory patients, with 132 patients treated with vemurafenib at a dose of 960 mg orally twice daily found to have a response rate of 53%, a median duration of response of 6.7 months, and a median overall survival of 15.9 months. BRIM-3 randomized 675 treatment-naive patients with BRAF mutations to treatment with either vemurafenib (960 mg orally twice daily) or dacarbazine. This study was terminated early due to interim analysis showing a significant overall survival benefit. Based on these studies, vemurafenib was approved by the US Food and Drug Administration (FDA) in August 2011 for the treatment of metastatic BRAF-mutant melanoma. Both studies demonstrated that approximately 80% of patients showed a reduction in tumor burden, with 50% showing a reduction of 30% or greater.

Dabrafenib is the second BRAF inhibitor to be approved by the FDA (May 2013). It is a reversible, adenosine triphosphate (ATP)-competitive inhibitor that selectively inhibits BRAF. Dabrafenib is very similar to vemurafenib pharmacodynamically, but does have a shorter half-life. This agent has also shown promising results in the treatment of BRAF V600E-mutant and V600K-mutant melanoma. A phase 3 trial randomized patients in a 3:1 ratio to dabrafenib (187 patients) or dacarbazine (63 patients). This study established a 50% response rate with dabrafenib and there was a statistically improved progression-free survival over dacarbazine (5.1 months vs 2.7 months). Based on these data, dabrafenib was approved for use in patients with V600E- or K-mutated metastatic melanoma in May 2013. Whether to use vemurafenib or dabrafenib in the treatment of BRAF-mutated metastatic melanoma is a difficult question because to our knowledge these drugs have not been compared head to head, and the efficacy in this population appears similar. Most experts base this decision on side effect profile (discussed in more detail below), with vemurafenib causing more skin toxicity and dabrafenib causing more pyrexia. More BRAF inhibitors are currently in development and how they will fit into this armamentarium of single-agent BRAF inhibitors is not yet known. In further sections, we will discuss combination therapy with these agents. It should be noted that many experts believe that combination therapy will replace single-agent BRAF inhibitors in the treatment of metastatic melanoma.

BRAF Mutation Testing
There are multiple methods of determining the BRAF mutation status of a tumor. Currently, Sanger sequencing, the proprietary cobas 4800 BRAF V600 Mutation Test (Roche Diagnostics, Indianapolis, Ind), and pyrosequencing are the most common methods used in the United States. Sanger sequencing has limited sensitivity for detecting mutations present in lower frequencies in tumor specimens. Therefore, it is not the ideal testing modality if there is only a small amount of tumor DNA present. The cobas 4800 BRAF V600 Mutation Test is more sensitive in detecting V600E mutations when compared with direct sequencing by the Sanger method. However, it is less sensitive at detecting the less-common BRAF mutations. This is especially important to note for elderly patients, in whom tumors are more likely to harbor the less-common BRAF mutations such as V600K, V600D, and V600R. Pyrosequencing is currently being used at academic medical centers because it is the most sensitive method available and can identify greater than 95% of known BRAF mutations. Currently, the cobas 4800 BRAF V600 Mutation Test is the only commercially available test. If the test comes back positive, then one should consider using BRAF inhibitor therapy. However, one must be aware that this testing method has less sensitivity to detect the less-common BRAF mutations.

Toxicity
Toxicities of single-agent BRAF inhibitor therapy are consistent among the agents. The most common toxicities of BRAF inhibitors include arthralgias, rash, photosensitivity, fatigue, alopecia, pyrexia, and cutaneous squamous cell carcinomas (keratoacanthoma type). The cutaneous squamous cell carcinomas occur in approximately 25% of patients treated and tend to occur early on in treatment with a median time to development of 8 weeks. Older age and greater sun exposure are risk factors for the development of the squamous cell carcinomas. Many of these tumors have been associated with a mutation in BRAF and are thought to develop because of paradoxical activation of BRAF in keratinocytes in patients who received BRAF inhibitors. Squamous cell carcinomas are managed with simple excisions, whereas other side effects are usually effectively managed with dose reductions and/or low-dose (10 mg daily) corticosteroids.

MAPK Inhibitors
Clinical studies using single-agent BRAF inhibitors have unfortunately shown short-term responses, which suggests that nearly all patients develop acquired resistance to BRAF inhibitors. In an attempt to overcome this resistance, scientists investigated ways to inhibit the activated MAPK pathway downstream of BRAF. Trametinib has been the most studied and is an oral, small-molecule, selective inhibitor of MEK1 and MEK2. A phase 3 study randomized patients with BRAF-mutant, stage IV melanoma to either trametinib or chemotherapy (dacarbazine or paclitaxel) and demonstrated an overall survival benefit at 6 months, with response rates of 81% and 67%, respectively, noted in the trametinib and dacarbazine arms. The median progression-free survival was also improved by trametinib (4.8 months vs 1.5 months, respectively). In May 2013, trametinib was approved by the FDA for unresectable or metastatic melanoma with BRAF V600E or V600K mutations. It should be noted that it was not approved for patients who have
received prior BRAF therapy. There were no responses in this category on the trials. Therefore, trametinib as a single-agent should not be used in patients who have developed disease progression while receiving BRAF inhibitors.

The toxicity profile for this agent is different from that of the single-agent BRAF inhibitors. Trametinib also can cause a rash, but the rash tends to be acneiform rather than the hyperkeratotic rash of agents such as vemurafenib. Peripheral edema and diarrhea were also more common with this agent whereas squamous cell carcinomas were not reported. More rare but serious events included decreased ejection fraction and blurred vision secondary to serous retinopathy. Any patients reporting visual symptoms while receiving this agent should be evaluated with a dilated eye examination for retinopathy.

