Commercial Plans Seek More Control over Oral Oncolytics

New Approaches in the Treatment of Melanoma: Better Therapeutics Based on the Biology of the Disease
Industry Thought Leaders

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ManagedCare Oncology recently sat down with Gavin P. Robertson, Ph.D., professor of pharmacology, pathology, dermatology and surgery at Penn State University, to gain his insights on the future of melanoma therapeutics that target multiple disease pathways.

Drug Therapy Reviews

Diagnosing, Staging and Treating Malignant Melanoma: Clinical Considerations for Managed Care Stakeholders
by Stuart M. Lichtman, M.D., FACP, attending physician, Memorial Sloan-Kettering Cancer Center; professor of medicine, Weill Cornell Medical College
When we consider the disease’s significant mortality, increasing incidence in young adults and potential for preventive measures at the plan level, melanoma should be among the top priorities for managed care stakeholders.

Improving Value

Commercial Plans Seek More Control over Oral Oncolytics
by Susan Weber, director of brand access analysis, Health Strategies Group
Increased utilization, costs, competition and payor confidence shift access strategies in this growing category.

Regulatory & Reimbursement

Malignant Melanoma: A Not-So-Sunny Story
Although melanoma accounts for only an estimated 5 percent of all skin cancers, it accounts for almost 9,000 of the nearly 12,000 skin cancer deaths each year.
The list of events that follows provides the dates and locations of upcoming meetings, workshops and conferences of interest to managed care oncology professionals.

January

February
14-16 American Society of Clinical Oncology 2013 Genitourinary Cancers Symposium Orlando, Fla.

March
6-8 Association of Community Cancer Centers 39th Annual National Meeting Washington, D.C.

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Today, just over 50 percent of health insurance members are subjected to a coinsurance for medical benefit injectable drugs, and that coinsurance averaged 26 percent this year. Since the average cost of a medical benefit drug claim is roughly $2,500, it can be said that half of members who have insurance will pay around $650 out of pocket per dose of chemotherapy, chemotherapy support, a biological response modifier or other drug that is provider administered under this benefit. We learned all too well during the election that the average 2011 household income is $50,501 (a 2.2 percent one-year decline and a 7.1 percent three-year decline for those of us who are counting). But we have talked about all this before. Since then, I did some snooping around to see what patients can do about this.

When I asked our colleagues about the solution for this financial burden to lower income patients, the most common answer was “How about one of those patient assistance programs (PAPs)?” Most of our readership will know the basics of such programs: If a patient qualifies financially, the product’s manufacturer provides drugs free of charge or covers the cost of member contribution. But many of us also know that physician practices are generally not fans of these PAPs. In fact, oncology practice office managers are remarkably outspoken as to their disappointment with many, but not all, PAPs. The reasons for this dissatisfaction are primarily that the programs largely differ from one another in what data are needed to qualify and that onerous amounts of time are spent to validate eligibility. According to industry experts, because of this, only about 5 to 10 percent of oncology drugs are provided under a PAP, while the statistics above suggest it could (should?) be much higher.

There is a terrific document published by the Association of Community Cancer Centers (ACCC) titled “2012 Patient Assistance and Reimbursement Guide.” This guide lists more than 150 drugs that have some kind of assistance program and outlines the types of help that are available, including benefit verification, drug company copay assistance, foundation assistance, oral prescription savings and/or free drug, and intravenous and injectable drug ongoing and/or replacement. So you can see. The process becomes even more complicated because five different types of assistance may be available. Each program happens to be truly different, of course; all have at least one form to complete, but many have three. All are available online, but many need to be printed and faxed. Income requirements to qualify are all over the board. Some are by family; many are by individual with a sliding scale for each additional family member. Oh, and they can differ by the state you happen to live in as well. Some programs even have different forms for different drugs! Template letters for providers to author and fax in are occasionally offered. Frankly, I was dizzy after perusing the individual program documents. Fortunately, the guide gives some structure to the process. See page S16 of the guide (www.accc-cancer.org/publications/pdf/PatientAssistanceReimbursement-Guide-2012.pdf).

I want to be clear that these programs are fantastic — manufacturers are giving help to those who need it. The problem lies in documenting who needs the help, and some programs make it much easier to determine this than others. As you know, we like to think about solutions to problems and not just problems. I know of at least one company that is developing a database for providers that will auto-populate all PAP eligibility information for patients, with the exception of income. This will dramatically reduce the time and effort to access these assistance programs and likely increase the number of patients who need assistance and actually receive it. I do urge you to review the ACCC guide. Thank goodness for these programs, for ACCC for describing how to get access in one document and for the forthcoming technology!

Looking forward to seeing you soon.

Kjel A. Johnson, Pharm.D.
Publisher
ManagedCare Oncology

References

In every issue, Facts & Figures provides snapshots of information key to managed care oncology professionals. This installment features data regarding malignant melanoma. We hope you find these facts and figures of value as you review your own health plan data.

Magellan Pharmacy Solutions analyzed paid medical claims for health plan members for calendar year 2011 with a malignant melanoma diagnosis (primary ICD-9 diagnosis code 172.0 through 172.9). The following table illustrates these claims across Medicare and commercial lines of business (LOBs), with an average of $2.5 million across both lines of business in allowed drug claims per 1 million member lives for those with a malignant melanoma diagnosis code. Although claims for other cancers tend to be more heavily weighted toward the Medicare LOB — consistent with the average age at the time of diagnosis — allowed dollars for malignant melanoma reflect an incidence of disease that is more uniform across pre- and post-retirement age groups.

**Medical Claims for Diagnosis Codes 172.0 through 172.9 per 1M Lives — Line of Business (LOB)**

<table>
<thead>
<tr>
<th>LOB Description</th>
<th>Average Allowed per 1M</th>
<th>Average Units per 1M</th>
<th>Average Claims per 1M</th>
<th>Average Members per 1M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>$2,543,895.72</td>
<td>92,792</td>
<td>6,381</td>
<td>1,170</td>
</tr>
<tr>
<td>Medicare</td>
<td>$2,498,509.25</td>
<td>82,084</td>
<td>5,440</td>
<td>890</td>
</tr>
<tr>
<td>Grand total</td>
<td>$5,042,404.97</td>
<td>174,876</td>
<td>11,821</td>
<td>2,060</td>
</tr>
</tbody>
</table>

Notes:
1. Population includes plans with commercial and Medicare members
2. Data calendar year 2011
3. Based on primary diagnosis of 172.0 through 172.9
4. Outliers excluded

Using the same data, Magellan Pharmacy Solutions analyzed these claims by site of service (SOS), revealing that drug administration services were received in the physician’s office in the vast majority of cases. This follows the fact that the physician’s office tends to be one of the more economical sites of service for drug administration. The SOS analysis confirms this assertion, with the hospital outpatient setting carrying a significantly higher average cost per claim than other settings.

**Medical Claims for Diagnosis Codes 172.0 through 172.9 per 1M Lives — Site of Service (SOS)**

<table>
<thead>
<tr>
<th>SOS</th>
<th>Average Members per 1M</th>
<th>Average Allowed per 1M</th>
<th>Average Units per 1M</th>
<th>Average Claims per 1M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital OP</td>
<td>224</td>
<td>$2,947,253.88</td>
<td>67,246</td>
<td>3,919</td>
</tr>
<tr>
<td>Other</td>
<td>1,104</td>
<td>$42,816.36</td>
<td>14,047</td>
<td>1,349</td>
</tr>
<tr>
<td>Physician</td>
<td>732</td>
<td>$2,052,334.73</td>
<td>93,584</td>
<td>6,553</td>
</tr>
<tr>
<td>Grand total</td>
<td>2,060</td>
<td>$5,042,404.97</td>
<td>174,877</td>
<td>11,821</td>
</tr>
</tbody>
</table>

**SOS**

<table>
<thead>
<tr>
<th>SOS</th>
<th>Average Members per 1M</th>
<th>Average Claims per 1M</th>
<th>Average Units Per Claim</th>
<th>Average $ Per Claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital OP</td>
<td>224</td>
<td>3,919</td>
<td>35</td>
<td>$3,799.92</td>
</tr>
<tr>
<td>Other</td>
<td>1,104</td>
<td>1,349</td>
<td>8</td>
<td>$37.61</td>
</tr>
<tr>
<td>Physician</td>
<td>732</td>
<td>6,553</td>
<td>15</td>
<td>$350.24</td>
</tr>
<tr>
<td>Grand total</td>
<td>2,060</td>
<td>11,821</td>
<td>58</td>
<td>$4,187.77</td>
</tr>
</tbody>
</table>

Notes:
1. Population includes plans with commercial and Medicare members
2. Data calendar year 2011
3. Based on primary diagnosis of 172.0 through 172.9
4. Outliers excluded
Of the top 10 drugs on these malignant melanoma claims, an interferon (Intron-A) featured the highest average allowed claims per 1 million lives, followed by Yervoy (indicated only for malignant melanoma) and Avastin (not indicated for malignant melanoma). Among traditional chemotherapeutics, Taxol was the leader for average allowed claims per 1 million lives. The supportive care agents Kytril (antiemetic), Zofran (antiemetic), Neupogen (colony-stimulating factor) and Zometa (bisphosphonate) rounded out the top 10 drugs in terms of spending for malignant melanoma.

Malignant Melanoma Drug Spend — Average Allowed Claims per 1M Lives for Diagnosis Codes 172.0 through 172.9

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average Allowed per 1M</th>
<th>Average Units per 1M</th>
<th>Average Claims per 1M</th>
<th>Average Members per 1M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intron-A</td>
<td>$3,264,104.11</td>
<td>125,168</td>
<td>4,417</td>
<td>171</td>
</tr>
<tr>
<td>Yervoy</td>
<td>$896,244.78</td>
<td>6,285</td>
<td>92</td>
<td>21</td>
</tr>
<tr>
<td>Avastin</td>
<td>$532,684.22</td>
<td>5,519</td>
<td>92</td>
<td>15</td>
</tr>
<tr>
<td>Taxol</td>
<td>$99,968.37</td>
<td>412</td>
<td>95</td>
<td>26</td>
</tr>
<tr>
<td>Zofran</td>
<td>$64,829.58</td>
<td>5,991</td>
<td>380</td>
<td>152</td>
</tr>
<tr>
<td>Kytril</td>
<td>$48,012.62</td>
<td>4,198</td>
<td>467</td>
<td>98</td>
</tr>
<tr>
<td>Neupogen</td>
<td>$37,213.75</td>
<td>87</td>
<td>95</td>
<td>21</td>
</tr>
<tr>
<td>Zometa</td>
<td>$36,315.30</td>
<td>162</td>
<td>525</td>
<td>40</td>
</tr>
<tr>
<td>Nonradioactive, noncontrast, visualization adjunct</td>
<td>$24,176.34</td>
<td>5,231</td>
<td>126</td>
<td>126</td>
</tr>
<tr>
<td>Saline solution</td>
<td>$11,237.61</td>
<td>2,068</td>
<td>1,848</td>
<td>281</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>$3,884.51</td>
<td>414</td>
<td>167</td>
<td>137</td>
</tr>
<tr>
<td>Benadryl</td>
<td>$3,622.46</td>
<td>1,474</td>
<td>2,144</td>
<td>153</td>
</tr>
<tr>
<td>Dexamethasone sodium phosphate</td>
<td>$2,866.98</td>
<td>3,300</td>
<td>232</td>
<td>75</td>
</tr>
<tr>
<td>Technetium TC-99M sulfur colloid, diagnostic, per study dose, up to 20 millicuries (code price is per one vial)</td>
<td>$2,315.43</td>
<td>19</td>
<td>48</td>
<td>19</td>
</tr>
<tr>
<td>Gadodiamine disodium</td>
<td>$2,112.84</td>
<td>75</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Sublimaze</td>
<td>$2,047.59</td>
<td>562</td>
<td>212</td>
<td>167</td>
</tr>
<tr>
<td>Midazolam</td>
<td>$2,015.88</td>
<td>502</td>
<td>212</td>
<td>167</td>
</tr>
<tr>
<td>Fluorodeoxyglucose F-18 FDG, diagnostic, per study dose, up to 45 millicuries [Pricing unavailable — suggest invoice pricing]</td>
<td>$1,811.98</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>$1,787.32</td>
<td>4,751</td>
<td>110</td>
<td>103</td>
</tr>
<tr>
<td>Lactated ringers</td>
<td>$1,631.45</td>
<td>107</td>
<td>84</td>
<td>76</td>
</tr>
<tr>
<td>Platinol</td>
<td>$831.44</td>
<td>121</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>$547.10</td>
<td>45</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Ketorolac tromethamine</td>
<td>$357.68</td>
<td>34</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Heparin</td>
<td>$301.41</td>
<td>6,024</td>
<td>153</td>
<td>12</td>
</tr>
<tr>
<td>Quelicin</td>
<td>$285.39</td>
<td>396</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>$272.25</td>
<td>460</td>
<td>46</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>$218.90</td>
<td>61</td>
<td>61</td>
<td>15</td>
</tr>
<tr>
<td>Cleocin</td>
<td>$154.01</td>
<td>19</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Adrenalin epinephrine inject</td>
<td>$107.29</td>
<td>1,131</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Dilaudid</td>
<td>$92.13</td>
<td>11</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Zantac</td>
<td>$90.81</td>
<td>67</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>Neo-synephrine</td>
<td>$81.45</td>
<td>73</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Prostigmin</td>
<td>$60.26</td>
<td>60</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>$53.70</td>
<td>11</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Kenalog</td>
<td>$40.95</td>
<td>23</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Reglan</td>
<td>$27.08</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td><strong>Grand total</strong></td>
<td><strong>$5,042,404.98</strong></td>
<td><strong>174,876</strong></td>
<td><strong>11,821</strong></td>
<td><strong>2,060</strong></td>
</tr>
</tbody>
</table>

Notes:
1. Population includes plans with commercial and Medicare members
2. Data calendar year 2011
3. Based on primary diagnosis of 172.0 through 172.9
4. Outliers excluded
In looking at claims by diagnosis code, Magellan Pharmacy Solutions found that malignant melanoma of the face carried the lowest average allowed claims per 1 million lives. Conversely, malignant melanoma of the lower limb and other unspecified sites carried the highest average allowed claims per 1 million lives. These various diagnosis codes also generally followed suit in terms of average units, claims and members per 1 million, with unspecified malignant melanoma of the face being less prevalent and malignant melanoma of the lower limb and other unspecified sites being the most commonly coded.

