



Strategies for Individualizing Management of Patients With Metastatic Melanoma: A Managed Care Perspective

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With 63,000 new diagnoses and 9000 deaths annually between 2007 and 2011, melanoma is not only the most lethal skin cancer in the United States, but also the third most common cancer among adolescents and young adults, increasing at a rate of 1.4% to 1.6% per year.¹ Although many patient- and disease-related issues factor into the treatment approach, tumor stage at diagnosis is most important in determining patient treatment options and overall prognosis. Eighty-four percent of patients with melanoma are diagnosed with local stage disease (stage I), while 4% are diagnosed with cancer that has metastasized (see Figure 1a² and 1b^{2,5}).

Treatment of local stage disease typically includes surgical excision with or without sentinel lymph node biopsy (stage Ib or II) and subsequent active surveillance, which consists of regular follow-up physical examinations, lab work, and possible radiographic studies. Due to an associated improved disease-free survival (DFS), patients with stage IIb, IIc, or III are typically offered adjuvant treatment with high-dose interferon alfa (1 year) or peginterferon alfa-2b (5 years). Patients with stage III disease, especially if the disease is deemed to be bulky, may also receive radiation therapy.⁶

Historically, patients with metastatic melanoma have had few treatment options. Systemic chemotherapy with dacarbazine offered a modest overall response rate and a limited overall survival (OS) benefit.^{6,7} However, a surge of recent advances in the screening, diagnosis, and multimodality treatment of melanoma has given hope to a disease that has seen a 10-year median survival of less than 10%.⁷ From 2011 to 2015, 6 immune-based and targeted agents have been approved by the FDA (Figure 2).⁸

Therapies that target mutated or activated genes have also transformed the treatment of metastatic melanoma over the past decade. The RAS/RAF/MEK/ERK (MAPK) signaling pathway is considered to be

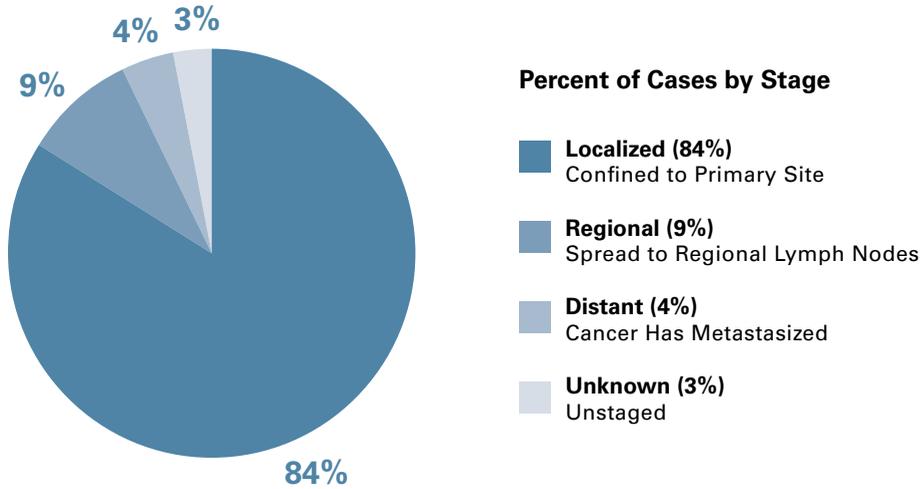
Abstract

The management of metastatic melanoma has been revolutionized in recent years with the development of both targeted therapy and immunotherapy. Although potentially extending the life expectancy for patients, these therapies also significantly increase the healthcare expenditure. In this paper, we review the monthly costs for drugs approved by the FDA since 2011. Additionally, factors that affect the cost, such as dosing strategies, biomarkers, combination therapies, and political/legislative issues, will be discussed.