**Combination Therapy**

Given that resistance to single-agent BRAF inhibition is almost universal, studies combining agents to prevent resistance have emerged. MAPK reactivation is one primary method of resistance. More recent studies have investigated the benefit of combination BRAF and MEK inhibition. Phase 1 and 2 studies comparing trametinib (1 mg or 2 mg daily) plus dabrafenib (150 mg daily) versus dabrafenib alone demonstrated a median progression-free survival of 9.4 months in the combination group versus 5.8 months in the dabrafenib-alone group. Overall response rates were 76% in the combination group compared with 54% in the dabrafenib-alone group. Because of the benefit seen in phase 1/2 trials, the combination of dabrafenib and trametinib was granted accelerated approval by the FDA in January 2014 contingent on the successful completion of the ongoing phase 3, double-blind, placebo-controlled trial. Many experts believe this combination will replace the use of single-agent BRAF inhibitors.

It is interesting to note that combination therapy has not led to an increase in toxicity and in actuality most physicians who treat patients with melanoma believe combination therapy is better tolerated than single-agent therapy. Fewer cutaneous side effects are noted in combination therapy, with fewer frequent rashes and substantially fewer squamous cell carcinomas. It should be noted that an increased incidence of pyrexia (75%) has been reported in the combination studies of dabrafenib with trametinib.

**Alternative Targets**

**c-KIT–Mutant Melanoma**

Approximately 15% to 20% of acral and mucosal melanomas have been found to express mutations in *c-KIT*, a transmembrane tyrosine kinase receptor. Amplifying mutations in *c-KIT* lead to the activation of signaling pathways, cancer cell proliferation, and inhibition of apoptosis. Preclinical studies using melanoma cell lines have demonstrated a response to imatinib mesylate. A phase 2 study by Carvajal et al evaluated 295 patients with metastatic melanoma with *c-KIT* mutations and found an overall response rate of 16% and a median overall survival of 46.3 weeks. Another study demonstrated overall response and survival rates of 51% and 23.3%, respectively, after treatment with imatinib mesylate at a dose of 400 mg per day in patients with *c-KIT*–mutant metastatic melanoma. The majority of patients demonstrating partial responses (PRs) had *c-KIT* mutations in either exon 11 or 13. Other tyrosine kinases inhibitors, such as sunitinib and sorafenib, have also demonstrated favorable responses in small cohorts of patients with *c-KIT*–mutant melanoma. It is important to emphasize that in all these studies, some patients with *c-KIT*–mutant melanomas did not respond to KIT inhibitors, suggesting that *c-KIT* may not always be the driver oncogene in the proliferation of melanoma. Although initially very promising, the inhibition of this pathway overall has led to some disappointment, with a smaller number of responses and less durability than was expected. Because of this and because of the advent of more effective systemic therapies, the *c-KIT* inhibitors are usually reserved for refractory cases of melanoma rather than as frontline treatment.

**NRAS-Mutant Melanoma**

NRAS mutations have been found in approximately 20% of cases of malignant melanoma. Tumors expressing *NRAS* mutations rarely coexpress *BRAF* mutations, and therefore these patients represent a distinct population that could benefit from targeted therapy. Melanoma cell lines treated with a combination of MEK and phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitors led to a synergistic decrease in cell survival and tumor size both in vitro and in vivo. MEK inhibition with agents such as MEK162 is currently being explored in clinical trials as options for this population. Trametinib currently is not approved for the treatment of *NRAS*-mutant melanoma.

**GNAQ-Mutant Melanoma**

GNAQ mutations are found in approximately one-half of cases of uveal melanoma and lead to downstream upregulation of the MEK pathway. Targeted therapies directed against MEK are being studied in this patient population. Studies using selumetinib (AZD6244; AstraZeneca, Wilmington, Del), a MEK inhibitor, have shown favorable responses. Interim analysis of a multicenter, randomized phase 2 trial comparing selumetinib with temozolomide was presented at the annual American Society of Clinical Oncology (ASCO) conference in June 2013 and demonstrated an improved progression-free survival and overall survival of 16 weeks and 11.8 months, respectively, in the selumetinib arm compared with 4 weeks and 4.7 months, respectively, in the
temozolomide arm. This study has now been completed (clinicaltrials.gov identifier: NCT01143402) and the final results are pending publication.\textsuperscript{36}

Overall mutational analysis of melanoma tumors is a must in deciding what therapeutic options are available. In most community centers, \textit{BRAF} mutational status is standard analysis at the time stage IV disease develops. However, the molecular analysis of tumors will likely be expanded in the near future as newer therapies against alternative genetic alternations become established. Many academic centers are currently offering expanded testing to include all the mutations discussed.

\textbf{Immunotherapy}

\textbf{Interleukin-2}

For many years, immunotherapy has been in the forefront of treatment for advanced melanoma. Interleukin-2 (IL-2) is an immunomodulatory agent that stimulates the immune system to attack cancer cells. The exact mechanism of action of IL-2 is not known. High-dose IL-2 was approved by the FDA for the treatment of metastatic melanoma in 1998 after several studies demonstrated that a small population of patients demonstrated durable responses (5\%-10\%).\textsuperscript{37,38} Due to the significant toxicities of this agent such as hypertension, arrhythmias, and liver and renal toxicities, IL-2 is only recommended in patients with few comorbidities and an excellent performance status. There is a 1\% to 2\% risk of mortality with IL-2, which highlights the importance of choosing a well-suited patient for this treatment modality.