### Malignant Melanoma Diagnosis — Average Allowed Claims per 1M Lives for Diagnosis Codes 172.0 through 172.9

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnosis Code</th>
<th>Average Allowed per 1M</th>
<th>Average Units per 1M</th>
<th>Average Claims per 1M</th>
<th>Average Members per 1M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mal melanoma of other unspecified face</td>
<td>172.3</td>
<td>$4,579.40</td>
<td>524</td>
<td>204</td>
<td>121</td>
</tr>
<tr>
<td>Mal melanoma of scalp and neck</td>
<td>172.4</td>
<td>$101,029.61</td>
<td>8,144</td>
<td>740</td>
<td>177</td>
</tr>
<tr>
<td>Mal melanoma of trunk</td>
<td>172.5</td>
<td>$126,325.14</td>
<td>16,903</td>
<td>988</td>
<td>782</td>
</tr>
<tr>
<td>Mal melanoma of upper limb</td>
<td>172.6</td>
<td>$732,578.68</td>
<td>21,673</td>
<td>1,347</td>
<td>179</td>
</tr>
<tr>
<td>Mal melanoma of lower limb</td>
<td>172.7</td>
<td>$2,010,086.17</td>
<td>75,072</td>
<td>4,508</td>
<td>354</td>
</tr>
<tr>
<td>Mal melanoma of other unspecified</td>
<td>172.9</td>
<td>$2,067,805.98</td>
<td>52,560</td>
<td>4,034</td>
<td>447</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>$5,042,404.98</strong></td>
<td><strong>174,876</strong></td>
<td><strong>11,821</strong></td>
<td><strong>2,060</strong></td>
</tr>
</tbody>
</table>

**Notes:**
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4. Outliers excluded
New Approaches in the Treatment of Melanoma: BETTER THERAPEUTICS BASED ON THE BIOLOGY OF THE DISEASE

A Discussion with Gavin P. Robertson, Ph.D.

Director of Penn State Melanoma Center and Foreman Foundation Melanoma Research Laboratory in the Department of Pharmacology and Penn State Cancer Institute

ManagedCare Oncology recently sat down with Gavin P. Robertson, Ph.D., professor of pharmacology, pathology, dermatology and surgery at Penn State University, to gain his insights on the future of melanoma therapeutics that target multiple disease pathways. Dr. Robertson is also the director of the Penn State Melanoma Center and director of the Foreman Foundation Melanoma Research Laboratory in the Department of Pharmacology and Penn State Cancer Institute. Beyond his role in academia, Dr. Robertson serves as chief scientific officer for Melanovus Oncology, a late preclinical stage oncology company focused on developing new approaches to treating melanoma and other skin cancers. Among his research interests and achievements are the targeting of AKT3 signaling in melanoma and the direct delivery of therapeutics into melanoma cells through nanoliposomas and ultrasound.

MCO: Can you give us a little background on melanoma and where there are unmet needs in the therapeutic armamentarium?

Dr. Robertson: Skin cancers are the most diagnosed kind of cancer in the U.S., and melanoma is the deadliest form of skin cancer, accounting for less than 5 percent of all skin cancer cases but 75 percent of skin cancer deaths. The incidence of melanoma has risen dramatically in recent years among young adults, and one person dies of the disease every hour. While the five-year relative survival rate of
early detected melanoma is around 98 percent, it drops to 15 percent when the disease has spread to distant organs. So people are dying from the disease because you have these cancers developing in your skin, and what makes melanoma different, is that the melanoma cells disseminate through the blood or lymphatic system and end up in distant organs. These secondary tumors can grow to be large and eventually disrupt organ function.

For about 30 years, there hadn’t really been a lot of progress in the treatment of melanoma. Most of the agents looked to poison the cancer cells before the disease affected normal cells, and most of them had been relatively ineffective. Clinicians tried quite a number of agents for the treatment of melanoma, but nothing was ever truly effective. Dacarbazine, for example, is one of the original agents that is still approved by the U.S. Food and Drug Administration (FDA) for melanoma, but it is generally ineffective. In fact, most oncologists today won’t even administer it; for some time, clinicians have tried these agents and offered radiation, which is still used for brain metastases.

Following these early chemotherapeutic treatments, immune therapy came into use. Presently, that’s part of the problem: A huge amount of the resources being used to develop melanoma therapies have been devoted to the immune modulators or immune system regulators or vaccines; however, none of them has really ever panned out to be successful. Then, five years ago, a gene was identified and found to be the most mutated gene in melanoma: the BRAF mutation. This discovery turned out to be very significant, as 50 percent of people with sporadic melanoma had the BRAF mutation. In other words, if two patients came into the clinic with melanoma, it was likely that one of them would have the mutation. This finding led to research focused on finding drugs that would bind to this mutant protein and shut it down. The first-step drug, vemurafenib (Zelboraf), binds to the site of the mutation and inhibits it. In a phase 1 clinical trial, vemurafenib demonstrated efficacy in 80 to 90 percent of patients. Subsequent phase 2 and 3 trials showed about 50 percent of patients had a sustained response to the drug. This is due to the fact that vemurafenib targets only a single protein and the cancer finds a way around it. As cancer cells develop resistance to the drug, they reactivate proteins downstream of the protein encoded by the mutant gene, and the disease recurs. It’s analogous to using an alternative route on a smaller side street to bypass a traffic jam on a main road. Although you’ve blocked the BRAF pathway, the cancer eventually finds a way around this original route. This persistence of the disease has led to confusion among the oncology community as to how to effectively treat melanoma. What most of the industry and clinicians are doing now is combining vemurafenib with other agents that they think will target other major pathways in melanoma. The idea is that we will be able to reduce disease resistance and prolong the therapeutic effect of treatment through various combinations of agents.

MCO: What is Melanovus Oncology’s approach to the treatment of melanoma? How does this approach differ from current treatments?
**Dr. Robertson:** Melanovus Oncology’s philosophy is that the current single-target drugs aren’t working because the disease will likely develop resistance. Furthermore, if you combine drugs, you’re going to have problems because each drug has its own toxicity profile. Sometimes drugs will cancel out one another’s effects, and sometimes they can lead to a whole series of adverse events that you don’t want. As an alternative approach, Melanovus is investigating a first-in-class single agent that targets multiple key disease pathways in melanoma. Since it’s a single agent, the severe toxicity and drug interaction issues associated with multidrug regimens can conceivably be avoided.

Building upon that principle, the company has licensed a patent portfolio from the Penn State Research Foundation and is developing a number of these first-in-class multitarget inhibitor-type drugs. Melanovus has a number of agents like this, but the lead compound is a nanodrug that serves as a base platform to which components targeting different pathways can be added. We believe this is where the field of melanoma treatment is going. A patient comes into the clinic and a blood sample is taken. In that blood sample, there are some of these circulating melanoma cells from the tumors in the patient. The melanoma cells are then profiled. The resulting profile reveals which of the various genes are aberrant in the patient’s disease. What the company is betting on is that we’ll be able to load drugs into the nanoparticle that are essentially able to shut down those particular pathways.

**MCO:** Can you talk a little more about the lead compound in the company’s R&D pipeline and describe how it works?

**Dr. Robertson:** The lead compound in development is Nanolipolee-007. The active ingredient in this nanoparticle — leelamine — is an agent isolated from the bark of pine trees. What’s unique about this agent is that it simultaneously targets the BRAF pathway, the AKT3 pathway, which is active in about 70 percent of melanomas, and the STAT3 pathway, which is equally important in melanoma. So far, it seems to be quite effective, even in cancer cells with the BRAF mutation that are resistant to an agent like vemurafenib. It also appears to be effective in cancer cells with wild-type BRAF; an aggressive form of metastatic melanoma that has fewer treatment options. This is in stark contrast to vemurafenib, which is effective in only half of melanoma patients: those who have the BRAF mutation. In patients with wild-type BRAF, vemurafenib actually promotes disease progression. For this reason, patients with wild-type BRAF typically receive treatment with ipilimumab or interleukin-2, but treatment resistance is developing with these agents as well. Those patients with wild-type BRAF who are resistant to ipilimumab don’t really have another viable treatment option. However, Nanolipolee-007 may elicit a response in these patients because leelamine also targets AKT3 and STAT3 in addition to BRAF. Using the traffic jam analogy I mentioned earlier, in addition to blocking the main road, the agent also eliminates the side streets as alternative routes, thereby reducing the cancer’s ability to bypass and resist treatment. The company has also identified a number of other agents that synergize with leelamine, so in the future, there may be potential to provide complete tumor shutdown if resistance to the base formulation of Nanolipolee-007 develops.

**MCO:** Can you provide us with further detail on the nanoformulation and how this technology facilitates drug delivery?

**Dr. Robertson:** Because of what the company wants to do — that is, have a
platform that you can add components to — you need to have a base that has hydrophobic and hydrophilic domains to adapt to different agents. In other words, agents that can dissolve in water and agents that can dissolve in fat can both be loaded into the nanoparticle. The nanoliposomal membrane that has been developed has a lipid membrane and an aqueous core, so it accommodates both types of agents and is customizable for the delivery of different agents with different chemical characteristics (Figure 1).

What nano means essentially is that it’s less than 100 nanometers in size. In addition, the outside surface of the nanoparticle can be pegylated, preventing it from being recognized by the liver or removed by the immune system and thus increasing circulation time and the chances that it will be taken up by the cancer cells. Furthermore, the nanoparticles allow for increased uptake into tumor cells because of an enhanced permeability and retention effect. What this means is that in tumor tissue you have vessels, but the vessels are very poorly formed. These poorly formed vessels tend to be very porous, so the nanoparticles tend to leak out of the vessels — due to their small size — and preferentially accumulate in the tumor tissue. Cumulatively, these characteristics of the nanoliposomal formulation allow for increased bioavailability, thereby maximizing the therapeutic effect of the drugs delivered.

**MCO:** Where is this product in terms of development and what are the next steps and timing?

**Dr. Robertson:** Investigational new drug (IND) enabling studies will be conducted to establish a method for measuring levels of leelamine contained in Nanolipolee-007 in the serum or tissues of animals over time, following intravenous administration. This will form the basis for dosing in terms of therapeutic efficacy, toxicokinetics and pharmacokinetics. Escalating dose and 10-day repeated intravenous dosing studies in animals will also be conducted, followed by measurement of leelamine levels present in the serum and tissues. Results from these studies will form the basis for IND status for systemic Nanolipolee-007 treatment from the FDA and enable evaluation of the agent in a phase 1 clinical trial. This will be a multicenter trial, with the Melanoma Center at Penn State likely serving as the coordinating site. We anticipate the trial to begin in the second half of 2013.

**MCO:** What do advances in the field of multitarget inhibitors mean for the future of melanoma treatment?

**Dr. Robertson:** For many decades, stage III or IV melanoma meant the patient had six to nine months to live. Now, for the first time in this field, we are seeing some light at the end of the tunnel. Targeted inhibitors hitting single pathways were the first step. And now, similar to the strides made with the introduction of biologic therapy, these developmental compounds represent the next step. So in the future, the treatment of melanoma will likely be centered on combination therapy or multitarget inhibitors such as those being developed by Melanovus. It may turn out that a researcher will stumble across a combination of agents that achieves a persistent treatment response, but I think these first-in-class multitarget inhibitors may be the way that we not just incrementally move the therapeutic field forward but make a giant progressive leap. Agents of this type don’t currently exist for melanoma, meaning we have the potential here to satisfy a real clinical need. It’s exciting stuff.

Figure 1. Leelamine and the Nanoliposomal Formulation Employed by Nanolipolee-007
In fact, there are more new cases of skin cancer each year than cases of breast, prostate, lung and colon cancer combined.¹ This widespread prevalence of skin cancer in the U.S. is not a recent development: Over the past three decades, more Americans have been diagnosed with skin cancer than all other cancers combined.² Leading in incidences are basal cell carcinoma (BCC), with an estimated 2.8 million cases diagnosed annually, and squamous cell carcinoma (SCC), with an estimated 700,000 cases diagnosed each year in the U.S.³,⁴ As many as half of all Americans who live to age 65 will be diagnosed with BCC or SCC at least once.⁵

Although far less prevalent than BCC or SCC, malignant melanoma is the most serious form of skin cancer. Accounting for the preponderance of skin cancer mortality, an estimated 76,250 new cases of invasive melanoma will be diagnosed in the U.S. in 2012, with an estimated 9,180 resulting in death.¹ This is in comparison with an estimated 3,010 deaths from nonmelanoma skin cancers.¹ In addition to the disease’s high mortality rate, melanoma is the only one of the seven most common cancers in the U.S. whose incidence is increasing.⁶ Between 2000 and 2009, the incidence of melanoma has climbed 1.9 percent annually in the general population, with even more alarming trends among younger demographics often not considered to be at high risk for other cancers.⁶ From 1970 to 2009, the incidence of melanoma has increased by 800 percent among young women and 400 percent among young men.⁷ This increasing incidence has culminated in melanoma being the most common form of cancer for young adults ages 25 to 29 and the second most common form of cancer for ages 15 to 29.⁸

While the incidence of melanoma is increasing dramatically in younger demographics, advanced age remains a key risk factor for the disease. The other factors predisposing to melanoma are the presence of many dysplastic nevi (congenital growth marks) on the skin; fair skin, freckling and/or light hair; family or personal history of melanoma; and gender, which varies according to age. Before age 40, females are at an increased risk; after age 40, males are at an increased risk. Above all these, exposure to ultraviolet (UV) light remains the single-most important risk factor for the disease, with approximately 86 percent of melanomas being attributed to UV radiation.⁹ For this reason, melanoma is most often diagnosed on sun-exposed areas of the skin but is not exclusive to these areas or even exclusive to the skin. Although melanoma can also arise at other sites — such as ocular and vulvar melanomas — these noncutaneous forms of the disease are less common and beyond the scope of this review.

When we consider the disease’s significant mortality, increasing...
incidence in young adults and potential for preventive measures at the plan level, melanoma should be among the top priorities in oncology for managed care stakeholders. Immunotherapies approved in recent years demonstrate promise in the treatment of the disease, but screening and early detection lay the foundation for effective therapeutic intervention.