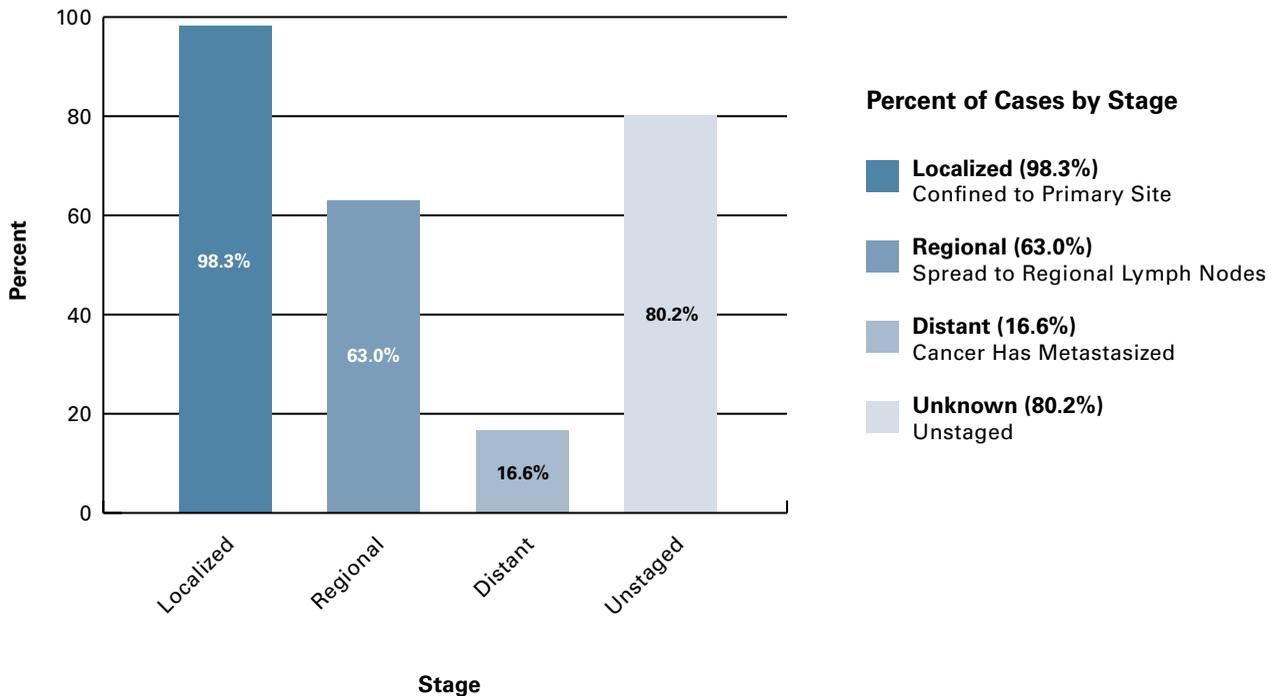
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■ **Figure 1a.** Percent of Cases by Stage at Diagnosis: Melanoma of the Skin²



■ **Figure 1b.** 5-Year Relative Survival by Stage at Diagnosis: Melanoma of the Skin²