With drugs such as ipilimumab also demonstrating durable responses and now approved for the treatment of stage IV melanoma, the role of IL-2 is now becoming more controversial. Ideal candidates tend to be younger patients with more limited disease because the response rate for IL-2 treatment tends to be higher in this population. No data are currently available regarding the correct sequencing of immunotherapies. Some melanoma experts believe that IL-2 is best used very early on in therapy when subjects have more limited disease (M1a disease) and have a good performance status. A small study has indicated that there may be a higher response rate (47\%) in patients with NRAS-mutant melanoma, but further validation of this study is needed.\textsuperscript{39}

\textbf{Ipilimumab}

The role of the immune system in the prevention of cancer cell growth continued to be a major area of investigation in the early 21st century. Preclinical studies demonstrated that suppression of cytotoxic T-lymphocyte antigen-4 (CTLA-4) augmented the host immune system’s recognition of tumor cells, thereby leading to cell death in patients with several solid and hematologic malignancies, including melanoma.\textsuperscript{40} These preclinical findings led to the development of a human immunoglobulin (Ig) G1 monoclonal antibody, ipilimumab, and IgG2 monoclonal antibody, tremelimumab, both of which bind to CTLA-4. Initial phase 1 and 2 clinical studies using CTLA-4 monoclonal antibodies demonstrated objective responses in patients with metastatic melanoma.\textsuperscript{41–43} These results led to a large, phase 3 trial of 676 patients with metastatic melanoma who were previously treated with chemotherapy or other immunotherapeutic agents and who were randomized to receive ipilimumab (3 mg/kg every 3 weeks for 4 treatments) plus a gp100 peptide vaccine, ipilimumab alone, or the gp100 vaccine alone. The results demonstrated for the first time in metastatic melanoma a statistically significant improvement in the median overall survival in the 2 ipilimumab-containing arms versus the gp100-alone arm (10 months vs 6.4 months; \(P < .001\)). The median progression-free survival was 2.86 months in the ipilimumab-alone arm versus 2.76 months for the ipilimumab plus gp100 and gp100-alone arms.\textsuperscript{44} However, the most significant benefit from ipilimumab is not the fact that the drug improves the median survival, but that even at 5 years of follow-up approximately 15\% to 30\% of patients treated with ipilimumab are still alive, thus suggesting that ipilimumab creates a small but durable response rate. These results led to the approval of ipilimumab (at a dose of 3 mg/kg every 4 weeks for up to 4 doses) by the FDA in March 2011 for the treatment of metastatic melanoma.

\textbf{Toxicity}

The durable responses observed with ipilimumab must be balanced with the approximately 15\% rate of clinically significant autoimmune adverse events. The significant grade 3 and 4 toxicities associated with ipilimumab include fatigue (6.9\%), colitis (5.3\%), dyspnea (3.9\%), anemia (3.1\%), hypopotuitarism (1.6\%), decreased appetite (1.5\%), hypophysitis (1.5\%), and rash (0.8\%).\textsuperscript{44} This grading was based on National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 3.0. Aggressive and timely management of these toxicities are paramount in caring for patients treated with this agent. Significant effort has been made to create guidelines for the management of these autoimmune adverse events, especially diarrhea and colitis, because appropriate management can prevent serious complications such as perforation or death. Diarrhea that is greater than 7 stools above baseline or associated with significant abdominal pain, fever, or ileus should be treated with high-dose steroids (1 mg/kg/day–2 mg/kg/day). If these adverse events do not resolve within 48 to 72 hours, then the addition of infliximab at a dose of 5 mg/kg is appropriate to manage the colitis. Once resolved, steroids should be tapered over 4 to 6 weeks. Surgery should be reserved for patients who are refractory to steroids and infliximab.\textsuperscript{45}

\textbf{Ipilimumab Combination Therapy}

Much effort has been made to increase the number of durable responses as well as the actual response rate noted
with the use of ipilimumab alone. Therefore, a number of preliminary studies have evaluated and are currently ongoing regarding the combination of ipilimumab with other immune therapies and targeted agents.

A rational thought is to combine the 2 approved immunotherapies for stage IV melanoma, ipilimumab and IL-2. In 2005, Maker et al published data on 36 patients with advanced melanoma who received a combination of ipilimumab (0.1 mg/kg-3 mg/kg every 3 weeks) and IL-2, which demonstrated an overall response rate of 22%. Studies evaluating the role of ipilimumab with adoptive cell therapy are currently ongoing.

Trials using ipilimumab in combination with dacarbazine have yielded mixed results. A phase 2 study by Hersh et al compared ipilimumab monotherapy (3 mg/kg every 4 weeks) with a combination of ipilimumab and dacarbazine (250 mg/m²/day for 5 days every 3 weeks, up to 6 cycles) and showed no survival benefit between the 2 groups. However, a phase 3 trial by Robert et al of 502 patients with previously untreated metastatic melanoma randomized patients to dacarbazine (at a dose of 850 mg/m² every 3 weeks for up to 22 weeks) plus placebo or ipilimumab (at a dose of 10 mg/kg every 3 weeks for 4 doses) and demonstrated a significantly improved overall survival in the combination therapy arm compared with patients treated with dacarbazine alone (11.2 months vs 9.1 months; P < .001). Approximately 38% of patients in the combination therapy arm developed limited to severe immune-mediated adverse events compared with 4.4% in the dacarbazine-alone arm. One must keep in mind that the comparison arm was chemotherapy alone, and therefore we cannot state that the combination is better than ipilimumab alone. Therefore, ipilimumab alone remains the standard of care.

Several combination studies with ipilimumab were presented at the 2013 ASCO conference. Ipilimumab combined with pegylated interferon-α-2b showed early promising results. Among 17 patients with unresectable treatment-naive melanoma, there were 5 confirmed PRs and 3 patients with stable disease, leading to a disease control rate of 47%. Hodi et al presented a study that randomized 245 patients to ipilimumab plus granulocyte-macrophage–colony-stimulating factor (GM-CSF) versus ipilimumab alone. The rationale behind this treatment approach is that GM-CSF induces immune responses and may synergize with CTLA-4 blockade. The results demonstrated a higher 1-year overall survival rate of 67.9% in the combination arm versus 51.2% in the ipilimumab-alone arm (P = .016) and no significant differences in toxicity were noted between the 2 treatment arms. Despite these positive results, many experts continue to have doubts regarding the additive efficacy of GM-CSF, primarily due to the negative results noted when it was combined with other therapies such as IL in the past. In another study presented at the recent ASCO meeting, patients with melanoma received ipilimumab at a dose of 10 mg/kg every 3 weeks for 4 doses followed by bevacizumab every 3 weeks. Of the 21 evaluable patients with advanced melanoma, 14 demonstrated an objective response. However, this study did have significant autoimmune toxicity, with 5 patients discontinuing treatment and requiring systemic steroids.