SCREENING, DIAGNOSIS AND STAGING

Melanoma is most often diagnosed when a clinician sees a suspiciously pigmented area (i.e., a dysplastic nevus) on the skin and takes a biopsy of the nevus. Different methods may be used to take the biopsy, depending on the size, location and other physical characteristics of the nevus. Shave, punch, excisional and incisional biopsies are all relatively common. Often if patients have one dysplastic nevus, they also have others, so a number of areas may be biopsied during the same visit. Individuals who have high numbers of benign moles and dysplastic nevi may have an autosomal dominant hereditary condition known as inherited or familial dysplastic nevus syndrome (DNS), predisposing them to melanoma. Dysplastic nevi are more likely to undergo malignant transformation when they occur among members of melanoma families, accounting for roughly half of melanomas.10 The other half arise de novo on clear skin.10 Although the U.S. Preventive Services Task Force has concluded that there is insufficient evidence to recommend for or against skin cancer screening for all patients by primary care clinicians, patients with DNS and/or any number of the aforementioned risk factors for melanoma may benefit from regular screenings.11

Any biopsies taken by the physician are sent to the laboratory for examination by a trained pathologist. The pathologist makes a definitive diagnosis of melanoma based on the appearance of the cells in the biopsy sample or with more complicated analyses — such as immunohistochemistry, fluorescence in situ hybridization or comparative genomic hybridization — if visual cues are too difficult to discern via microscopy. If melanoma is identified, characteristics such as tumor thickness and mitotic rate are considered for staging purposes. In cases where the melanoma is suspected to have spread beyond the skin based on the characteristics of the tumor cells, additional biopsies may be taken of appropriate lymph nodes (e.g., fine needle aspiration, excisional or sentinel lymph node biopsies) to assess the extent of cancer metastasis. In the event of melanoma confirmed to have spread to the lymph nodes and beyond via these biopsies, imaging studies may be employed to assess the potential spread of melanoma to distant organs. Chest X-ray, computed tomography, magnetic resonance imaging and positron emission tomography provide imaging options for clinicians seeking to investigate the spread of cancer to different tissues or organ systems. Cumulatively, the results of these aforementioned biopsies and imaging studies are used to stage a patient’s melanoma. Similar to other solid tumor cancers, melanoma is staged according to the American Joint Committee on Cancer (AJCC) TMN system. In this system, cancers are assigned values based on tumor characteristics, metastatic extent and node involvement (hence TMN). Tumors are primarily graded on thickness, mitotic rate and ulceration. Thinner tumors (< 1 mm) according to the Breslow measurement have a better prognosis and are less likely to spread, while thicker tumors are more likely to metastasize and have a poorer prognosis.12 Mitotic rate essentially assesses how many melanoma cells are dividing at a given point in time and hence is a fairly accurate measure of how quickly the tumor is growing. A lower mitotic rate is indicative of a better prognosis, while a higher mitotic rate indicates a poorer prognosis and an increased likelihood of spreading.12 The final characteristic by which tumors are assessed is ulceration, a visible breakdown of the skin over the melanoma, tending to indicate a poorer prognosis.12 Lymph node involvement is graded according to how many lymph nodes the melanoma has spread to, with a higher number of lymph nodes indicating a poorer prognosis. Similarly, metastasis is graded by how far the melanoma has
spread, with no metastases indicating a better prognosis and metastases in distant organs indicating a poorer prognosis. These TMN characteristics are grouped to assign a stage of 0 through IV for a patient’s melanoma. Prognosis and overall survival generally decline as the stage advances, with stage 0 having the best prognosis and stage IV having the poorest prognosis. These stages and descriptions can be found in Table 1, along with observed five- and 10-year survival rates from the 2008 AJCC Melanoma Staging Database.

In addition to biopsy and subsequent pathology analyses and imaging studies, some laboratory tests may be employed prior to initiating treatment. These tests are not used for the purpose of diagnosis, but rather to assess disease severity and design an individualized therapeutic approach. In patients with disseminated melanoma that has spread to distant organs, high lactate dehydrogenase levels are indicative of treatment-resistant disease. Likewise, in patients with advanced disease, the melanoma cells may be assayed for a mutation in the BRAF gene. Approximately half of metastatic melanomas have the BRAF mutation, and one recently approved biologic therapy — vemurafenib — targets this pathway as a means of initiating programmed cell death in melanoma cell lines. As such, patients whose disease features wild-type BRAF are unlikely to respond to treatment with a B-Raf kinase inhibitor, making this assay a critical step in determining viable treatment options in melanoma.

### TREATMENT CONSIDERATIONS

Appropriate treatment for malignant melanoma varies based on the pathologic stage, location and genetic profile of the disease. Surgical excision is the primary mode of treatment and is often curative in stage 0 or IA disease if the lesion is superficial and has adequate margins. In addition to constituting initial treatment, surgery also serves the purpose of further characterizing the disease, with information gathered during surgery driving the course of future treatment. In fact, the clinical/surgical margins discussed in the National Comprehensive Cancer Network’s (NCCN) clinical guidelines refer to those taken at the time of surgery and do not necessarily correlate with gross pathological/histological margins taken by pathologists. Furthermore, due to the highly unpredictable nature of the disease, it is often unknown exactly what level of therapeutic intervention is warranted until after initial surgery. In what appears to be stage I disease, extensive depth of invasion revealed upon surgery or a positive sentinel node biopsy may uncover melanoma that is actually in stage III. Beyond the resection of primary lesions, surgery also plays a significant role in the treatment of patients presenting with clinically positive nodes. These patients should undergo complete lymph node dissection of the involved nodal basin in addition to excision of the primary site if present. However, even after a seemingly curative resection, it is important for clinicians to remain vigilant. Melanoma’s propensity for recurrence has led the

### Table 1. Melanoma Staging and Accompanying Observed Five- and 10-Year Survival Rates

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Survival 5-Year</th>
<th>Survival 10-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>In situ: in the epidermis but has not spread to the dermis</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>IA</td>
<td>&lt; 1.0 mm in thickness, not ulcerated and has a mitotic rate of less than 1/mm²; not found in lymph nodes or distant organs</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>IB</td>
<td>&lt; 1.0 mm in thickness, ulcerated or has a mitotic rate ≥ 1/mm²; or between 1.01 mm and 2.0 mm and is not ulcerated; not found in lymph nodes or distant organs</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>IIA</td>
<td>Between 1.01 mm and 2.0 mm in thickness and is ulcerated, or between 2.01 mm and 4.0 mm and is not ulcerated; not found in lymph nodes or distant organs</td>
<td>81%</td>
<td>67%</td>
</tr>
<tr>
<td>IIB</td>
<td>Between 2.01 mm and 4.0 mm in thickness and is ulcerated, or &gt; 4.0 mm and is not ulcerated; not found in lymph nodes or distant organs</td>
<td>70%</td>
<td>57%</td>
</tr>
<tr>
<td>IIC</td>
<td>&gt; 4.0 mm and ulcerated; not found in lymph nodes or distant organs</td>
<td>53%</td>
<td>40%</td>
</tr>
<tr>
<td>IIIA</td>
<td>Any thickness, not ulcerated; spread to one to three lymph nodes near affected skin area, but nodes not enlarged and only visible via microscopy; no distant spread</td>
<td>78%</td>
<td>68%</td>
</tr>
<tr>
<td>IIIB</td>
<td>Any thickness, may or may not be ulcerated; spread to one to three lymph nodes, nodes may or may not be enlarged, or spread to small areas of nearby skin or lymphatic channels around the original tumor, but the nodes do not contain melanoma; no distant spread</td>
<td>59%</td>
<td>43%</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any thickness, may or may not be ulcerated; spread to one to four or more lymph nodes, or nearby cluster of lymph nodes, nodes enlarged when involved; or spread to small areas of nearby skin or lymphatic channels around the original tumor, but the nodes do not contain melanoma; no distant spread</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td>IV</td>
<td>The melanoma has spread beyond the original area of skin and nearby lymph nodes to other organs, such as the lung, liver or brain, or to distant areas of the skin, subcutaneous tissue or distant lymph nodes</td>
<td>15%-20%</td>
<td>10%-15%</td>
</tr>
</tbody>
</table>
NCCN to recommend that clinicians consider monitoring even patients with stage IIB on a regular basis via radiologic imaging up to five years after surgical resection.\textsuperscript{14}

While surgical excision remains the standard of care for in situ disease, it may not be indicated in some cases due to comorbidity or a cosmetically sensitive tumor location.\textsuperscript{14} In these cases, topical imiquimod (Aldara) has emerged as a treatment option, particularly for lentigo maligna, an in situ melanoma that does not show invasive growth.\textsuperscript{14} Imiquimod may also be prescribed for patients at risk for local recurrence, such as those with positive margins remaining after surgery or with superficial dermal lesions that are not amenable to complete surgical resection.\textsuperscript{14} Also, in the adjuvant setting, interferon and radiation may be employed for patients with stage IB to III melanoma who are at high risk for local or nodal recurrence, although radiation is rarely necessary for excised local disease; the exception is desmoplastic nevotrophic melanoma (a rare variant of a spindle cell melanoma), which tends to be locally aggressive.\textsuperscript{14} Low-dose interferon is most commonly employed in the adjuvant setting for stage IB and II patients, but pegylated interferon and high-dose interferon are options for patients with completely resected stage III melanoma with either positive sentinel nodes or clinically positive nodes, but not for in-transit disease. It should be noted, however, that these forms of aggressive interferon therapy have a low benefit-to-risk ratio.\textsuperscript{14} Adjuvant radiation therapy to the nodal bed should be considered for patients with stage III high-risk nodal disease, according to the NCCN guidelines.\textsuperscript{14} In patients with stage IV melanoma, radiation therapy takes on a palliative role in the treatment of patients with brain metastases.\textsuperscript{14}

Effective therapies for the treatment of stage IV metastatic disease are limited primarily to the newer biologic therapies vemurafenib (Zelboraf) and ipilimumab (Yervoy). Traditional agents such as dacarbazine (DTIC-Dome) (the only chemotherapy for metastatic melanoma approved by the U.S. Food and Drug Administration [FDA]), temozolomide (Temodar), high-dose interleukin-2 (IL-2) and paclitaxel (Taxol) with or without cisplatin (Platinol) or carboplatin (Paraplatin) have demonstrated modest response rates, around 20 percent in first- and second-line settings.\textsuperscript{14} As such, there have been no noteworthy developments in the treatment of metastatic melanoma until the past two years, when ipilimumab and vemurafenib were approved. Ipilimumab is a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), approved in March 2011. Approval was based on a clinical trial showing a median survival of 10 months in advanced melanoma patients treated with ipilimumab compared with six months for those treated with an experimental vaccine (n = 676).\textsuperscript{14} One-year survival was 46 percent in those treated with ipilimumab compared with 25 percent in those treated with the vaccine, a significant improvement.\textsuperscript{15} Vemurafenib received FDA approval in August 2011 based on the results of a clinical trial in which 675 people with previously untreated metastatic melanoma with the BRAF mutation were randomized to vemurafenib or dacarbazine. At six months, overall survival was 84 percent (95 percent confidence interval [CI], 78 to 89) in the vemurafenib group and 64 percent (95 percent CI, 56 to 73) in the dacarbazine group.\textsuperscript{16} In the interim analysis for overall survival and final analysis for progression-free survival, vemurafenib was associated with a relative reduction of 63 percent in the risk of death and 74 percent in the risk of either death or disease progression, as compared with dacarbazine (p < 0.001 for both comparisons).\textsuperscript{16}

Due to the BRAF mutation-dependent activity of vemurafenib, this targeted biologic should only be used in patients with metastatic melanoma with the BRAF mutation as determined by the cobas® 4800 BRAF V600 assay. This genetic element, present in approximately half of patients with metastatic melanoma, in addition to the aggressiveness of the disease and the presence or absence of cancer-related symptoms, drives treatment selection in stage IV disease.\textsuperscript{14} Patients with low-volume, asymptom-
omic metastatic melanoma may be good candidates for immunotherapy with ipilimumab or IL-2, and in those patients without the mutation, vemurafenib therapy is excluded from the menu of options. In stage IV patients with the mutation whose disease is symptomatic or has progressed despite immunotherapy with ipilimumab or IL-2, vemurafenib is indicated. Ipilimumab may be considered as second-line therapy in patients whose disease has progressed after vemurafenib treatment.

Despite offering significant promise in the treatment of metastatic melanoma, ipilimumab and vemurafenib are not without their own unique limitations. As is the case with most biologic response modifiers, both agents carry a high price tag: A single course of ipilimumab (i.e., four infusions) costs approximately $120,000, and vemurafenib costs nearly $10,000 per month and a total of $56,000 for an estimated six months of treatment. In terms of clinical characteristics, ipilimumab therapy has the potential to cause serious autoimmune toxicity similar to other immunomodulators. And while the agent demonstrates a durable response, the overall response rate is approximately 20 percent and may take months before becoming apparent. Conversely, vemurafenib is associated with a 40 to 50 percent response rate that may be seen in weeks or even days after initiating therapy, but the median duration is only five to six months. Careful management of the agent is also crucial considering vemurafenib’s exclusive activity in patients with BRAF-mutant melanoma, requiring attention on the part of managed care stakeholders.

THE FUTURE OF MELANOMA IN MANAGED CARE

Once disadvantaged and relatively overlooked with a paucity of treatment options, melanoma is now coming under increased scrutiny with the advent of costly biologic response modifiers. In a single year, two new specialty therapies — along with one accompanying genetic test — received FDA approval and changed the face of melanoma management. In fact, a third of the cancer therapeutics approved in 2011 were designated for melanoma, indicating that this is an area of significant unmet need and clinical interest. These developments could not have come at a more opportune time, as the disease’s incidence has been growing steadily in young adults over the past decade. Fortunately, managed care stakeholders have thus far been liberal in their coverage of ipilimumab and vemurafenib, and thus clinicians should use these agents judiciously.

And while the BRAF assay associated with vemurafenib represents an additional cost in the short term, health plan leadership has wisely recognized that it represents an opportunity for potential savings in the future as it drives appropriate use of a costly treatment. The latest trend toward the development and approval of agents for melanoma appear to be a sign of things to come, as researchers seek to overcome the issues associated with treatment resistance and duration of response. Recent estimates cite 108 drugs in the melanoma pipeline, with 7 percent in phase 3 and 49 percent in phase 2 trials. Drug developers are investigating new therapeutic targets entrenched in the biology of the disease, such as the mitogen-activated protein kinase pathway and immunomodulator targets such as the programmed death-1 receptor. As these agents are eventually approved, clinicians and plan stakeholders alike should familiarize themselves with the various mechanisms of action to determine their place in treatment algorithms. Coupled with interventions to facilitate and promote appropriate skin cancer screening in high-risk groups, a focus on development in the pipeline for melanoma indicates that the future is certainly bright in the treatment of this deadly and increasingly prevalent disease.

References
Commercial Plans Seek More Control over Oral Oncolytics

Increased utilization, costs, competition and payor confidence shift access strategies in this growing category.

by Susan Weber, director of brand access analysis, Health Strategies Group

Although these agents escaped payors’ focus in the past, more plans fear the combined pressures of increasing utilization and high drug costs. But it’s not all bad news for payors. Many new brands are likely to enter the market in the next few years, offering new options to treat previously unmanageable cancers. In addition to filling unmet clinical needs, these new treatments provide more competition among drugs — and more opportunities for payors to ride out the storm.