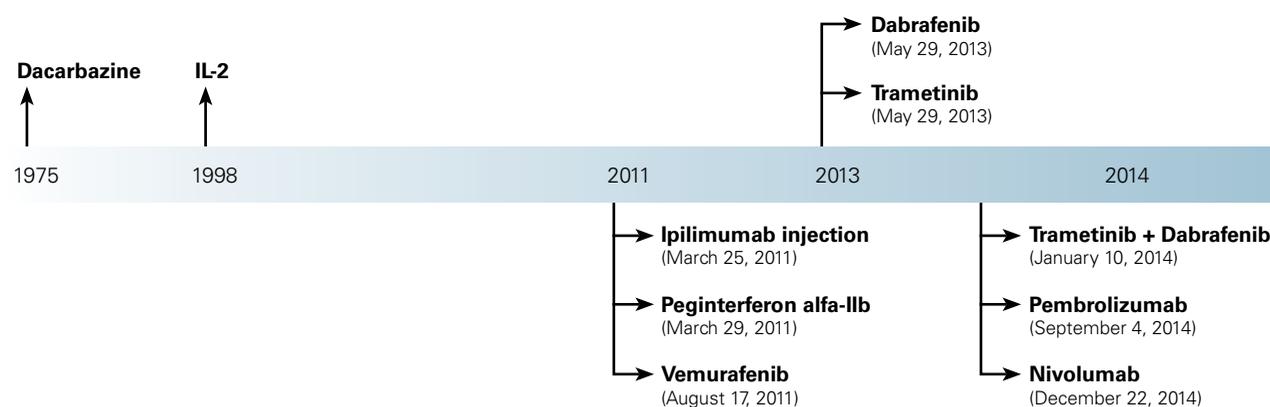


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a critical signal transduction pathway responsible for mediating cellular responses to growth signals. Mutated proteins within this pathway, such as BRAF (50% of melanomas), may lead to uncontrolled proliferation

of melanocytes.^{9,10} Recently, the FDA approved BRAF inhibitors vemurafenib (2011) and dabrafenib (2013) for the treatment of patients with BRAF V600E mutated advanced melanoma. The approval was based on two

■ **Figure 2.** FDA Approval Timeline: Melanoma Treatment⁸



phase 3 trials that demonstrated a significantly improved overall response rate and progression-free survival (PFS) among patients who received these agents, compared with those who received dacarbazine.^{11,12} In a study of treatment-naïve metastatic melanoma patients with BRAF V600E mutations, patients in the vemurafenib group had a significantly improved median PFS (6.9 months vs 1.6 months, respectively; $P < .0001$) and median OS compared with those in the dacarbazine group (13.6 months vs 9.7 months; $P = .0008$).¹² In a study of 250 randomized patients with BRAF V600E-mutated metastatic melanoma, dabrafenib also demonstrated significantly improved median PFS compared with dacarbazine (5.1 months vs 2.7 months, respectively; $P < .0001$).¹¹

Similar to other cancer types, melanoma typically acquires resistance mutations after being continually exposed to BRAF inhibitors. These mutations render the BRAF inhibitor ineffective and lead to subsequent tumor progression/growth.^{13,14} To prevent the development of these resistance mutations, BRAF-MEK inhibitor combinations were developed to target MAPK pathway components. MEK inhibitors, which target a protein downstream from BRAF, also have activity in BRAF V600-mutant melanoma.^{10,15} Randomized studies have supported the hypothesis that concurrent MEK inhibition mitigates MAPK reactivation without additional significant adverse events (AEs), thereby establishing the combination as standard first-line targeted therapy for patients with BRAF V600E- or BRAF V600K-mutant melanoma.^{14,16-18} Despite proven activity as combination first-line treatment, these agents have yet to show their effectiveness when used for metastatic melanoma in a sequential fashion.^{19,20}

Immunotherapy uses regulatory cell surface molecules to reverse immune suppression, thereby using the body's immune system to effectively attack melanoma cells.²¹ FDA-approved immunotherapy includes interleukin-2 (IL-2; 1998), the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, ipilimumab (2011), and programmed death-1 (PD-1) blockers, pembrolizumab (2014) and nivolumab (2014). Pembrolizumab, the first PD-1 inhibitor approved in patients with advanced melanoma, demonstrated efficacy in patients with disease refractory to ipilimumab.²² Nivolumab, a humanized monoclonal antibody targeting PD-1, demonstrated significant improvement in PFS and OS compared with dacarbazine in patients with ipilimumab-refractory metastatic melanoma.¹⁶ Nivolumab alone or in combination with ipilimumab demonstrated significantly longer PFS than ipilimumab alone in previously untreated patients with metastatic melanoma.¹⁷

With the surge in innovation comes an important discussion regarding the cost, management, and sequencing of new therapies. There is significant concern regarding the ability of public and private payers to keep up with the high cost of such innovations. Cost-effective strategies are difficult to devise, partly because of the lack of long-term survival data from recently approved agents.