Despite the early promising data with combination therapy, ipilimumab as a single agent is still the standard of care. Further study is needed to establish not only the additional benefit of the combinations but also to establish their toxicity profiles.

### Programmed Cell Death 1 and Programmed Cell Death Ligand 1 Inhibitors

**Biology**

Programmed cell death 1 (PD-1) is a negative costimulatory molecule expressed on T cells that inhibits the activation and proliferation of T cells, thereby causing immunosuppression. PD-1 exerts its effects through interaction with specific ligands: programmed cell death ligand 1 (PD-L1) and 2 (PD-L2). PD-L1 is constitutively expressed on B cells, dendritic cells, macrophages, and T cells. Overexpression of PD-1 and PD-L1 leads to dysregulation of the immune system, causing persistence of pathogens and tumor growth.

Early preclinical studies demonstrated that inhibiting the interaction between PD-1 and PD-1 ligands can restore T-cell responses in vitro leading to the suppression of tumor growth. A more recent study used melanoma cell lines to demonstrate that inhibition of the PD-1/PD-L1 pathway promotes CD8+ T-cell responses and inhibits T regulatory cells, thus restoring T-cell recognition of tumor-bearing hosts. These preclinical studies also showed that expression of PD-1 on the cell surface is necessary for optimal response to antibodies directed against PD-1. In June 2012, the results of a phase 1 study with nivolumab (BMS-936558) were published and demonstrated objective responses in heavily pretreated patients with different types of solid tumors, including non-small cell lung cancer, melanoma, and renal cell cancer. Nivolumab is a fully human IgG4-blocking monoclonal antibody directed against PD-1. Patients with melanoma demonstrated an overall response rate of 28%, and the majority of patients received treatment for 1 year or longer, thus indicating the durability of response. Autoimmune adverse events were noted to be similar to those of ipilimumab, with rash, hepatitis, and hypophysitis reported to occur, although at a lesser rate than historic trials with ipilimumab alone, and only 15 of 296 patients discontinued treatment due to an adverse event. Interstitial pneumonitis occurred in 3% of patients, with death from the pneumonitis occurring in 3 patients (1%). A recently published follow up of 107 metastatic melanoma patients treated with nivolumab between 2008-2012 demonstrated median overall survival of 16.8 months, with 2-year survival rate of 43%. A phase 3
randomized trial of nivolumab in patients with ipilimumab-refractory disease is currently ongoing.

Nivolumab was also evaluated in combination with a peptide vaccine and demonstrated objective response rates of 28% and 32%, respectively, in patients with metastatic melanoma who were either therapy-naive or had failed prior ipilimumab. The peptide vaccine did not appear to add any additional activity to the agent. It is interesting to note that biomarker studies demonstrated an increase in the expression of CTLA-4 in CD4 T cells and regulatory cells in nonresponders, suggesting that sequential treatment with the combination may be effective. Sequential treatment of ipilimumab and nivolumab as well as combination studies of the 2 treatments are currently ongoing.

MK-3475 is another monoclonal IgG4 antibody against PD-1 that has been studied extensively in patients with melanoma. One study evaluated 294 patients with advanced melanoma with or without prior ipilimumab treatment and showed a significant overall response rate of 35%. The median duration of response had not been reached at the time of last follow-up; however, all objective responses had lasted up to 8 months or longer. Grade 3/4 adverse events were noted in 10% of the study cohort and primarily consisted of autoimmune toxicity similar to what was noted with nivolumab. A larger study with MK-3475 has recently completed the enrollment of patients who are ipilimumab-naive and ipilimumab-refractory and results are eagerly awaited.

The study that showed the most impressive responses with the anti–PD-1 antibody was a phase 1 study combining nivolumab and ipilimumab. A total of 53 patients received combined therapy and 33 patients received sequenced treatment. Although there was significant toxicity, with 53% of patients experiencing a grade 3 or 4 adverse event, just over one-half of the patients had an objective response with rapid and deep regression of the tumor burden. In fact, all objective responders had a greater than 80% reduction in tumor burden.

Inhibition of the PD-1 receptor counterpart PD-L1 has also been explored. The PD-1 receptor binds 2 ligands: PD-L1 and PD-L2. PD-L1 is expressed on many tumors, including melanoma, and tumors can decrease host immune response via its expression. BMS-93559 is a fully human PD-L1–specific IgG4 monoclonal antibody that has been evaluated in many tumor types. Nine objective responses among 52 patients with melanoma were observed, with the highest response rate (29%) noted at the dose of 3 mg/kg. Immune-related adverse events were observed in 39% of patients treated and included rash, hypothyroidism, and hepatitis.

Adjuvant Treatment of Melanoma

Patients with a high risk of disease recurrence characterized by resected lymph node-positive disease (stage III) or lymph node-negative disease with increased Breslow tumor thickness (stage IIB or IIC) should be considered for adjuvant therapy because many of these patients have a high risk of systemic recurrence.