COMMERCIAL PLANS: AT THE READY

Over the past 10 years, the U.S. Food and Drug Administration (FDA) has approved more than 15 oral oncology agents treating a wide range of cancers. The pipeline for oral oncolytics is also bursting, accounting for more than half of the 300 oncology drugs currently in phase 2 or 3 clinical trials (Figure 1). As a result, health plans have more options for convenient, cost-effective administration — as well as greater opportunities to influence treatment selections for specific cancer indications.

We have identified several trends in this increasingly important category, based on surveys and interviews with 52 pharmacy executives and medical directors representing 38 health plans and 153.8 million lives, as well as

Figure 1. FDA Approval Dates for Oncology Indications*

*Timeline represents a subset of oral oncalytics on the market.
five executives from pharmacy benefit managers (PBMs) representing 63.5 million lives. While PBMs and specialty pharmacy managers (SPMs) are influencers, it is the commercial plans that are driving this market. This is particularly true for new agents.

While tenured drugs, such as Xeloda and Temodar, face fewer access barriers at commercial plans, it’s a different story for agents that have won approval in the past five years. Most plans are implementing access barriers for late-to-market agents not demonstrating significant improvements in survival. Specifically, these plans are increasing cost-sharing burdens and use of restrictions — typically prior authorizations (PAs) — for these oral oncolytics (Figure 2).

Simply put, the days of low member cost-sharing are over. Cost-sharing is rising in the oral oncolytics category, as it is in other categories. Newer oral oncolytics, in particular, face high cost-sharing requirements at commercial plans. Most commercial plans reimburse the four newest oral oncolytics on the highest tier. One of these drugs is Xalkori (Figure 3). Beyond price, lack of comparative efficacy data and lack of post-launch marketing experience offer plans two rationales for limiting access to Xalkori and other recently approved drugs. Wary of safety issues that go unnoticed during accelerated FDA approval processes, payors may wait years to get the significant evidence of benefit they feel is necessary to make changes.

However, cost-sharing is just a piece of the access puzzle, particularly for commercial members. Typically, these patients aren’t sensitive to copays, due to their strong desire for treatment and the fact that many patient assistance programs eliminate copay differentials for commercial members. As a result, plans primarily rely on restrictions like PAs to influence use. For example, recently approved agents such as Zelboraf, Zytiga, Xalkori and Caprelsa are facing more PA requirements as plans complete formal product reviews. We expect the use of such restrictions to grow in the coming years.

While PAs remain plans’ most effective tool to reduce inappropriate use, payors realize that their current utilization management efforts aren’t cutting it. As one executive at a regional independent pharmacy admitted, “We use PAs to limit use to the indication, study or compendia listing. That’s about it.”

One example of how plans are using cost-sharing, restrictions and other strategies to control access is Gleevec. Most plans place Gleevec on the second tier due to its strong efficacy, tenure and market share. Fifteen percent of plans use copay differentials to advantage Gleevec over two competitive agents, Sprycel and Tasigna. Another 14 percent use copay differentials to advantage Gleevec and Sprycel over Tasigna. In addition,
some plans encourage Gleevec use by limiting restrictions on it while requiring PAs for Sprycel and Tasigna. While plans have typically shielded away from system-based step edits because they lack the clear, defensible evidence they need to limit access to these oral oncology drugs, some have implemented step edits to further increase Gleevec use. As commercial plans step up their management efforts, however, they continue to lack tactics that effectively balance cost management and clinical imperatives. And that’s what worries them. As one plan executive said, initiatives such as “cost-sharing, specialty pharmacy, pathways and medical necessity are all high on payor lists, but there’s no credible solution that will limit the long-term cost impact of the extraordinary oral oncolytic pipeline.”

GOVERNMENT PAYORS TEST THE WATERS
While commercial plans drive access decisions for oral oncology drugs, Part D plans are also employing management tactics. Most require higher member cost-sharing for oral oncology drugs. Part D plans consider drugs that cost more than $600 to be “specialty” drugs, allowing them to reimburse these agents on the coinsurance tier. This may be the fourth or fifth tier, depending on the plan’s benefit design.

Cost-sharing tactics have a greater impact in this market because the Centers for Medicare & Medicaid Services (CMS) does not allow pharmaceutical and biotech companies to provide patient assistance to Medicare Part D beneficiaries. To help pay for their medication, Medicare patients must secure assistance from nonprofit agencies, which is a more cumbersome process. As a result, Medicare members must pay more until they reach their out-of-pocket maximums. In addition, CMS’s designation of oncology agents as a protected drug class discourages Part D plans from aggressively using step edits and PAs to restrict use.

In contrast to Part D plans, managed Medicaid plans do not prioritize management of oral oncology drugs, largely because state coverage mandates limit their ability to manage this category. With patient access a priority, one-half of Medicaid plans cover all 18 oral oncology drugs studied in Health Strategies Group’s 2012 research. Those that cover all oral oncology drugs due to state coverage mandates often rely on PAs to confirm appropriate use, including dosing. As one executive in a Medicaid-only pharmacy said, “We put a PA on every new oral oncology drug. We go beyond the labeled indication and into the literature to see if there is efficacy for the cancer.”

Another reason Medicaid plans are not motivated to manage oral oncology is that they have limited expertise in this area, in part because these drugs are not heavily used in their patient population. Lacking resources and expertise, some Medicaid plans delegate utilization management to a third-party expert in oncology, such as their contracted PBM, and refrain from using pathways.

However, Medicaid plans that also have commercial and Part D enrollment may extend effective policies in those populations to their Medicaid members. “We’ll be reactionary to the market,” said one Medicaid pharmacy executive. “We’ll follow commercial and Part D, for example, in managing the new targeted molecules. That’s a big concern for us.”

PBMs AND SPMs: BEST SUPPORTING PARTNERS
PBMs and SPMs play supportive roles in the management of oral oncology, particularly in the areas of distribution and the promotion of compliance goals.

Currently, most PBMs lack control over formulary decisions for oral
Most include all oral oncolytics on their preferred drug lists, deferring to health plan and employer clients to customize their access approaches. However, expanding oncology expertise at national PBMs may translate to increased influence on access. Today, many PBMs are collaborating with their health plan clients to expand SPM distribution in an effort to reduce waste and keep patients on their therapies. “SPMs help us keep a pulse on the member in terms of tolerability,” said an executive with a regional independent plan. “We’re not gangbusters on specialty, but we’ll use them to enhance compliance and adherence. That will help improve outcomes.” To address compliance and adherence, some SPMs use specially trained pharmacists and nurses who contact members every two weeks to address side effects and other issues that can interfere with treatment plans.

Plans also rely on SPMs to improve adherence by supplying “short fills” to patients receiving their first prescriptions. This also reduces the costly exposure plans face if patients fail to refill their prescriptions.

Still, plans typically limit SPMs to distribution and compliance tasks, reducing their opportunity to influence access. However, as SPMs expand distribution volume and internal capabilities, their influence may slowly rise (Figure 4). We expect most national and regional independent plans to mandate SPM distribution of oral oncolytics by 2014. Here’s why: SPMs are the most cost-effective distribution channel, and SPMs can help plans improve patient compliance while reducing costs. Payors often negotiate lower reimbursement rates when drugs are distributed through SPMs rather than retail pharmacies.

**FUTURE TREND: PLANS PROMOTE GENERICS**

During the next few years, a number of factors will affect how plans manage this category. For instance, pathways — which several plans are now piloting in their networks — are unproven today but may emerge as a tool for controlling access. What’s more, growing concerns about costly treatment at the end of life will prompt more plans to seek solutions in this area.

While these issues are important in determining access, so is the effect of new generic alternatives on the market (Figure 5). Plans are already taking steps to increase use of generics for aromatase inhibitors currently on the market, such as Femara and Arimidex. When generics for Gleevec and Xeloda become available, plans will have an opportunity to seize sizable cost savings. In addition, plans already have a foundation in managing small molecules in less sensitive drug categories, such as proton pump inhibitors for digestive disorders.

This year, more than twice as many plans as in 2010 say they will take some action to increase use of generic oral oncolytics. For example, most plans will require imatinib use prior to covering Sprycel and Tasigna. As one plan executive put it, “We’ve already taken steps to maximize Gleevec use despite Sprycel’s and Tasigna’s first-line label.” Plans that already require Gleevec-first trials will easily transition to generic-first step edits for Sprycel and Tasigna.

On the other hand, plans not currently advantaging Gleevec may refrain from requiring imatinib before these competing brands. Reluctant to create barriers to treatment, some plans are not ready for a step edit requiring imatinib before Tasigna.

**FUTURE TREND: PLANS PICK “PREFERRED” AGENTS**

Over the next few years, we also expect plans to leverage growing market competition to encourage first-line use of specific agents for certain tumors. In fact, this is happening already. Some plans are advantaging certain drugs that treat chronic myelogenous leukemia.

**Figure 4. SPM Distribution Policies**

(Average estimated percentage enrollment at plans utilizing SPMs)

<table>
<thead>
<tr>
<th></th>
<th>Optional</th>
<th>Mandated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td>Predicted (2014)</td>
<td>14%</td>
<td>86%</td>
</tr>
</tbody>
</table>

*Assumes generic imatinib net pricing is 50 percent lower than Gleevec.

**Figure 5. Anticipated Plan Actions to Optimize Generic Imatinib Use in 2014**

(Percentage plans)

<table>
<thead>
<tr>
<th>Action Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reimburse Gleevec on a higher copay tier</td>
<td>55%</td>
</tr>
<tr>
<td>Eliminate coverage for Gleevec</td>
<td>34%</td>
</tr>
<tr>
<td>Reimburse Sprycel and Tasigna on higher copay tiers</td>
<td>30%</td>
</tr>
<tr>
<td>No action</td>
<td>9%</td>
</tr>
</tbody>
</table>

* Assumes generic imatinib net pricing is 50 percent lower than Gleevec.
and a few are using step edits to advantage drugs for advanced renal cell carcinoma, often encouraging Sutent or Nexavar as first-line therapies.

Nearly nine out of 10 plans anticipate using a mix of tactics to encourage use of a specific agent in 2014 if competition leads to more choices in treating specific tumors. Plans will apply new rigor in evaluating agents and will use PA criteria and clinical protocols to encourage trials of specific agents when treatment choice and contracting opportunities exist (Figure 6).

Certain factors will likely affect plans’ ability to advantage a particular oral oncolytic. Specifically, plans that have coverage guidelines, strong physician relations, a robust IT infrastructure and in-house clinical pharmacists specializing in oncology will be more effective with this strategy.

In the coming years, we expect plans to focus on agents that target the same receptors (e.g., vascular endothelial growth factor, epidermal growth factor), ideally relying on overall survival data comparing market entrants to current treatment standards. However, plans are waiting for overall survival data that show an improvement over the standard of care before advantaging new agents. “If there is real-world data demonstrating a meaningful difference in overall survival, it can impact our pathways,” said one executive at a regional independent plan. “We’re looking for survival to double or add more than what hospice adds, which is six months.”

However, when competing brands lack clear differentiation on patient survival rates, almost one-half of plans prioritize cost savings (up from one-third in 2011), advantaging the brand with the lowest net price (Figure 7). Nearly half of plans say lower net pricing is one of the top three factors they consider when making access decisions on new oral agents. This means that if agents fail to have a strong clinical story, contracts may create a difference down the road. In terms of contracting, we expect plans to become more price sensitive in the next few years as they encounter growing treatment choices and gain greater influence over treatment decisions.

With more competition, savvy plans — namely, those with a greater ability to enforce step edits or PAs to require first-line use — will seek opportunities for better pricing.

Clearly, what these trends point to is that payors are preparing to meet the rising costs and utilization in this unique category. By taking advantage of increased competition and other market dynamics, plans will be able to provide more options to their growing member populations while managing their own significant business challenges.

Figure 6. Likely Plan Actions to Encourage Use of a Specific Oral Oncolytic in 2014* (Percentage plans in 2011 or 2012 predicting future action)

<table>
<thead>
<tr>
<th>Action</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refine PA criteria</td>
<td>59%</td>
<td>63%</td>
</tr>
<tr>
<td>Use copay differentials</td>
<td>40%</td>
<td>54%</td>
</tr>
<tr>
<td>Use step edits</td>
<td>36%</td>
<td>54%</td>
</tr>
<tr>
<td>No action</td>
<td>13%</td>
<td>23%</td>
</tr>
</tbody>
</table>

*Data assess likely plan tactics to encourage specific agent use when product choice increases within certain classes (e.g., tyrosine kinase inhibitors, aromatase inhibitors) of oral oncolytics.

Figure 7. Attribute Ability to Drive Improved Access for New Oral Agent in 2014 (Percentage plans ranking as top-three driver)

<table>
<thead>
<tr>
<th>Attribute</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved OS relative to standard chemotherapy</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td>Improved OS relative to Avastin</td>
<td>48%</td>
<td>44%</td>
</tr>
<tr>
<td>Lower net pricing</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Fewer side effects relative to oral competitors</td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>Contract offers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity against multiple tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First to market of new oral agents</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 46
Promising New Therapies in the Treatment of Melanoma

by Howard “Skip” Burris, M.D., CMO and executive director, drug development, Sarah Cannon Research Institute

The marked improvement in the therapeutic alternatives for the treatment of malignant melanoma is among the greatest success stories in this era of targeted therapy, or personalized medicine.

From effective small-molecule inhibitors to revolutionary immunotherapy, the alternatives and the outcomes are dramatically different than just a few years ago. The upcoming challenges are now centered on the choice of therapy, proper sequencing and strategies to overcome resistance.

Melanoma is rising in incidence at a rate of 3 percent annually, which will result in approximately 76,000 cases in the U.S. in 2012. Nearly 10,000 patients will die from this cancer this year.

The risk of recurrence is lifelong, and traditional treatments have provided very modest benefits. In 2011, the U.S. Food and Drug Administration approved two new agents for the treatment of melanoma: ipilimumab (Bristol-Myers Squibb’s Yervoy) and vemurafenib (Roche/Genentech’s Zelboraf).

Cancer is often able to take advantage of the body’s natural efforts at avoiding immune system overactivation and potential harm to healthy tissues. By utilizing escape mechanisms designed to limit autoimmunity, cancer cells are able to hide from the immune system. One such mechanism is taking over the checkpoints of immune cells that are induced on T-cell activation.