Lost Productivity

Unlike diseases that typically affect elderly populations, melanoma commonly affects a younger population and patients often sacrifice significant long-term productivity. The worker-related costs associated with metastatic melanoma (ie, lost workdays and restricted-activity days) are estimated at \$29.4 million in losses to the US economy annually.^{23,24} Using national mortality

Table 1. Monthly Cost of Drugs for Regimens Approved Since 2011^{17,27-32}

The monthly cost of the drugs is based on a 28-day month cycle; the approved dosing, as described in the agent's prescribing information; body weight of 82 kg based on mean US values; and a body surface area of 1.86 m². Does not include cost of infusion.

Drug	Dose	ASP
Vemurafenib	960 mg twice daily continuously	\$6239.25
Dabrafenib + trametinib	dabrafenib 150 mg twice daily, trametinib 2 mg once daily	\$10,849.83
Ipilimumab	3 mg/kg every 3 weeks	\$44,919.60
Nivolumab	3 mg/kg every 2 weeks	\$12,498.76
Nivolumab/ipilimumab ^a	1 mg/kg every 3 weeks of nivolumab plus 3 mg/kg every 3 weeks of ipilimumab	\$47,697.10
Pembrolizumab ^b	2 mg/kg every 3 weeks	\$9991.32
Pembrolizumab ^c	10 mg/kg every 2 weeks	\$74,934.88

ASP indicates average sale price.

^aThis combination was recently published and is expected to soon gain FDA approval.

^bFDA recommended dose based on phase 1b trial.

^cDose used in subsequent phase 3 trial.

data and US life tables (2000-2006) to estimate years of potential life lost (YPLL), one study found that women had a higher premature mortality associated with metastatic melanoma and lost 21.4 years of potential life compared with men who lost 19.0 years of potential life. An individual who died from metastatic melanoma was estimated to lose an average of \$413,370 in lifetime earnings compared with \$309,879 for all other malignant cancers, which would result in an annual productivity loss of \$3.5 billion.^{24,25}

Cost of Healthcare Utilization

Healthcare utilization associated with metastatic melanoma is substantial. Based on a commercially insured patient population, patients with metastatic melanoma were found to have a greater per-patient per-month (PPPM) utilization than noncancer controls for inpatient stays (0.07 vs 0.01), outpatient visits (2.42 vs 0.64), and office visits (1.05 vs 0.41) ($P < .0001$ for all). The total cost of PPPM was 7.5 times higher for the metastatic melanoma population than for the non-cancer control population (\$3118 vs \$415, $P < .0001$).²⁶

Although significant, healthcare utilization is only a small part of the cost of metastatic melanoma; the cost of medication acquisition is much larger. However, a systemic search of the published literature did not identify substantial findings of studies evaluating cost-effectiveness of the new metastatic melanoma treatments. Comparative data are lacking because of the relative infancy of the treatments; there is also a lack of prospective randomized data describing their sequencing in