In the adjuvant setting, high-dose interferon-α-2b has demonstrated a statistically significant recurrence-free survival compared with observation alone in studies conducted by the Eastern Cooperative Oncology Group and Intergroup trials E1684, E1690, and E1694. Updated analysis of the E1684 trial has shown a continued benefit in terms of recurrence-free survival after a median follow-up of 12.6 years. Unfortunately, none of these studies has demonstrated an overall survival benefit with the use of high-dose interferon-α-2b in long-term follow-up. However, a meta-analysis did show an overall survival benefit. In 2011, the FDA approved pegylated interferon-α-2b for use in the adjuvant setting in patients with melanoma with microscopic or macroscopic lymph node involvement within 84 days of definitive surgical resection, including complete lymphadenectomy. This approval was based on the European Organization for Research and Treatment of Cancer 18991 Trial of 1256 patients with resected stage III melanoma, which demonstrated a significant improvement in recurrence-free survival of 34.8 months compared with 25.5 months in the placebo group. No differences in overall survival and distant metastasis-free survival were noted on long-term follow-up. More clinical benefit was observed in patients with ulcerated melanomas and those with earlier stage III (N1) disease, with an overall survival benefit in this population based on subset analysis. It is interesting to note that patients were treated on this trial for up to 5 years, although the median duration of treatment on the study was fewer than 2 years. No direct comparison study of high-dose interferon versus pegylated interferon has been performed.

Clearly, the advances described in patients with stage IV melanoma have yet to be fully evaluated in patients with stage III resected disease. Studies with ipilimumab in this setting are ongoing and studies with PD-1 antibodies are planned.

Surgical Management of Melanoma

Workup and Clinical Staging

Once a patient has been diagnosed with a melanoma, usually based on biopsy of a suspicious mole or skin lesion, the focus is on clinical staging. Clinical staging begins with a detailed pathology report describing critical features of the tumor as outlined by the NCCN. Physical examination should include a comprehensive skin examination to evaluate for any other suspicious skin moles. The other critical aspect of the examination is the lymphatic system, with emphasis on the regional draining lymphatic basin. If the
The physical examination shows clinically negative lymph nodes, then no further workup is usually undertaken. With certain high-risk melanomas, such as thick primary tumors, those with a high mitotic rate, or those with microscopic satellitosis, ultrasound of the regional nodal basin or cross-sectional body imaging can be performed to rule out subclinical regional disease or systemic disease. However, regional ultrasound or cross-sectional imaging should not be performed in all cases due to low yield. The tumor can be resected with margins based on depth as detailed below.

Buzaid et al. examined the usefulness of computed tomography (CT) in the staging of patients with primary melanoma with clinical stage I to stage III disease. Of the 151 patients, 29 (19%) had CT scan findings considered suspicious for metastasis, 24 of whom subsequently were proven to have benign processes by biopsy or follow-up studies. Three patients had a second primary tumor and only 2 were found to have metastatic melanoma. One patient had regional lymph node disease that was missed on physical examination and the other had distant lymph node disease. The authors concluded that CT is not useful for the detection of occult primary metastases in patients with primary melanoma. Yancovitz et al. conducted a systematic review of the role of radiologic imaging at the time of the initial diagnosis of T1b to T3b melanoma. They reviewed a total of 348 studies (chest x-ray, CT, and positron emission tomography [PET]/CT) performed on 158 patients. Only 1 of the 344 studies (PET/CT) correlated with confirmed metastatic disease. Yancovitz et al. concluded that imaging at the time of initial diagnosis of T1b to T3b disease was of low yield with a high false-positive rate and did not lead to upstaging or a change in initial surgical management.

The advent of PET and PET/CT scan capabilities led to some early optimism that this new modality may perform better than clinical examination and CT alone in detecting clinically occult metastatic disease. However, several authors who have examined the use of PET/CT scans for staging melanomas of all depths have stated that it does not perform any better than the other radiologic imaging modalities currently in use. The recommendation from these authors is to omit this imaging modality in the workup of a patient in whom clinical evaluation did not reveal any metastatic disease.

For patients with clinically positive lymph nodes at the time of presentation, the risk of systemic metastasis is substantially increased. The use of whole-body imaging in these patients is strongly encouraged to rule out distant disease before any surgery on primary tumors or involved lymph node basins is attempted. We recommend either full-body PET/CT fusion or a CT scan of the neck, chest, abdomen, and pelvis with intravenous and oral contrast as well as dedicated brain imaging such as brain magnetic resonance imaging or CT scan for this purpose.

### Localized Disease

The surgical treatment of melanoma has not undergone significant change over the last decade, especially with regard to the treatment of localized primary tumors. The current recommendations for surgical management of localized melanoma continue to be based on randomized prospective clinical trials that were completed years ago, as summarized in Table 1. For localized melanoma, the treatment continues to be wide local excision (WLE). The margin of resection is dependent on the depth of the tumor. It is interesting to note that margins are measured macroscopically from the biopsy scar or residual pigmentation at the time of surgery, not by the pathologist after resection.

### Melanoma In Situ

A prospective study that assessed 1120 patients with melanoma in situ treated with Mohs surgery showed that 99% of all melanoma in situ tumors could be removed with a 0.9-mm margin and a margin of 0.6 mm resulted in successful resection in 86% of cases. There are no randomized prospective studies that have examined surgical margins for melanoma in situ, and therefore the
The recommendation is based on expert consensus. For melanoma in situ, the NCCN-recommended margin is 0.5 cm to 1 cm. At the Moffitt Cancer Center (MCC), we use margins of at least 0.5 cm for in situ melanomas and 1-cm margins if there is a significant amount of residual pigment near the biopsy site. Furthermore, we routinely use a 0.5-cm margin in cosmetically and functionally sensitive areas (face, neck, hands and feet, etc).