Ipilimumab is a monoclonal antibody that blocks the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). This effect results in an improvement in overall survival for the treatment of patients with metastatic melanoma, an endpoint never before achieved against this aggressive cancer. CTLA-4 is normally expressed and provides negative signaling 24 to 72 hours after T-cell activation. Blocking antibodies such as ipilimumab, which inhibit CTLA-4, results in response rates of 15 to 20 percent in metastatic melanoma patients. Clinically significant toxicities are unfortunately seen in 25 to 30 percent of patients, usually of an inflammatory or autoimmune nature. These side effects are often manifested as diarrhea or skin rashes, and the management can be challenging. In a phase 3 study comparing ipilimumab plus dacarbazine versus dacarbazine alone, the combination arm had an improved median survival of 11.2 months versus 9.1 months (p < 0.001, hazard ratio [HR] 0.72).

An emerging class of programmed death-1 (PD-1) receptor or ligand inhibitor is in development and holds great promise for similar or better efficacy with reduced toxicities. The PD-1 receptor is an inhibitory T-cell receptor with two known ligands, PD-L1 and PD-L2, that operates primarily within the tumor microenvironment. PD-1 activity
focuses on T-cell inhibition during chronic antigen exposure, as is seen in cancer. BMS-936558 (Bristol-Myers Squibb’s MDX-1106) has recently been reported in the New England Journal of Medicine and at the 2012 American Society of Clinical Oncology’s meetings to have marked clinical activity across a variety of tumors, including melanoma, renal cell cancer and non-small cell lung cancer, among others. In Brahmer et al., nine of 52 (18 percent) melanoma patients had objective responses; and in Topalian et al., 26 of 94 (28 percent) melanoma patients demonstrated a response, with more than half lasting over one year. The therapy is delivered intravenously every two weeks, and toxicities have included grade 1/2 fatigue, rash and diarrhea in 10 to 15 percent of patients, with minimal grade 3 side effects documented.

In addition to the recently approved vemurafenib, a small-molecule BRAF inhibitor, there are a number of other such targeted therapies in development. Dabrafenib (GlaxoSmithKline), a BRAF inhibitor, and trametinib (GlaxoSmithKline), a MEK inhibitor, are being studied in phase 3 clinical trials, with encouraging results recently published and presented in peer-reviewed journals and at international meetings. BRAF is a member of the RAF kinase family of serine/threonine-specific protein kinases. Oncogenic BRAF mutations have been found in a variety of human cancers, including 44 to 60 percent of melanoma and 50 percent of papillary thyroid cancers, of which almost 90 percent are the V600E mutations targeted by the BRAF inhibitors in development.

The vemurafenib phase 3 study, BRIM-3, randomized 675 metastatic melanoma patients with V600E BRAF mutations to either vemurafenib 960 mg by mouth twice a day or dacarbazine 1,000 mg/m² intravenously every three weeks. The results were overwhelmingly positive in favor of the BRAF inhibitor: median progression-free survival (PFS) of 6.9 versus 1.6 months (HR 0.38) and median overall survival of 13.6 versus 9.7 months (HR 0.70). An interesting toxicity, the occurrence of squamous cell skin cancer (SCC), was seen in 19 percent of patients; other toxicities included arthralgias, rash, elevated liver function tests and fatigue, all seen at grade 3 levels in less than 10 percent of patients.

The dabrafenib phase 3 trial, BREAK-3, screened 733 subjects to enroll 250 patients in a 3:1 fashion to either dabrafenib 150 mg by mouth twice a day (187 patients) or dacarbazine 1,000 mg/m² intravenously every three weeks (63 patients). Again, the outcomes favored the BRAF inhibitor, with a PFS of 5.1 versus 2.7 months (HR 0.30), median follow-up of five months and an objective response rate of 50 percent versus 6 percent by independent review. Toxicities included a 7 percent incidence of SCC and a 5 percent rate of grade 3 pyrexia. Rates of arthralgias, rash and fatigue were less with dabrafenib than those reported previously with vemurafenib, although no comparative trials have been performed.

MEK (mitogen-activated protein kinase/extracellular-signal-regulated kinases [MAPK/ERK]) is downstream of RAF in the well-described RAS pathway, and abnormal MEK signaling leads to uncontrolled cell growth and resistance to apoptosis. The first MEK inhibitors entered clinical trials in 2000, and development has been difficult due to potency/toxicity issues and a resulting lack of efficacy. Trametinib (GlaxoSmithKline) is a novel specific small-molecule inhibitor of MEK with a narrow dosing window but early efficacy in melanoma and other cancers.
After showing activity in phase 1 and phase 2 clinical trials, the METRIC phase 3 study was conducted comparing trametinib 2 mg by mouth daily to chemotherapy, either dacarbazine or paclitaxel. A total of 1,059 patients were screened to enroll 322 BRAF V600E/K mutation-positive metastatic melanoma patients in a 2:1 randomization (214 trametinib patients and 108 chemotherapy patients). The primary endpoint of PFS was statistically positive at p < 0.001 with HR 0.45 (4.8 versus 1.5 months), and the secondary endpoints of overall survival (p = 0.01, HR 0.54) and response rate (22 percent versus 8 percent) were also significantly different. The six-month overall rate of survival was 81 percent with trametinib and 67 percent in the chemotherapy group, despite crossover.

There is much enthusiasm around the combination of BRAF and MEK inhibitors. Early studies show that the use of both agents together in a chronic oral dosing schedule reduces the rate of SCC diagnosis to less than 4 percent and improves objective response rates to greater than 70 percent in a phase 1 trial of 77 melanoma patients. A median PFS of 7.4 months was reached, and in a group of 24 patients treated at the recommended phase 2 dose, PFS actually was documented at 10.8 months. A phase 3 randomized double-blinded placebo-controlled trial comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in V600E/K mutation-positive metastatic melanoma has been initiated.

A unique small-molecule inhibitor, E7080 (Eisai) has shown activity against melanoma in early clinical trials. This tyrosine kinase inhibitor targets vascular endothelial growth factor receptors 1 to 3, fibroblast growth factor receptors 1 to 4, RET, KIT and platelet-derived growth factor receptor. In a phase 1 study, 43 melanoma patients received E7080 with five objective responses and a median duration of response of 15 months. Additional trials in molecularly profiled patients are under way, with combination studies in development. Agents such as E7080 may be particularly useful in blocking the resistance that occurs with BRAF inhibitors.

Glembatumumab vedotin (Celldex’s CDX-011) is an antibody drug conjugate targeting glycoprotein NMB (GPNMB), which is a protein overexpressed by multiple tumor types, including melanoma, breast cancer and gliomas. The antibody, CR011, is linked to the potent cytotoxic monomethyl auristatin E (MMAE) using Seattle Genetic’s proprietary technology. Among 34 melanoma patients treated in a phase 1 study of CDX-011, five objective responses were noted along with a median PFS of four months. Phase 2 trials with CDX-011 in metastatic melanoma patients are under way. Other antibody drug conjugates targeting melanoma are also entering the clinic.

The future for the therapy of melanoma has been altered substantially by the development of targeted therapies against specific oncogenic mutations and the discovery of antibodies that can essentially normalize the immune response to these cancer cells. Strategies to deliver these agents in combination, in earlier stages of disease and in the adjuvant setting will yield even greater results.

References
It is rather fitting that I am on a flight from sunny Florida as I write about malignant melanoma. I am reminded of my youth, growing up in northern New York State, where the summers were extremely short. My friends and I would slather on a mixture of iodine and baby oil and entice what sun’s rays we had to give us a hint of a tan. Sadly, on more than one occasion, the result was a blistering burn, which prompts me now to ensure that my annual dermatology appointment is scheduled due to the risk I’ve created for myself. When we consider additional risks, such as having a family history of melanoma, being fair-skinned, having a large number of moles and generally being exposed to UV radiation as an adolescent, there is significant risk across our entire population for the incidence of malignant melanoma.

During my years as a youth, there was little to no concern about spending unprotected time in the sun. Flash forward to more recent years: The education around skin cancer is everywhere, and the risk for it has become more common knowledge. However, how we apply that knowledge is not always consistent. Simply look at the success of the tanning industry across the nation, with a constant desire to have the “healthy glow” of a tan. International studies have demonstrated a clear association between indoor tanning UV exposure and increased cases of melanoma. That has added to the doubling of the incidence in malignant melanoma since 1973, with a significant growth in younger populations. Therefore, it is not surprising that melanoma is the most common form of cancer for young adults ages 25 to 29 and the second most common form of cancer for young people ages 15 to 29.
Although melanoma accounts for only an estimated 5 percent of all skin cancers, it accounts for almost 9,000 of the nearly 12,000 skin cancer deaths each year. Malignant melanoma has been coined “the silent killer,” likely due to the lack of significant systemic symptoms that would make a person sit up and take notice. This and the fact that select cases of melanoma occur on parts of the body that see no sun exposure (mouth, between toes and genital areas), melanoma commonly may not be detected until in a very late stage of disease.

If diagnosed early, melanoma is highly curable — with surgical excision as the definitive intervention. However, for late-stage disease (which, as indicated in Figure 1, is a large portion of diagnosed cases), survival is an approximate six months, making it one of the most aggressive forms of cancer.

**GEOGRAPHIC DIVERSITY OF MELANOMA INCIDENCE AND DEATH**

States with the highest reported incidence of melanoma (per 100,000 of population) include several that might not necessarily come to mind quickly when thinking of skin cancer (see Figure 2). Melanoma cancer registries have been rich with data on melanoma, which has helped build the reality of incidence, and information captured by the Centers for Disease Control and Prevention (CDC) indicates that most cases are diagnosed and treated in the physician office setting.

Higher death rates from melanoma also don’t necessarily align with states of highest incidence. As seen in Figure 3, which lists those states with the highest death rates, only two states (those bolded) are also states with high incidence.

**THE CHANGING TREATMENT ENVIRONMENT**

Treatment options have conventionally run a wide gamut, including surgery for early-stage disease, progressing to chemotherapeutic agents/regimens (carmustine, dacarbazine, cisplatin, .......
and carboplatin, taxanes and temozolomide) and immunotherapy (high-dose interferon alfa-2b [Sylatron] and interleukin 2 [Proleukin]) for advanced/metastatic disease. In 2011, the treatment dynamics changed significantly with U.S. Food and Drug Administration (FDA) approval for two new options:

- ipilimumab, a cytotoxic T-lymphocyte-associated antigen 4 blocker (Yervoy)
- vemurafenib, a BRAF inhibitor (Zelboraf)

Both products have provided incremental benefit and new patient options for later stage disease. However, with the increased treatment costs associated with Yervoy and Zelboraf, payors have denoted concern about how to best ensure appropriate patient application for what is a growing cancer population.

PAYOR PERSPECTIVES
When focusing on newer agents, such as Yervoy and Zelboraf, payors have applied wide variation in their approach to drug management. Payors may simply align utilization with the product’s FDA-approved label and, in the case of Zelboraf, require documentation of BRAF mutation. However, other payors have applied more detail to guidance on utilization for both Yervoy and Zelboraf. The following limited excerpts from published Yervoy and Zelboraf payor policies and utilization management criteria demonstrate various requirements on which payors may focus to support appropriate utilization. (Note: Although only one payor policy may be represented for a given drug, a similar policy may also be in effect for the other drug.)
One interesting phenomenon that occurred upon FDA approval for Zelboraf was related to the requirement to use an FDA-approved platform for BRAF testing. National reference laboratories may not necessarily use FDA-approved platforms but rather have lab-developed platforms to execute the test.

In select cases, this can create a contract/cost dilemma for payors — and for patients. To ensure use of an FDA-approved diagnostic as per the drug’s label, the use of a non-network lab might be required. Therefore, patient cost-share is increased in doing so. This is still a topic of discussion among some payors.

Continuing with the theme of diagnostics, it is well-known that commercial payors take the lead from Medicare related to policy development. In the past year, the Centers for Medicare & Medicaid Services (CMS) implemented a program called the Molecular Diagnostic (MolDx) Services Program with the intent to create appropriate diagnostic coverage, coding and payment guidance that will support claims processing without documentation review.7 One driver for the MolDx program is the expansion of personalized medicine and the integration of diagnostics to support that process.

To establish appropriate coverage and reimbursement for MolDx claims, Medicare (through Palmetto GBA as the primary contractor) required laboratory providers to submit information on various diagnostic procedures. This one-time submission on each diagnostic was assessed by Medicare and then assigned a unique test identifier that Medicare crosswalks to codes and a subsequent reimbursement for a given test.

Effective September 7, 2012, Medicare created a BRAF MolDx policy, as follows:10

Palmetto GBA has determined the FDA-approved cobas 4800 BRAF V600 Mutation Test for the detection of the presence of a mutation in the BRAF gene in melanoma meets the reasonable and necessary criteria for Medicare reimbursement. The cobas test determines patient eligibility for Zelboraf (vemurafenib), a treatment indicated for patients with melanoma that cannot be removed by surgery or has spread in the body.

To report a cobas service, please submit the following claim information:

- CPT code 84999 — unlisted chemistry procedure
- Enter 'ZB794' in the comment/narrative field for the following claim field/types:
  - Loop 2400, NTE02 or SVT101-7 for the 5010A1 837P
  - Submit ‘ZB794’ on an attachment to the claim form for paper claim
- Select at least one diagnosis from the following:
  - 172.0-172.9: malignant melanoma of skin
  - 198.2: secondary malignant neoplasm of other specified sites; skin

Note: Palmetto GBA is performing a review of all MolDx test applications that detect the presence of the BRAF gene and do not use the FDA-approved cobas methodology or use the cobas kit in addition to other methodologies. If you perform such a test, please prepare to submit a MolDx Technical Assessment (TA) Request as outlined in the MolDx section on www.PalmettoGBA.com/J1B.

It is interesting to note that Palmetto is assessing all BRAF testing platforms, not only those that are FDA-approved, and will be a process to watch over time.

**KEEPING A SUNNY DISPOSITION**

There is no denying that malignant melanoma is increasing in incidence — our education and awareness needs to continue to somehow redirect the trend lines for this cancer. However, that is a longer-term focus, and we are currently faced with cases that are being diagnosed, many of which are in advanced stage disease. With the advent of newer agents, such as Yervoy and Zelboraf, added to the armamentarium of treatment options, we can hopefully reduce current death rates for malignant melanoma. Careful application of clinical outcomes to guide coverage and access can likely demonstrate an impact on one of the most aggressive deadly cancers.

References

With each publication, ManagedCare Oncology’s Drug & Administration Compendia highlights a single medication or a group of medications that could be utilized in the management of one of the featured oncology diseases.