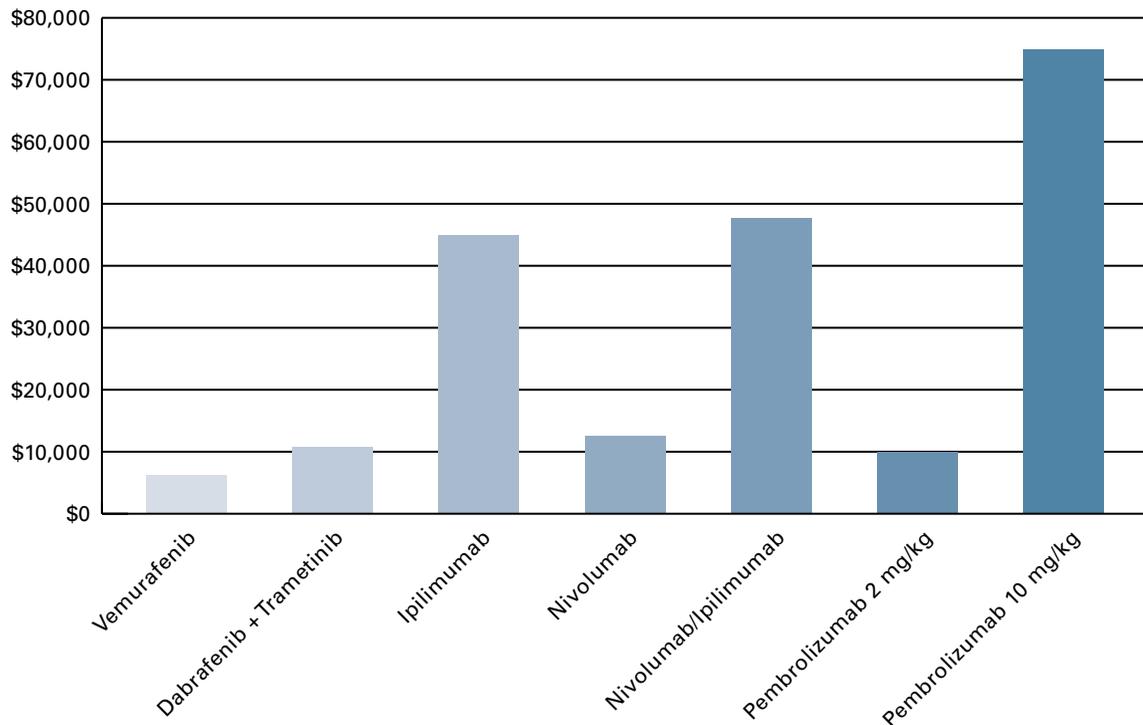
patient care. Current sequencing of these agents is based mostly on anecdotal evidence. A thorough evaluation of cost-effectiveness will require the gathering of data on acquisition cost, deciphering dosing strategies, estimating the cost of managing treatment-related AEs, and enumerating drug-related healthcare utilization values.

Cost of Medication Acquisition

Table 1^{17,27-32} and Figure 3^{17,27-32} identify all drugs approved by the FDA for use in the treatment of metastatic melanoma since 2011.^{17,27-32} Drugs labeled only for the management of symptoms or treatment-related AEs were not included. The cost of infused drugs indicated in Table 1 is based on the April 2015 Medicare Part B average sales price set by the CMS. These are calculated as described in a prior study.³³ The cost of oral drugs was collected using the method previously described by Peter Bach.³⁰ The monthly cost of the drugs is based on a 28-day month cycle; the dosing strategy is based on the dosing used in the associated clinical trial. We used a body weight of 82 kg based on mean US values and a body surface area of 1.86 m².³⁴

The calculations do not indicate the completion of a particular treatment course and do not include the cost of a diagnostic test, such as determining the presence of a genetic mutation, or administrative costs such as those related to treatment infusion. The calculations also do not take into account any portion of the drug that may be discarded if the vial is not completely used. The table shows that the monthly cost of treatment based only on acquisition costs was lowest for vemurafenib, and for all

■ **Figure 3.** Monthly Drug Costs Approved by the FDA Since 2011^{17,27-32}



other regimens approved in the past 4 years was \$10,000 per month or greater. Notably, ipilimumab costs \$45,000 per month.³¹ We recognize that providing drug costs on a monthly basis has its limitations. Notably, some regimens are given until progression of disease or unacceptable toxicity, while others, such as ipilimumab, are given for a predefined number of cycles. This difference has large implications in the overall cost of care.

Different Dosing Regimens and Impact on Cost

Clinical researchers often discuss the most appropriate dosing strategy for anticancer agents. These discussions usually involve a tradeoff between efficacy and toxicity, in an attempt to find the balancing point. Cost is rarely discussed, but as Dr. Leonard Saltz recently pointed out in his speech during the American Society of Clinical Oncology (ASCO) 2015 plenary session, cost should be considered.³⁵ Although pembrolizumab was initially recommended by the FDA at a 2-mg/kg dose every 3 weeks, there are ongoing studies using a 10-mg/kg dose every 2 weeks.^{28,36-38} A strategy that incorporated this dose would cost approximately \$75,000 per month.³²

Biomarkers and Their Impact on Cost-Effectiveness

There is currently an increasing focus on the development of biomarkers to select the patients most likely to benefit from particular therapies. This focus could not only help limit drug toxicity incurred by patients, but also improve a drug's cost-effectiveness. One of the best examples in metastatic melanoma of such a biomarker is the aforementioned BRAF mutation, which has not only spared some patients unnecessary toxicity, but also significantly reduced the expenditure on ineffective targeted agents. Optimism exists among the research community that PD-1 expression will yield a biomarker that will identify patients expected to benefit from immune-based therapy. This "personalized" strategy would decrease the costs for society as a whole.