**Invasive Primary Cutaneous Melanoma**

For invasive melanomas measuring less than 1 mm in depth, WLE with 1-cm margins is recommended by the NCCN (Table 2). For melanomas measuring between 1 and 2 mm, 1-cm to 2-cm margins are recommended. The wider margin is preferred but a 1-cm margin is acceptable if it would minimize local tissue loss and result in better cosmetic or functional outcome, such as avoiding the use of a skin graft. This is applicable in areas such as the face, across joints, hands and feet, or the genitalia. For melanomas thicker than 2 mm, 2-cm margins are recommended, including thick melanomas measuring greater than 4.0 mm. Unlike the recommendation for in situ melanoma, these recommendations are supported by several of the following multicenter, prospective, randomized trials (Table 1). In a study performed by the World Health Organization, 612 patients with melanomas measuring less than 2-mm thick were randomized to radical excision with 0.9 mm and 2.0 mm who were treated with margins of 2 cm or 5 cm. There was no difference noted in overall survival between 0.9 mm and 2.0 mm who were treated with margins of 2 cm or 5 cm. There was no difference noted in overall survival (79% vs 76%, respectively) or recurrence-free survival (71% vs 70%).

**Lymph Node Disease**

**Sentinel Lymph Node Biopsy**

Lymph node involvement has been shown to be the most important prognostic factor in melanoma. Before sentinel lymph node biopsy (SLNB) was developed, there were 2 options to address the draining lymphatic basin after WLE for invasive melanoma. The first option was concurrent elective complete lymph node dissection (ELND) at the time of WLE. The second option was observation with therapeutic lymph node dissection if and when there was a clinical lymph node recurrence. Neither of these options was satisfactory given that only approximately 20% of these patients are expected to have metastasis in the regional lymph nodes at the time of diagnosis. In addition, delaying lymph node dissection until clinical recurrence may result in some patients presenting with unresectable lymph node disease, thus compromising their survival. SLNB has emerged as a way to better select patients who need a complete lymph node dissection (CLND). The goal of SLNB is to evaluate the draining lymphatic basin for occult micrometastatic disease. It is therefore fundamentally a staging procedure. The findings from pathologic evaluation of the SLN can be used to guide further treatment. SLNB has not been shown to improve survival in patients with melanoma.

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**Table 2. Summary of Current NCCN Recommended Wide Resection Margins for Melanoma**

| MELANOMA THICKNESS (in mm) | RECOMMENDED SURGICAL MARGIN (in cm) |
|---------------------------|------------------------------------|
| In situ                   | 0.5-1                              |
| ≤ 1.0                     | 1.0                                |
| 1.01-2                    | 1-2                                |
| 2.01-4                    | 2                                  |
| ≥ 4                       | 2                                  |

NCCN indicates National Comprehensive Cancer Network.

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| MELANOMA THICKNESS (in mm) | RECOMMENDED SURGICAL MARGIN (in cm) |
|---------------------------|------------------------------------|
| In situ                   | 0.5-1                              |
| ≤ 1.0                     | 1.0                                |
| 1.01-2                    | 1-2                                |
| 2.01-4                    | 2                                  |
| ≥ 4                       | 2                                  |

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A Swedish trial examined 468 patients with melanomas measuring less than 2 mm that were resected with 2-cm or 5-cm margins reported similar results. The 10-year recurrence-free survival rates were 85% and 83%, respectively, and the 10-year overall survival rates were 87% and 86%, respectively. A UK trial studied 900 patients with melanomas of at least 2-mm thickness resected with margins of 1 cm versus 3 cm. The 1-cm margin was associated with a significantly increased risk of locoregional recurrence (hazards ratio [HR], 1.26; 95% confidence interval [95% CI], 1.00-1.59 [P = .05]). However, overall survival was found to be similar in both groups (HR, 1.24; 95% CI, 0.96-1.61 [P = .1]). A second Swedish trial examined 936 patient with melanomas measuring greater than 2 mm that were resected with margins of 2 cm versus 4 cm. The 5-year overall survival rate was similar in both groups. Lastly, a meta-analysis and systematic review showed that for patients with invasive primary melanoma, surgical margins of no more than 2 cm are sufficient and they should not be less than 1 cm.
Role of SLNB in Patients With Thin Melanomas (Less Than 1 mm)

Current ASCO/Society of Surgical Oncology (SSO) and NCCN guidelines state that SLNB could be considered for patients with thin melanomas (those measuring less than 1 mm) with high-risk features such as ulceration and mitotic rate of 1/mm² or higher, especially in patients with melanomas measuring between 0.75 mm and 0.99 mm, in whom the benefits of SLNB outweigh the risks. The guidelines state that there is insufficient evidence to support routine SLNB for patients with thin melanomas (T1; Breslow thickness of less than 1 mm), although it may be considered in selected cases with high-risk features when staging benefits outweigh the risks of the procedure. For patients with stage IA melanoma (measuring 0.76-1 mm with no ulceration and a mitotic rate of less than 1/mm²), it is recommended that a discussion of SLNB should be considered. SLNB is not routinely recommended for patients with melanomas measuring less than 0.76 mm without adverse prognostic features. A recent, large, single-institution study of the use of SLNB in patients with thin melanomas by Han et al showed an overall positive SLN rate of 8.4% in patients with melanomas measuring 0.76 mm to and no more than 1.0 mm. The rate was 5% for T1a melanomas measuring 0.76 mm or more and 13% for T1b melanomas measuring 0.76 mm or more. Logistic regression analysis demonstrated that ulceration and a mitotic rate of 1/mm² or higher correlated with SLN metastasis (P < .05 in both cases). A multiinstitutional study also performed by Han et al examined 1250 patients with thin melanomas who underwent SLNB. SLN metastases were detected in 65 patients (5.2%). Multivariate analysis showed that a Breslow thickness of 0.75 mm or more, Clark level of 4 or higher, and ulceration significantly predicted SLN disease in 6%, 7.0%, and 11.6%, respectively, of patients. As a result of these studies, at MCC we routinely offer SLNB to all patients who are fit for general anesthesia with melanomas measuring 0.76 mm or more in thickness or any patient with an ulcerated primary thin melanoma.