**TREATMENT OF Melanoma**

This section addresses such topics as:
- Associated ICD-9-CM codes
- Drugs that have been FDA-approved
- Drugs that are compendia-listed for off-label use based on clinical studies that suggest beneficial use in some cases
- Ancillary medications used in cancer treatment
- Reimbursement and coding information
  - HCPCS/CPT® codes and code description
  - Current code price (AWP-based pricing)
  - Most recent Medicare allowable (ASP + 6%), if applicable
  - Possible CPT administration codes that can be utilized with each drug

**Associated ICD-9-CM Codes:**

172  Malignant melanoma of skin  
    *Includes* melanocarcinoma  
    melanoma (skin) NOS
    melanoma in situ of skin
    *Excludes* skin of genital organs (184.0-184.9, 187.1-187.9)
    sites other than skin-code to malignant neoplasm of the site

172.0  Lip  
    *Excludes* vermilion border of lip (140.0-140.1, 140.9)

172.1  Eyelid, including canthus

172.2  Ear and external auditory canal
    Auricle (ear)
    Auricular canal, external
    External [acoustic] meatus
    Pinna

172.3  Other and unspecified parts of the face
    Cheek (external)
    Chin
    Eyebrow
    Forehead
    Nose, external
    Temple

172.4  Scalp and neck

172.5  Trunk, except scrotum
    Axilla
    Perianal skin
    Breast
    Perineum
    Buttock
    Umbilicus
    Groin
    *Excludes* anal canal (154.2)
    anus NOS (154.3)
    scrotum (187.7)

172.6  Upper limb, including shoulder
    Arm
    Forearm
    Finger
    Hand

172.7  Lower limb, including hip
    Ankle
    Leg
    Foot
    Popliteal area
    Heel
    Thigh
    Knee
    Toe

172.8  Other specified sites of skin
    Malignant melanoma of contiguous or overlapping sites of skin whose point of origin cannot be determined

172.9  Melanoma of skin, site unspecified
# FDA-Approved Medications Currently Available to Treat Melanoma

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code — Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 9/1/12</th>
<th>Medicare Allowable (ASP + 6%) — Effective 7/1/12-9/30/12</th>
<th>Possible CPT Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aldesleukin (Proleukin)</td>
<td>J9015 — injection, aldesleukin, per single-use vial</td>
<td>$1,411.68</td>
<td>$1,246.98</td>
<td>96409</td>
</tr>
<tr>
<td>dacarbazine (DTIC-Dome)</td>
<td>J9130 — dacarbazine, 100 mg</td>
<td>$11.34</td>
<td>$3.34</td>
<td>96409, 96413</td>
</tr>
<tr>
<td>ipilimumab (Yervoy)</td>
<td>J9228 — injection, ipilimumab, 1 mg</td>
<td>$144.00</td>
<td>$125.17</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>interferon alfa-2b (Intron-A)</td>
<td>J9214 — injection, interferon, alfa-2b, recombinant, 1 million units</td>
<td>$219.00</td>
<td>$18.50</td>
<td>96372, 96401</td>
</tr>
<tr>
<td>hydroxyurea (Hydrea)</td>
<td>J8999* — prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC-level pricing</td>
<td>NDC-level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>hydroxyurea (Hydrea)</td>
<td>S0176 — hydroxyurea, oral, 500 mg</td>
<td>$1.28</td>
<td>S0176 — not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>peginterferon alfa-2b (Sylatron)</td>
<td>C9399* — unclassified drugs or biologicals (hospital outpatient use only)</td>
<td>NDC-level pricing</td>
<td>NDC-level pricing</td>
<td>96372, 96401</td>
</tr>
<tr>
<td>peginterferon alfa-2b (Sylatron)</td>
<td>J9999* — not otherwise classified, antineoplastic drugs</td>
<td>NDC-level pricing</td>
<td>NDC-level pricing</td>
<td>96372, 96401</td>
</tr>
</tbody>
</table>

*When billing a nonclassified medication using a CMS 1500 claim form, you must include both the HCPCS code (i.e., J8999 for Zelboraf) in column 24D and the drug name, strength and National Drug Code (NDC) in box 19 or 24A to ensure appropriate reimbursement. Please note: Check with payor regarding correct placement of medication information.
# Compendia-Listed Off-Label Use Medications Currently Available to Treat Melanoma

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HPCPCS Code — Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 9/1/12</th>
<th>Medicare Allowable (ASP + 6%) — Effective 7/1/12-9/30/12</th>
<th>Possible CPT Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amifostine (Ethyol)</td>
<td>J0207 — injection, amifostine, 500 mg</td>
<td>$564.95</td>
<td>$314.56</td>
<td>96374</td>
</tr>
<tr>
<td>bleomycin (Blenoxane)</td>
<td>J9040 — injection, bleomycin sulfate, 15 units</td>
<td>$41.40</td>
<td>$25.67</td>
<td>96401, 96409</td>
</tr>
<tr>
<td>carboplatin (Paraplatin)</td>
<td>J9045 — injection, carboplatin, 50 mg</td>
<td>$85.10</td>
<td>$3.64</td>
<td>96409, 96413, 96413</td>
</tr>
<tr>
<td>carmustine (BiCNU)</td>
<td>J9050 — injection, carmustine, 100 mg</td>
<td>$205.69</td>
<td>$175.30</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>cisplatin (Platinol AQ)</td>
<td>J9060 — injection, cisplatin, powder or solution, per 10 mg</td>
<td>$4.25</td>
<td>$1.90</td>
<td>96409, 96413, 96413</td>
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<tr>
<td>dactinomycin (Cosmegen)</td>
<td>J9120 — injection, dactinomycin, 0.5 mg</td>
<td>$684.36</td>
<td>$575.16</td>
<td>96409</td>
</tr>
<tr>
<td>docetaxel (Taxotere)</td>
<td>J9171 — injection, docetaxel, 1 mg</td>
<td>$22.24</td>
<td>$8.41</td>
<td>96413</td>
</tr>
<tr>
<td>lomustine (CeeNu)</td>
<td>J8999* — prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC-level pricing</td>
<td>NDC-level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>lomustine (CeeNu)</td>
<td>S0178 — lomustine, oral, 10 mg</td>
<td>$10.59</td>
<td>S0178 — not payable by Medicare</td>
<td>N/A</td>
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<tr>
<td>melphalan (Alkeran)</td>
<td>J9245 — injection, melphalan hydrochloride, 50 mg</td>
<td>$1,922.50</td>
<td>$1,314.58</td>
<td>96409, 96413</td>
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<tr>
<td>paclitaxel (Taxol)</td>
<td>J9265 — injection, paclitaxel, 30 mg</td>
<td>$15.54</td>
<td>$7.51</td>
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<tr>
<td>peginterferon alfa-2b (Peg-Intron)</td>
<td>J3590* — unclassified biologics</td>
<td>NDC-level pricing</td>
<td>NDC-level pricing</td>
<td>96372</td>
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<tr>
<td>peginterferon alfa-2b (Peg-Intron)</td>
<td>S0148 — injection, pegylated interferon alfa-2b, 10 mcg</td>
<td>$137.95</td>
<td>S0148 — not payable by Medicare</td>
<td>96372</td>
</tr>
<tr>
<td>sargramostim (Leukine)</td>
<td>J2820 — injection, sargramostim (GM-CSF), 50 mcg</td>
<td>$47.36</td>
<td>$25.12</td>
<td>96365, 96366, 96372</td>
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<tr>
<td>temozolomide (Temodar)</td>
<td>J8700 — temozolomide, oral, 5 mg</td>
<td>$12.31</td>
<td>$10.12</td>
<td>N/A</td>
</tr>
<tr>
<td>vemurafenib (Zelboraf)</td>
<td>C9399* — unclassified drugs or biologicals (hospital outpatient use only)</td>
<td>NDC-level pricing</td>
<td>NDC-level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>vemurafenib (Zelboraf)</td>
<td>J8999* — prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC-level pricing</td>
<td>NDC-level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>vinblastine (Velban)</td>
<td>J9360 — injection, vinblastine sulfate, 1 mg</td>
<td>$3.18</td>
<td>$1.29</td>
<td>96409</td>
</tr>
<tr>
<td>vincristine (Vincasar PFS)</td>
<td>J9370 — vincristine sulfate, 1 mg</td>
<td>$5.60</td>
<td>$3.64</td>
<td>96409</td>
</tr>
</tbody>
</table>

*When billing a nonclassified medication using a CMS 1500 claim form, you must include both the HCPCS code (i.e., J8999 for Zelboraf) in column 24D and the drug name, strength and National Drug Code in box 19 or 24A to ensure appropriate reimbursement. Please note: Check with payor regarding correct placement of medication information.
## Ancillary Medications Used in Cancer Treatment

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code — Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 9/1/12</th>
<th>Medicare Allowable (ASP + 6%) — Effective 7/1/12-9/30/12</th>
<th>Possible CPT Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aprepitant (Emend)</td>
<td>J8501 — aprepitant, oral, 5 mg</td>
<td>$8.00</td>
<td>$6.23</td>
<td>N/A</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>J1626 — injection, granisetron hydrochloride, 100 mcg</td>
<td>$4.42</td>
<td>$0.44</td>
<td>96374</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>Q0166 — granisetron hydrochloride, 1 mg oral, FDA-approved prescription antiemetic, for use as a complete therapeutic substitute for an IV antiemetic at time of chemotherapy treatment, not to exceed a 24-hour dosage regimen</td>
<td>$59.01</td>
<td>$2.92</td>
<td>N/A</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>S0091 — granisetron hydrochloride, 1 mg (for circumstances falling under the Medicare statute, use Q0166)</td>
<td>$59.01</td>
<td>S0091 — not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>J2405 — injection, ondansetron hydrochloride, per 1 mg</td>
<td>$0.60</td>
<td>$0.07</td>
<td>96372, 96374</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>Q0162 — ondansetron 1 mg, oral, FDA-approved prescription antiemetic, for use as a complete therapeutic substitute for an IV antiemetic at the time of chemotherapy treatment, not to exceed a 48-hour dosage regimen — see also S0119</td>
<td>$6.05</td>
<td>$0.07</td>
<td>N/A</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>S0119 — ondansetron, oral, 4 mg (for circumstances falling under the Medicare statute, use HCPCS code Q0162)</td>
<td>$24.20</td>
<td>S0119 — not payable by Medicare</td>
<td>N/A</td>
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<tr>
<td>palonosetron (Aloxi)</td>
<td>J2469 — injection, palonosetron HCl, 25 mcg</td>
<td>$45.48</td>
<td>$18.88</td>
<td>96374</td>
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</table>
## CPT Administration Code Descriptions

<table>
<thead>
<tr>
<th>CPT Administration Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>96401</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; nonhormonal antineoplastic</td>
</tr>
<tr>
<td>96402</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; hormonal antineoplastic</td>
</tr>
<tr>
<td>96409</td>
<td>Chemotherapy administration; intravenous, push technique, single or initial substance/drug</td>
</tr>
<tr>
<td>96413</td>
<td>Chemotherapy administration, intravenous infusion technique; up to one hour, single or initial substance/drug</td>
</tr>
<tr>
<td>96415</td>
<td>Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure.) (Use 96415 in conjunction with 96413.)</td>
</tr>
<tr>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis or diagnosis (specify substance or drug); initial, up to one hour</td>
</tr>
<tr>
<td>96366</td>
<td>Intravenous infusion, for therapy, prophylaxis or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure.) (Use 96366 in conjunction with 96365, 96367.)</td>
</tr>
<tr>
<td>96372</td>
<td>Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
<tr>
<td>96374</td>
<td>Therapeutic, prophylactic or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
</tr>
</tbody>
</table>

### References
- FDA-approved indication (product prescribing information).
- CMS (Centers for Medicare & Medicaid Services) — Medicare-Allowable Third Quarter 2012 — Effective Dates 7/1/12-9/30/12.

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### Oncology-Related HCPCS Codes

This reference chart will assist the oncology office (office manager, oncology nurse, physician and ancillary staff) and payor with the appropriate codes to utilize when billing or reimbursing for medication(s).