Quality of Life

When evaluating the value of a specific therapy, it is important to evaluate not only cost and efficacy, but also quality of life (QOL). Because patients with advanced cancer often have a lower QOL than people without cancer, survival gains from a particular ther-

apy can be adjusted to account for QOL. This is often incorporated into an incremental cost-effectiveness ratio (ICER) in terms of quality-adjusted life years (QALYs). Furthermore, AEs related to the specific therapy can further decrease QOL and are often incorporated into the ICER. In assessing cost from the perspective of quality and duration of life, vemurafenib compared with dacarbazine costs \$353,993 per QALY gained. Meanwhile, the ICER for vemurafenib followed by ipilimumab, compared with vemurafenib alone, was \$158,139.³⁹ Both of these cost-effectiveness analyses produced ICERs that exceeded a commonly cited willingness-to-pay threshold of \$150,000/QALY.

Cost of Treatment-Related AEs

The cost of managing AEs related to therapy is an additional significant concern. A retrospective analysis of commercial and Medicare databases examined the incremental healthcare costs of specific AEs in 2621 patients with metastatic melanoma treated with paclitaxel, vemurafenib, ipilimumab, dacarbazine, temozolomide, high-dose interleukin 2, or interferon alfa. The 30-day incremental costs were \$9135 (95% CI, \$6404-\$12,392) for management of metabolic events, \$8450 (95% CI, \$6528-\$10,633) for hematologic/lymphatic events, \$6476 (95% CI, \$4667-\$8541) for cardiovascular events, \$6338 (95% CI, \$4740-\$8122) for gastrointestinal events, \$5903 (95% CI, \$3842-\$8313) for central nervous system/psychiatric events, and \$5078 (95% CI, \$3392-\$7012) for pain.⁴⁰

In a comparative assessment of the cost of AEs, a recent study examined data from a large claims database of 55 health plans to compare healthcare costs and AEs in patients with metastatic melanoma who initiated treatment with a targeted therapy (vemurafenib), immunotherapy (ipilimumab), or chemotherapy (dacarbazine, paclitaxel, or temozolomide) between July 2009 and September 2012. The study identified 541 eligible patients with 809 total treatment events. Temozolomide had the highest number of treatment-related AEs (291), followed by vemurafenib (143) and ipilimumab (147). Total mean (SD) all-cause costs (MACC) for vemurafenib were \$77,687 (\$60,329), similar to paclitaxel, a commonly prescribed generic chemotherapy agent. Ipilimumab had the highest total MACC at \$153,062 (\$134,048); dacarbazine at \$35,243 (\$33,641); temozolomide at \$42,870 (\$41,384); and paclitaxel at \$58,991 (\$81,306). However, vemurafenib, compared with all of the other study drugs, had significantly lower monthly costs for management of treatment-related AEs.⁴¹

The recently published data for combined nivolumab and ipilimumab therapy showed a significantly improved PFS among patients receiving the drug combination compared with either drug alone. However, 95% of patients had AEs of any grade, with 55% of these AEs being grade 3/4 in severity. The costs related to these AEs would be expected to be significant, especially those related to grade 3/4 AEs that required patient hospitalization. Anticipation and prevention of AEs related to targeted therapies and immunotherapies in metastatic melanoma may be an important factor in curbing the overall financial burden.¹⁷