Intermediate-Thickness Melanomas (1.01 to 4 mm)

The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) examined 1347 patients with intermediate-thickness melanoma (1.2 mm-3.5 mm), 1269 of whom were evaluable. The patients were randomly assigned to either WLE and SLNB with immediate CLND for positive SLNs or WLE alone and subsequent therapeutic lymph node dissection of the regional lymph node basin if a clinical lymph node recurrence developed. The MSLT-I demonstrated that the SLNs could be identified in 95% of cases, with low false-negative and complication rates reported. Results of the third interim analysis of this study showed no difference in melanoma-specific survival between the groups (87.1% and 86.6%, respectively). There was an improvement in the estimated 5-year disease-free survival in favor of the WLE and SLNB group (78.3% and 73.1%; HR for recurrence [corrected], 0.74 [95% CI, 0.59-0.93] [P = .009]). In the subset of patients who had CLND for lymph node-positive disease, those diagnosed with micrometastatic disease by SLNB had a significantly higher 5-year survival rate than those who underwent therapeutic lymphadenectomy for clinically positive disease after a recurrence in the regional lymph node basin (72.3% vs 52.4%; HR for death, 0.51 [95% CI, 0.32-0.81] [P = .004]).

Thick Melanomas (More Than 4 mm)

The role of SLNB in patients with melanomas measuring greater than 4 mm was not addressed by the MSLT-I trial. The current ASCO guidelines state that there are few studies focusing on patients with thick melanomas (T4; Breslow thickness of greater than 4 mm). SLNB may therefore be recommended for staging purposes and to facilitate regional disease control. One study specifically examining thick melanomas and SLNB was performed by Gershenwald et al and reported a successful SLNB rate of 96%. The SLN positivity rate was 39%. As in intermediate- and thin melanomas, patients with positive SLN are offered CLND of the affected lymph node basin, which is consistent with NCCN guidelines.

Desmoplastic Melanoma

The role of SLNB in patients with desmoplastic melanoma (DM) is somewhat controversial. Much of this controversy may result from the fact that studies have reported lower rates of positive SLN in DM (typically less than 5%). NCCN guidelines do not recommend SLNB for pure DM. In its most recent guidelines on SLNB in melanoma, ASCO does not address DM as a separate category. A recent large, single-institution, retrospective review of SLNB in patients with DM showed that the overall risk of SLN metastasis in DM is 13.7%. For patients with mixed DM, the rate is 24.6%, whereas for those with pure DM it is 9.0%. The authors concluded that these rates are high enough to justify the use of SLNB in both variants of DM. As such, at MCC we routinely offer SLNB to patients with DM. However, other major cancer centers do not perform SLNB in patients with DM.
Alternatives to SLNB
In certain situations, SLNB might not be possible or might be associated with a higher false-negative rate. This includes patients in whom there has been an unsuccessful attempt at lymphatic mapping or unsuccessful SLNB after lymphoscintigraphy. It also includes patients who have undergone previous radical WLE prior to a definitive diagnosis of melanoma, patients with extensive flap or graft reconstruction, patients who have medical contraindications to general anesthesia, and patients who decline the procedure. In these cases, close surveillance of the involved lymph node basin with serial ultrasounds is a reasonable alternative. Uren et al have shown that ultrasound is superior to clinical palpation during follow-up after WLE of melanoma.\(^8^5\) When ultrasound was combined with fine-needle aspiration of suspicious lymph nodes, it allowed for the earliest possible detection of lymph node recurrence and therapeutic lymphadenectomy.\(^8^5\) Blum et al examined 6328 lymphatic basins over 42 months in 1288 patients after resection of histologically proven melanoma. Suspicious lymph nodes were resected and evaluated for disease. They showed a sensitivity and specificity of 89.2% and 99.7%, respectively, for ultrasound compared with 71.4% and 99.7%, respectively, for clinical examination.\(^8^6\) Chai et al examined 325 patients with melanoma over a 4-year period who underwent ultrasound prior to SLNB. They demonstrated an overall sensitivity and specificity for ultrasound of 33.8% and 85.7%, respectively, compared with immunohistochemical staining of the SLN.\(^8^7\) Only 6 patients avoided SLNB due to a suspicious ultrasound prior to SLNB, with fine-needle aspiration confirming lymph node-positive disease. The authors concluded that preoperative ultrasound is not very useful in identifying lymph node metastasis in patients with melanoma undergoing SLNB.\(^8^7\)

The Future of SLNB
In patients with positive SLNs, only 15% to 20% are subsequently found to have additional metastatic disease in the remaining non-SLNs after completion lymphadenectomy.\(^8^8\) McMasters et al examined 274 patients with at least 1 positive SLN who underwent CLND. Of 282 positive lymph node basins, 45 (16%) were found to have positive non-SLNs. After studying Breslow thickness, Clark level, and ulceration, among other factors, they could not identify any primary tumor characteristic that indicated minimal risk of non-SLN metastasis.\(^8^9\) The ongoing MSLT-II trial is examining patients with positive SLNs who are randomized to either immediate completion lymphadenectomy or close monitoring with serial ultrasounds of the lymph node basin.\(^9^0\) At completion, this will hopefully shed some light on the question of which patients should undergo a CLND versus those not at high risk of non-SLN disease.

Clinically Positive Lymph Node Disease (Stage IIIB/IIIC)
For patients with clinically positive lymph nodes (Stage IIIB/IIIC) at the time of presentation with an intact primary tumor or any time after WLE has been performed, surgical treatment consists of WLE with appropriate resection margins of the primary tumor if still intact and complete lymphadenectomy of the involved lymphatic basin (if there are no contraindications to surgery and all disease can be safely removed). It is highly desirable that these patients have full body cross-sectional imaging to rule out distant disease before any surgery on primary tumors or involved lymph node basins is attempted. We recommend either full-body PET/CT fusion or a CT scan of the neck, chest, abdomen, and pelvis with intravenous and oral contrast as well as dedicated brain imaging such as brain magnetic resonance imaging or CT scan.