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code — Code Description</th>
<th>FDA-Approved Uses</th>
<th>Compendia-Listed Off-Label Uses</th>
<th>Current Code Price <em>(AWP-Based Pricing)</em></th>
<th>Medicare Allowable (ASP + 6%)*</th>
<th>Possible CPT Admin Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>azacitidine (Vidaza)</td>
<td>J9025 — injection, azacitidine, 1 mg</td>
<td>Myeloid leukemia — chronic (205.1_) Low-grade myelodysplastic syndrome lesions (238.72) High-grade myelodysplastic syndrome lesions (238.73) Myelodysplastic syndrome with 5q deletion (238.74) Myelodysplastic syndrome, unspecified (238.75)</td>
<td>Malignant neoplasm of retroperitoneum and peritoneum — specified parts of peritoneum (158.6) Malignant neoplasm of retroperitoneum and peritoneum — peritoneum, unspecified (158.9) Malignant neoplasm of pleura (163..) Malignant neoplasm of thymus, heart and mediastinum — heart (164.1) Myeloid leukemia — acute (205.0) Hereditary hemolytic anemias — other thalassemia (282.49) Sickle-cell disease (282.6)</td>
<td>$6.33</td>
<td>$5.39</td>
<td>96401 96409 96413</td>
</tr>
<tr>
<td>cetuximab (Erbitux)</td>
<td>J9055 — injection, cetuximab, 10 mg</td>
<td>Malignant neoplasm of lip (140..) Malignant neoplasm of tongue (141..) Malignant neoplasm of major salivary glands (142..) Malignant neoplasm of gum (143..) Malignant neoplasm of floor of mouth (144..) Malignant neoplasm of other and unspecified parts of mouth (145..) Malignant neoplasm of oropharynx (146..) Malignant neoplasm of nasopharynx (147..) Malignant neoplasm of hypopharynx (148..) Malignant neoplasms of other and ill-defined sites within the lip, oral cavity and pharynx (149..) Malignant neoplasm of colon (153..) Malignant neoplasm of rectum, rectosigmoid junction and anus (154..) Malignant neoplasm of nasal cavities, middle ear and accessory sinuses (160..) Malignant neoplasm of larynx (161..) Malignant neoplasm of other and ill-defined sites — head, face and neck (195.0) Secondary and unspecified malignant neoplasm of lymph nodes — lymph nodes of head, face and neck (196.0)</td>
<td>Malignant neoplasm of trachea, bronchus and lung (162..)</td>
<td>$60.23</td>
<td>$51.13</td>
<td>96413 96415</td>
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<tr>
<td>generic (Brand) Name</td>
<td>HCPCS Code — Description</td>
<td>FDA-Approved Uses</td>
<td>Compendia-Listed Off-Label Uses</td>
<td>Current Code Price (AWP-Based Pricing)*</td>
<td>Medicare Allowable (ASP + 6%)**</td>
<td>Possible CPT Admin Code(s)</td>
</tr>
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<tr>
<td>clofarabine (Clolar)</td>
<td>J9027 — injection, clofarabine, 1mg</td>
<td>Lymphoid leukemia — acute (204.0)</td>
<td>Myeloid leukemia — acute (205.0) Low-grade myelodysplastic syndrome lesions (238.72) High-grade myelodysplastic syndrome lesions (238.73) Myelodysplastic syndrome with 5q deletion (238.74) Myelodysplastic syndrome, unspecified (238.75)</td>
<td>$141.75</td>
<td>$126.07</td>
<td>96413 96415</td>
</tr>
<tr>
<td>daunorubicin (Cerubidine)</td>
<td>J9150 — injection, daunorubicin, 10mg</td>
<td>Lymphoid leukemia (204.0) Myeloid leukemia (205.0) Monocytic leukemia (206.0) Other specified leukemia (207.0) Megakaryocytic leukemia (207.2) Leukemia of unspecified cell type (208.0) Lymphoid leukemia — acute (204.0) Myeloid leukemia — acute (205.0) Myeloid leukemia — chronic (205.1) Malignant neoplasm of bone and articular cartilage (170) Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue (200) Other malignant neoplasms of lymphoid and histiocytic tissue (202) Chronic myeloid leukemia (205.1)</td>
<td>$28.11</td>
<td>$18.96</td>
<td>96409 96413</td>
<td></td>
</tr>
<tr>
<td>decitabine (Dacogen)</td>
<td>J0894 — injection, decitabine, 1mg</td>
<td>Low-grade myelodysplastic syndrome lesions (238.72) High-grade myelodysplastic syndrome lesions (238.73) Myelodysplastic syndrome with 5q deletion (238.74) Myelodysplastic syndrome, unspecified (238.75) Lymphoid leukemia — acute (204.0) Myeloid leukemia — acute (205.0) Myeloid leukemia — chronic (205.1)</td>
<td>$40.25</td>
<td>$33.74</td>
<td>96413 96415</td>
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<tr>
<td>Degarelix (Firmagon)</td>
<td>J9155 — injection, degarelix, 1mg</td>
<td>Malignant neoplasm of prostate (185)</td>
<td>N/A</td>
<td>$6.07</td>
<td>$3.00</td>
<td>96402</td>
</tr>
<tr>
<td>melphalan (Alkeran)</td>
<td>J9245 — injection, melphalan hydrochloride, 50mg</td>
<td>Multiple myeloma and immunoproliferative neoplasms (203) Malignant neoplasm of retroperitoneum (158) Malignant neoplasm of bone and articular cartilage (170) Malignant neoplasm of connective and other soft tissue (171) Malignant melanoma of skin (172) Malignant neoplasm of female breast (174) Malignant neoplasm of male breast (175) Malignant neoplasm of ovary and other uterine adnexa (183) Malignant neoplasm of other and unspecified female genital organs (184) Malignant neoplasm of prostate (185) Malignant neoplasm of testis (186) Malignant neoplasm of penis and other male genital organs (187) Malignant neoplasm of eye (190) Hodgkin’s disease (201) Myeloid leukemia — chronic (205.1) Neoplasm of uncertain behavior of other and unspecified sites and tissues — polycythemia vera (238.4) Disorders of plasma protein metabolism — macroglobulinemia (273.3) Other and unspecified disorders of metabolism — amyloidosis, unspecified (277.30) Other and unspecified disorders of metabolism — other amyloidosis (277.39) Other hypertrophic and atrophic conditions of skin — other specified hypertrophic and atrophic conditions of skin (701.8)</td>
<td>$1,922.50</td>
<td>$1,314.58</td>
<td>96409 96413</td>
<td></td>
</tr>
<tr>
<td>generic (Brand) Name</td>
<td>HCPCS Code — Code Description</td>
<td>FDA-Approved Uses</td>
<td>Compendia-Listed Off-Label Uses</td>
<td>Current Code Price (AWP-Based Pricing)*</td>
<td>Medicare Allowable (ASP + 6%) **</td>
<td>Possible CPT Admin Code(s)</td>
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</tr>
<tr>
<td>panitumumab</td>
<td>J9303 — injection, panitumumab, 10 mg</td>
<td>Malignant neoplasm of colon (153.) Malignant neoplasm of rectum, rectosigmoid junction and anus (154.)</td>
<td>Malignant neoplasm of trachea, bronchus and lung (162.)</td>
<td>$103.89</td>
<td>$88.87</td>
<td>96413 96415</td>
</tr>
<tr>
<td>vinorelbine tartrate (Navelbine)</td>
<td>J9390 — injection, vinorelbine tartrate, per 10 mg</td>
<td>Malignant neoplasm of trachea, bronchus and lung (162.)</td>
<td>Malignant neoplasm of lip (140.) Malignant neoplasm of tongue (141.) Malignant neoplasm of major salivary glands (142.) Malignant neoplasm of gum (143.) Malignant neoplasm of floor of mouth (144.) Malignant neoplasm of other and unspecified parts of mouth (145.) Malignant neoplasm of oropharynx (146.) Malignant neoplasm of nasopharynx (147.) Malignant neoplasm of hypopharynx (148.) Malignant neoplasm of other and ill-defined sites within the lip, oral cavity and pharynx (149.) Malignant neoplasm of esophagus (150.) Malignant neoplasm of retroperitoneum (158.) Malignant neoplasm of nasal cavities, middle ear and accessory sinuses (160.) Malignant neoplasm of larynx (161.) Malignant neoplasm of connective and other soft tissue (171.) Malignant neoplasm of female breast (174.) Malignant neoplasm of male breast (175.) Kaposi’s sarcoma (176.) Malignant neoplasm of cervix uteri (180.) Malignant neoplasm of ovary and other uterine adnexa (183.) Malignant neoplasm of head, face and neck (195.) Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck (196.) Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue (200.) Hodgkin’s disease (201.) Other malignant neoplasms of lymphoid and histiocytic tissue (202.) Carcinoma in situ of lip, oral cavity and pharynx (230.) Carcinoma in situ of esophagus (230.1) Carcinoma in situ of larynx (231.0) Neoplasm of uncertain behavior of connective and other soft tissue (238.1)</td>
<td>$32.04</td>
<td>$9.87</td>
<td>96409</td>
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</tbody>
</table>

*Current code prices are effective as of 9/1/12. The code price is based on the Healthcare Common Procedure Coding System (HCPCS) code description. HCPCS codes are a component of the Centers for Medicare & Medicaid Services. The code price is an AWP-based pricing methodology developed by RJ Health Systems International, LLC, Rocky Hill, Conn.

**Effective 7/1/12-9/30/12

Oncology-Related J-Code References

- HCPCS Level II Expert 2012
- Full prescribing information for each drug listed
- CMS (Centers for Medicare & Medicaid Services) — Medicare-Allowable Third Quarter — Effective Dates 7/1/12-9/30/12.

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Other investigational targeted therapy, such as dabrafenib and trametinib, may also prove to be of great benefit to this patient population.

**Title:** Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre open-label phase 3 randomized controlled trial.

**Authors:** Hauschild A., Grog J.-J., Demidov L.V., et al.


**Purpose:** Approximately 46,000 people worldwide died of melanoma in 2008. Standard therapy for metastatic disease has centered around chemotherapy (e.g., dacarbazine [DTIC-Dome]) or immunotherapy (e.g., high-dose interleukin 2 [Proleukin]). The identification of the BRAF gene mutation identified a possible means of targeted therapy for this patient population. Nearly 50 percent of all melanomas have an active mutation of the gene, and 80 to 90 percent of the BRAF-mutated melanomas have a V600E mutation, with the other 10 to 20 percent having the V600K mutation. The mutation drives cell proliferation in many cases. Vemurafenib (Zelboraf) was the first BRAF inhibitor introduced on the market, and studies showed an objective response rate of 48 percent with improved overall survival (OS) and progression-free survival (PFS). Dabrafenib is a reversible adenosine triphosphate (ATP)-competitive inhibitor that selectively inhibits BRAF V600E kinase. Preclinical studies show the drug inhibits the MEK pathway in BRAF V600E-mutated melanoma cells, leading to a decrease in cell proliferation. Phase 2 studies confirmed high response rates, which led to this phase 3 study.
Methods: Patients with histologically confirmed, measurable metastatic myeloma (stage IV or unresectable stage III) with a BRAF V600E mutation were eligible for the study. Antitumor therapy other than interleukin 2 was not allowed. Other eligibility criteria included age 18 and older, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and adequate end-organ function. Patients were randomized (ratio 3:1) to receive either oral dabrafenib (n = 187) or dacarbazine (n = 63). The treatment groups were well balanced for age, sex, race and disease status. An analysis at one year showed 57 percent of the dabrafenib group still on treatment compared with 22 percent of those receiving dacarbazine. Median PFS was 5.1 months for the patients receiving dabrafenib and 2.7 months for those receiving dacarbazine (hazard ratio [HR] 0.30; 95 percent confidence interval [CI], 0.18-0.51; p value <0.0001). A total of 30 patients died, 21 (11 percent) in the dabrafenib group and nine (14 percent) in the dacarbazine group. The OS HR was 0.61 (95 percent CI, 0.25-1.48) favoring dabrafenib, with additional follow-up ongoing. The ORR was 50 percent (six complete and 87 partial responses) in those patients treated with dabrafenib and 6 percent (one complete and three partial responses) in those patients treated with dacarbazine. A total of 28 patients who progressed on dacarbazine crossed over to dabrafenib. Thirteen, or 46 percent, had a partial response to the drug. Treatment-related side effects ≥ grade 2 occurred in 100 (53 percent) of the 187 patients who received dabrafenib and 26 (44 percent) of the 59 patients who received dacarbazine. The most common adverse events noted with dabrafenib were skin related, primarily hyperkeratosis and palmar-plantar hyperkeratosis. Other side effects of dabrafenib included fever, fatigue, arthralgia and headache. Fortunately, grade 3 or 4 toxicity was uncommon in either treatment arm.

Conclusion: The authors concluded that dabrafenib significantly improved PFS when compared with dacarbazine in patients with metastatic melanoma.

Managed Care Implications: Dabrafenib offers new oral-targeted therapy for patients with BRAF V600E-mutated melanoma. Additional studies will identify its place in the treatment of metastatic melanoma either as a single agent or in combination with other drugs found to be effective in the treatment of this disease.

Title: Improved survival with MEK inhibition in BRAF-mutated melanoma.

Authors: Flaherty K.T., Robert C., Hersey P., et al.


Purpose: Among cancer patients younger than 40 years of age, melanoma is second in incidence to that of breast cancer in women and leukemia in men. Prior to 2010, no systemic therapy had been shown to improve OS in those patients with metastatic disease. Subsequently, ipilimumab (Yervoy), a monoclonal antibody targeting cytotoxic T-lymphocyte-associated antigen (CTLA-4), and vemurafenib (Zelboraf), a selective BRAF inhibitor, have both shown to improve survival in patients with metastatic melanoma in randomized clinical trials. Activating mutations in serine-threonine protein kinase BRAF, a constituent of the mitogen-
activated protein kinase (MAPK) signal-transduction pathway, have been identified in 50 percent of patients with metastatic melanoma. The two most common BRAF mutations, V600E and V600K, are found in 95 percent of all patients with this disease. Activated BRAF phosphorylates activate MEK proteins (MEK1 and MEK2), which regulate proliferation and survival of tumor cells in a number of malignancies, including melanoma. Trametinib is an orally active small molecule that selectively inhibits MEK1 and MEK2. Phase 1 and 2 studies showed evidence of tumor regression and disease stabilization in patients with melanoma and a BRAF mutation. This trial evaluates the effectiveness of trametinib in a phase 3 randomized, open-label setting in patients with metastatic melanoma.

Methods: Patients with histologically confirmed, unresectable stage IIIC or IV cutaneous melanoma with a V600E or V600K BRAF mutation were eligible for the study. Additional eligibility criteria included age 18 and older, measurable disease, an ECOG performance status of 0 or 1 and adequate end-organ function. Patients could have received one previous chemotherapy regimen of advanced or metastatic melanoma with the exclusion of a BRAF or MEK inhibitor or ipilimumab. Patients were randomized (2:1) to receive oral trametinib, 2 mg once daily, or intravenous chemotherapy consisting of dacarbazine (DTIC-Dome) 1,000 mg/m² or paclitaxel (Taxol) 175 mg/m² administered on an every-three-week schedule. The primary endpoint was PFS. Secondary endpoints included OS, ORR and safety. Therapy continued until disease progression, death or withdrawal from the study. Patients receiving intravenous chemotherapy were allowed to cross over and receive trametinib after disease progression was confirmed by an independent review.

Results: A total of 322 patients were randomized to receive trametinib (n = 214) or intravenous chemotherapy (n = 108). Patients were well-balanced with regard to age, performance status, extent of disease and previous immunotherapy. In the intent-to-treat population, the median duration of PFS was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group (HR 0.45; 95 percent CI, 0.33-0.63; p < 0.001). At six months, the OS was 81 percent in the trametinib arm and 67 percent in the chemotherapy arm (HR 0.54; 95 percent CI, 0.32-0.92; p = 0.01). Median OS had not yet been reached. The median ORR assessed by RECIST (Response Evaluation Criteria in Solid Tumors) was 22 percent (95 percent CI, 17-28) in the trametinib group, with four complete and 43 partial responses, and 8 percent (95 percent CI, 4-15) in the chemotherapy group (p = 0.01), with nine partial responses. Fifty-one of 108, 47 percent, of the patients initially treated with chemotherapy crossed over and received trametinib. Median OS has yet to be reached in this group. The most common adverse events were rash (57 percent overall, 19 percent grade 2 and 8 percent grade 3 or 4), diarrhea (43 percent overall, 6 percent grade 2), fatigue (26 percent overall, 5 percent grade 2) and peripheral edema (26 percent overall, 4 percent grade 2 and 1 percent grade 3) in those patients treated with trametinib. These were managed by dose interruption and dose reduction. Asymptomatic and reversible reduction in cardiac ejection fraction and ocular toxicity (blurred vision being most commonly reported) were infrequent. Secondary skin neoplasms were not observed.
**Conclusion:** Trametinib improves the rate of PFS and OS among patients with metastatic melanoma with a BRAF V600E or V600K mutation when compared with intravenous chemotherapy.

**Managed Care Implications:**
Trametinib is another targeted oral therapy for the treatment of metastatic melanoma that selectively blocks the MEK pathway. Like dabafenib, and based upon FDA approval, its use as a single agent or in combination with other therapy for metastatic melanoma remains to be delineated.