Long-Term Costs of Treatment

To examine treatment patterns, MarketScan claims data was identified for adult patients with newly diagnosed stage III unresectable/stage IV melanoma who were treated with chemotherapy, biologics, or immunotherapy between April 1, 2011, and June 30, 2013. Of the 634 eligible patients, 34.4% were treated with ipilimumab, 20.2% with vemurafenib, 17.4% with temozolomide, and 36.3% with other therapies. The average length of time on therapy ranged from 150 days for vemurafenib to 53 days for ipilimumab. The bulk of the total healthcare expenditures was incurred during the first 6 months of treatment, with an average of \$24,844 PPPM. The costs after 12 months of treatment averaged \$13,288 PPPM. For patients treated with ipilimumab, total healthcare expenditures were greatest in the first 6 months of treatment (\$29,562 PPPM on average, n = 218), with an average of \$12,897 PPPM beyond 12 months (n = 101). For vemurafenib, on the other hand, costs were lower initially (\$20,823 PPPM on average for the first 6 months, n = 128), with higher average costs in months 13 through 18 (\$16,704 PPPM on average, n = 48).⁴²

Are Triple-Drug Combinations on the Horizon?

Given the unique mechanisms of action of the agents approved in the last 5 years, it is possible that combination therapy may become the new standard of care in the management of metastatic melanoma. The combination of nivolumab and ipilimumab has already demonstrated improved PFS compared with ipilimumab alone.¹⁷ Recent clinical trials have focused on triple-drug combinations and combination-dose therapies in sequence, including the combinations of nivolumab, ipilimumab, and sargramostim; dabrafenib and trametinib followed by nivolumab and ipilimumab; nivolumab with dabrafenib and/or trametinib; and MEDI4736, a programmed death-

ligand 1 inhibitor, in combination with vemurafenib and/or cobimetinib.⁴³ These combinations and sequences are likely to provide future challenges to payers.

Legislative and Political Issues

Guidelines developed for oncologists by the National Comprehensive Cancer Network (NCCN) and academic societies historically have not factored cost into their treatment recommendations. Since 2003, a series of legislative actions have impeded the ability of Medicare, the largest payer in the United States, to control costs. Medicare is no longer allowed to utilize its strategies of least-costly-alternative reimbursement or implement competitive bidding through third-party intermediaries, both programs that had demonstrated significant cost-savings. In oncology specifically, Medicare has been mandated to provide coverage for anticancer therapies as long as they have an appropriate FDA indication, thus preventing the agency from limiting utilization based on cost.²⁶ It should be noted that the FDA does not base indications or approvals on the need for or novelty of a drug, but rather on its safety and efficacy. As such, Medicare would be forced to pay for an expensive brand if prescribed, even if a cheaper and equivalent generic were available. Furthermore, being forced to carry a drug eliminates a payer's negotiating power of taking a drug off-formulary if reasonable prices cannot be negotiated. The disabling of Medicare's bargaining power for cancer drugs results not only in higher costs on the state and federal level, but also higher out-of-pocket payments for some patients.

DISCUSSION

The conundrum of optimizing treatment efficacy, safety, and adherence while balancing costs plays itself out across all indications, and in all aspects of health-care. In the United States, policy makers, clinicians, and researchers must consider the economic burden created by metastatic melanoma when considering new and emerging treatments.

Despite the issues surrounding initial drug acquisition cost, it is important to evaluate these agents as continually prescribed agents, as is done with other chronic diseases like type 2 diabetes or hypertension. Although the cost of new metastatic melanoma drugs is high, their price tag may turn out to be well justified based on their ability to produce significant improvements in tumor overall response rate, patient PFS, and patient OS, com-

pared with traditional systemic chemotherapies. As more treatments are developed, if they continue to provide even better long-term responses, these agents could be more cost-effective at an even higher acquisition cost. A more comprehensive understanding of costs, including administration costs, acquisition costs, and the cost of treatment-related AEs, long-term disease control, and administration strategies (ie, combination therapy, sequential therapy, treatment rechallenge), will enable payers to develop and utilize economic models that accurately characterize both the cost-effectiveness and the budget impact of metastatic melanoma management.

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