In Transit and Satellite Disease
For patients with in transit or satellite disease, the mainstay of therapy is resection to negative margins for those with resectable disease (ie, the ability to completely resect all disease with negative margins without compromising esthetics and function). Dong et al examined a series of 648 patients with primary melanoma who developed local recurrence.\(^9^1\) The patients were all treated with surgical resection. Of the 648 patients, 124 (19%) had no further recurrence of disease, 196 patients (30%) developed a new local recurrence, 178 patients (27%) developed further in transit recurrence, and 150 patients (23%) subsequently developed systemic disease. The 5-year survival rate was greater than 50%. However, some limitations from this study include a highly selected group for surgical resection and that many of the patients with further recurrences received other aggressive treatment such as regional perfusion and chemotherapy.\(^9^1\)

Other options include isolated limb infusion (ILI) or hyperthermic isolated limb perfusion (HILP). The most commonly used agent is melphalan, either alone (United States and Europe) or in combination with tumor necrosis factor (Europe). Boesch et al examined 152 patients with locoregionally metastasized melanoma who were treated with HILP with melphalan and dactinomycin. The overall response rate was 80.7%. There was a 62.7% complete response (CR) rate and a 19.7% PR rate. No response was noted in 19.3% of patients.\(^9^2\) The American College of Surgeons Oncology Group Z0020 trial conducted a randomized, prospective, clinical trial for patients with in transit melanoma using HILP with melphalan with or without TNF. The results showed an overall response rate of 64% in the melphalan-alone arm compared with 69% in the melphalan plus TNF arm (\(P\) value not significant). The CR rate was 25% with melphalan alone versus 26% with...
the addition of TNF (P value not significant). The Z0020 trial was stopped early due to a significantly higher rate of toxicity observed in the TNF arm and no response benefit noted in the same arm over melphalan alone.93

ILI is a less invasive and less complex procedure compared with HILP. A recent multicenter study of ILI in 128 patients showed a CR rate of 31%, a PR rate of 33%, and a nonresponse rate of 36%.94 Another benefit of ILI over HILP is the ability to perform repeat treatments with minimal toxicity. With ILI, it is easier to perform repeat perfusions than the complex surgical procedure required with HILP.

Metastatic Disease

The role of surgery in the treatment of metastatic melanoma is limited. However, most would agree that if all disease can be removed surgically with acceptable morbidity, surgery is likely the best approach. Surgery is also used for palliation in cases of gastrointestinal bleeding, or obstruction or bulky disease that impairs function or quality of life. With the advent of newer, more effective systemic therapies detailed above, surgery for patients with stage IV disease might be found to play a bigger role with resection of residual disease after downstaging with systemic therapy, but only time will tell how surgery and systemic therapy will be used in conjunction.

Brain Metastases

Brain metastases warrant special consideration. Most patients with brain metastases are usually excluded from clinical trials. Although there are no data specific to patients with melanoma only, a look at the treatment of metastatic disease from all cancers to the brain does offer some guidance. Historically, only patients with a single brain metastasis were offered surgical resection. This was usually followed by whole-brain radiation therapy (WBRT). A study by Patchell et al randomized patients with a solitary brain metastasis to surgical resection only versus surgical resection with adjuvant WBRT. Adjuvant WBRT was associated with a drastic reduction in local recurrence (18% vs 70%; P < .01).95 Surgery is usually limited to biopsy for diagnostic purposes in patients with more than one metastatic lesion in the brain. Although there have been reports of patients with up to 3 metastatic lesions deriving a survival benefit from surgical resection, these are not enough to recommend routine surgery for these patients.96 Stereotactic radiosurgery (SRS) has emerged as an alternative method for treating patients with metastatic disease to the brain. A Japanese study randomized 132 patients with 1 to 4 metastatic brain lesions measuring less than 3 mm in diameter to SRS or SRS plus WBRT. The addition of WBRT did not improve median survival when compared with SRS alone (7.5 months vs 8 months). However, the addition of WBRT resulted in a lower 1-year recurrence rate (47% vs 76%; P < .01).97 Two retrospective studies have shown that SRS plus WBRT resulted in equal or better survival compared with surgery and WBRT.98,99 As a cautionary note, these studies examined metastases from all cancers, and not just from melanoma. There are not enough data to make firm recommendations on the role of surgery versus SRS and adjuvant WBRT in the treatment of patients with melanoma with metastases to the brain.

Conclusions

The treatment of metastatic melanoma has been revolutionized over the past decade. Both surgical and medical options for patients are expanding, and the optimal way to integrate these novel approaches is yet to be determined. Patients are living longer and better, but clearly research for melanoma treatment is not complete. Now more questions are arising about the correct sequencing of immune and targeted therapies as well as to establish the best combination of treatments. Another challenge in melanoma is the treatment of the brain metastases that continue to plague patients. Unfortunately, the clinical progress of treatment in this population has been limited because this group is excluded from most of the ongoing stage IV melanoma trials. The other hurdle in melanoma is the area of more effective adjuvant therapies. Although the progress in stage IV disease has been rapid, the promise in stage III disease remains to be seen. Most of the newer therapies such as vemurafenib, dabrafenib, trametinib, and ipilimumab are in current trials to evaluate their benefit in patients with resected melanoma, but for now the standard of care remains the controversial treatment with interferon.

Understanding the biology of melanoma and translating that into clinical trials has already made the future much brighter for patients with metastatic melanoma, but a continued commitment and vigilance to melanoma research is essential to moving the field forward.

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