**Title:** Ipilimumab plus dacarbazine for previously untreated metastatic melanoma.

**Authors:** Robert C., Thomas L., Bondarenko I., et al.


**Purpose:** Survival rates for patients with metastatic melanoma are low, with a two-year survival rate of 10 to 20 percent. Dacarbazine (DTIC-Dome) is the most frequently used antineoplastic but has never been shown to improve survival in randomized controlled studies in this patient population. High-dose interleukin (Proleukin) has shown durable complete responses and survival benefit but can only be used in a small percentage of patients with metastatic melanoma. Ipilimumab (Yervoy), the fully humanized IgG1 monoclonal antibody that blocks CTLA-4, augments T-cell activation and proliferation and has also shown survival benefit in this patient population. The dosing in the phase 3 study was 3 mg/kg intravenously. Other phase 2 studies showed that the combination of dacarbazine (250 mg/m² intravenously daily × five every three weeks) in combination with ipilimumab (2 mg/kg intravenously every four weeks × four doses) was associated with durable objective responses and no new adverse events. This phase 3 study was initiated to determine whether ipilimumab (10 mg/kg) plus dacarbazine versus dacarbazine plus placebo improves OS in patients with previously untreated metastatic melanoma.

**Methods:** Eligible patients were at least 18 years of age, had previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions, an ECOG performance status of 0 or 1 and a life expectancy of at least 16 weeks. Patients were deemed ineligible if they had received prior treatment for metastatic disease, but not if they had received any adjuvant therapy. The multinational randomized double-blind phase 3 trial randomly assigned patients in a 1:1 ratio to receive either ipilimumab 10 mg/kg intravenously plus dacarbazine 850 mg/m² intravenously or dacarbazine 850 mg/m² intravenously and placebo at weeks one, four, seven and 10, followed by dacarbazine alone every three weeks through week 22 (induction phase). Treatment was discontinued if toxic effects associated with the drug(s) or progressive disease were noted during weeks 12 and 24. At week 24, patients with stable disease or an objective response during the induction phase who did not have a dose-limiting adverse event were eligible for the maintenance phase in which they received ipilimumab or placebo every 12 weeks until disease progression, development of toxicity or the end of the study. The primary endpoint of the study was OS. Secondary endpoints included PFS, best overall response, duration of response and safety.

**Results:** A total of 502 patients were randomized to receive either ipilimumab and dacarbazine (n = 250) or dacarbazine...
and placebo (n = 252). The baseline characteristics between the two groups were balanced. The median OS for the ipilimumab and dacarbazine group was 11.2 months (95 percent CI, 9.4-13.6) versus 9.1 months (95 percent CI, 7.8-10.5) in the dacarbazine and placebo group. There was a higher survival rate in the ipilimumab plus dacarbazine arm at one year (47.3 percent versus 36.6 percent), two years (28.5 percent versus 17.9 percent) and three years (20.8 percent versus 12.2 percent) (HR 0.72; p < 0.001). There was also a 24 percent reduction in the risk of progression in the ipilimumab-dacarbazine treated patients (HR 0.76; p = 0.006). Response rates did not differ between the two groups: 33.2 percent in the combination arm and 30.2 percent in the dacarbazine-alone group (p = 0.41). Grades 3 and 4 adverse events occurred in 56.3 percent of the patients treated with ipilimumab and dacarbazine versus 27.5 percent treated with dacarbazine and placebo (p < 0.001). The most commonly reported toxicity in the ipilimumab and dacarbazine group was diarrhea (36.4 percent overall, 4 percent grade 3), rash (29.6 percent overall, 1.2 percent grade 3), increase in alanine aminotransferase or aspartate aminotransferase (62.4 percent overall, 30.8 percent grade 3 and 9.3 percent grade 4) and colitis (4.5 percent overall, 1.6 percent grade 3 and 0.4 percent grade 4). No drug-related deaths or gastrointestinal perforations occurred in the ipilimumab-dacarbazine treated patients.

**Conclusion:** Ipilimumab dosed at 10 mg/kg in combination with dacarbazine improved OS when compared with dacarbazine alone in patients with previously untreated metastatic melanoma. Types of adverse events were consistent with prior studies, except for the rates of elevated liver function tests, which were higher, and rates of gastrointestinal events, which were lower.

**Managed Care Implications:** The higher response rates reported with higher doses of ipilimumab (3 mg/kg versus 10 mg/kg) may lead to a change to a higher dosage. Combination therapy with other drugs with different mechanisms of action will continue to evolve for the treatment of metastatic melanoma in both the untreated and relapsed/refractory patient.

**Title:** BEAM: a randomized phase 2 study evaluating the activity of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced melanoma.

**Authors:** Kim K.B., Sosman J.A., Freuhauf J.P., et al.


**Purpose:** Metastatic melanoma causes more than 8,600 deaths annually in the U.S. Currently, dacarbazine (DTIC-Dome), high-dose interleukin-2 (Proleukin) and ipilimumab (Yervoy) are approved for stage IV disease. Phase 3 studies with dacarbazine have shown a median PFS of 1.5 to 1.6 months and an OS ranging from 5.6 to 7.8 months. Treatment with carboplatin (Paraplatin) plus paclitaxel (Taxol) and ipilimumab have reported median OS of 9.8 and 10.0 months, respectively. Despite this improvement, the prognosis for these patients remains grim, and additional, more effective therapies are needed. Malignant melanoma is a highly vascular tumor in which vascular endothelial growth factor (VEGF) is strongly expressed. Increased levels of VEGF are correlated with a worse prognosis. Bevacizumab (Avastin)
is a monoclonal antibody that selectively binds to VEGF and blocks receptor binding. This phase 2 study will evaluate the effectiveness of the three-drug combination — carboplatin, paclitaxel and bevacizumab — in patients with previously untreated malignant melanoma.

Methods: Patients with histologically confirmed stage IV malignant melanoma who had not received any systemic therapy were eligible. Additional eligibility criteria included age 18 and older, an ECOG performance status of 0 or 1 and adequate end-organ function. In this multicenter randomized double-blind placebo-controlled trial, patients were assigned in a 2:1 ratio to receive either carboplatin, paclitaxel and bevacizumab or carboplatin, paclitaxel and placebo. Patients were stratified by ECOG performance status (0 or 1) and disease stage (IV M1a/b or IV M1c).

Patients received bevacizumab 15 mg/kg or placebo with carboplatin (AUC = 5) and paclitaxel (175 mg/m²), all intravenously on an every-three-week cycle. Bevacizumab or placebo was continued until disease progression, unacceptable toxicity or patient withdrawal. Due to the increased risk of hypersensitivity, carboplatin administration was capped at 10 cycles. Paclitaxel alone could be continued with bevacizumab or placebo after the carboplatin was discontinued. The primary endpoint of the study was PFS. Secondary endpoints included OS, ORR, OS at six months, PFS at 24 weeks and safety.

Results: A total of 214 patients were randomized, 71 to the carboplatin, paclitaxel and placebo (CP) arm, of which 69 received therapy, and 143 to the carboplatin, paclitaxel and bevacizumab (CPB) arm. The median number of treatment cycles was six for the CPB arm and five for the CP arm. With a median follow-up of 13 months, the median PFS was 4.2 months in the CP arm and 5.6 months in the CPB arm (HR 0.78; p = 0.1414). The ORR was 16.4 percent versus 25.5 percent, respectively (p = 0.1577). Complete response was observed for one patient (1.5 percent) in the CP arm and three (2.1 percent) in the CPB arm. The median OS was 8.6 months in the CP group compared with 12.3 months in the CPB group (HR 0.67; p = 0.0366). The OS four months later was 9.2 months versus 12.3 months, respectively (HR 0.79; p = 0.1916). The median duration of response was shorter in the CPB arm compared with the CP arm (6.9 months versus 7.7 months). The six-month OS rates were 74.6 percent for the CP arm and 78.2 percent for the CPB arm, a difference that was not statistically significant. The incidence of grade 3 to 5 adverse reactions was higher in those patients treated with CPB (57.4 percent versus 44.9 percent). In the CPB arm, the most common grade 3 or higher events included neutropenia (23.8 percent with 4.9 percent fever, versus 18.8 percent with 1.4 percent fever), peripheral neuropathy (9.1 percent versus 0.0 percent), arterial thromboembolic events (2.1 percent versus 1.4 percent) and hypertension (3.5 percent versus 0.0 percent).

Conclusion: The study did not meet the primary objective of a statistically significant improvement in PFS with the addition of bevacizumab to carboplatin and paclitaxel. A larger phase 3 trial will be needed to assess its potential benefits.

Managed Care Implications: Even though malignant melanoma is a highly vascular tumor in which VEGF is strongly expressed, the addition of bevacizumab to carboplatin and paclitaxel does not improve PFS or OS in this patient population. Combining bevacizumab with other drugs with known efficacy in this disease state may be another avenue of research to follow.

Title: Randomized phase 2 trial of sorafenib with temsirolimus or tipifarnib in untreated metastatic melanoma.


Purpose: The most common oncogenic mutations in patients with cutaneous melanoma are BRAF V600E substitutions (approximately 50 percent), resulting in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway. There is also loss of expression of the
Methods: Eligible patients were required to have biopsy-proven melanoma of cutaneous, mucosal or unknown primary origin with measurable metastatic disease and no central nervous system involvement. No prior therapy for metastatic disease was permitted, but prior adjuvant therapy was permitted if relapse occurred at least 90 days after the last therapy. Patients were also required to have adequate end-organ function and a Zubrod performance status of 0 or 1. Arm A received oral sorafenib 200 mg twice a day and temsirolimus 25 mg intravenously weekly. Arm B received oral sorafenib 400 mg every morning and 200 mg every evening and oral tipifarnib 100 mg twice daily for three of every four weeks. The trial design provided for accrual sufficient to test each regimen separately in comparable patients, using a two-stage design for each treatment cohort to screen for activity and ultimately select the combination with the most favorable therapeutic index for further study. The primary objectives were to evaluate PFS, ORR and safety.

Results: A total of 102 patients were treated in the study, of which 63 were enrolled to receive sorafenib and temsirolimus (arm A). After the first stage of accrual was completed, the sorafenib plus tipifarnib arm (arm B, 39 evaluable patients) did not show sufficient activity to open the second stage of accrual. Thus, the second stage of accrual to arm A was no longer randomized. Arm A had three confirmed partial responses (PR) for an ORR of 5 percent (95 percent CI, 1-13 percent). The duration of the three confirmed PRs was four, nine and 13 months. In arm B, one confirmed PR was documented out of the 39 patients for an ORR of 3 percent (95 percent CI, 0-13 percent). The estimated PFS on arm A was 2.1 months (95 percent CI, 1.9-3.3 months), the four-month estimate was 29 percent (95 percent CI, 19-41 percent) and the six-month estimate was 18 percent (95 percent CI, 10-29 percent). In arm B, the estimated median PFS was 1.8 months (95 percent CI, 1.7-1.9 months), the four-month estimate was 18 percent (95 percent CI, 8-31 percent) and the six-month estimate was 5 percent (95 percent CI, 1-15 percent). There were two treatment-related deaths in arm A (sorafenib plus temsirolimus), one due to pneumonitis and the other due to pancreatitis. An additional four patients experienced grade 4 toxicity, including hypokalemia, hypophosphatemia, left ventricular dysfunction and a severe infusion reaction. There was only one grade 4 adverse event recorded in arm B (sorafenib and tipifarnib), that being an elevation in amylase and lipase. Less serious adverse events in arm A included anemia, thrombocytopenia, hypotension, diarrhea, rash and an increase in liver function tests. In arm B, the most common side effects were rash, mucositis, diarrhea and an increase in liver function tests.

Conclusion: The combination of molecularly targeted agents tested did not show sufficient activity to warrant further investigation.

Managed Care Implications: Targeted therapy is becoming more common in the treatment of malignant disease. As additional pathways are identified, new drugs will be developed and potentially have activity in malignant melanoma.

Title: Dabrafenib in patients with melanoma, untreated brain metastases and other solid tumors: a phase 1 dose-escalation trial.


Purpose: Oncogenic mutations that cause activation of BRAF occur in many tumor types, including cutaneous melanoma (50 percent of cases), papillary thyroid cancer (46 percent), borderline ovarian tumors (34 percent), biliary tract cancer (11 percent) and non-small cell lung cancer (2 percent). Mutated BRAF correlates with poor prognosis in the majority of these malignancies. The median OS for patients with malignant melanoma is poor at only
nine to 11 months. It is even shorter, four to five months, in patients with melanoma and brain metastases. Systemic treatments are not highly effective in this group of patients, with a response to therapy noted in 10 percent or less. Dabrafenib is a potent ATP-competitive inhibitor of BRAF kinase. This study was designed to establish a phase 2 dose for the drug in patients with BRAF-mutant cancers, including a cohort with melanoma and untreated, asymptomatic brain metastases.

Methods: Eligible patients had a histologically confirmed diagnosis of a solid tumor for which no curative treatment was available, were 18 and older, had an ECOG performance status of 0 or 1 and had adequate end-organ function. Presence of a BRAF mutation was initially optional, but later mandatory, due to the absence of activity in three patients with BRAF-wild-type tumors. Patients were divided into one of three groups: those with metastatic melanoma; those with asymptomatic, untreated melanoma brain metastases; and those with nonmelanoma solid tumors. Patients with melanoma and brain metastases were required to have lesions 3 mm or more in diameter and no previous surgical resection, stereotactic radiosurgery or whole-brain radiation. Dabrafenib was started at a dose of 12 mg orally administered daily in a 21-day cycle. After each dose was established, cohorts were expanded to include up to 20 patients. The primary objective of the trial was to establish safety and tolerability of the drug. Secondary objectives included tumor response as well as pharmacokinetic and pharmacodynamic profiles. For tumor response, baseline radiological assessment was done within 35 days of initiating treatment. Initial restaging occurred at nine weeks in the escalation cohort and at six weeks in the expansion cohort.

Results: One hundred and eighty-four patients were enrolled. One hundred and fifty-six had melanoma, of which 153 had a BRAF mutation. A total of 10 patients had melanoma with untreated, asymptomatic brain metastases. At all doses, the most common grade 2 or higher adverse events were cutaneous squamous cell carcinoma (11 percent), fatigue (8 percent) and pyrexia (6 percent). The dose of dabrafenib was increased to 300 mg orally twice a day without reaching the maximum tolerated dose. No adverse events worse than grade 2 were seen in 140 (76 percent) of all patients treated. A dose of 150 mg twice a day was chosen for the phase 2 study. At the recommended phase 2 dose, 25 of 36 patients (69 percent; 95 percent CI, 51.9-83.7) with a Val600 BRAF-mutant melanoma had a partial or complete response to treatment with 18 (50 percent; 95 percent CI, 32.9-67.1) having a confirmed response. An additional 21 of 27 patients (78 percent; 95 percent CI, 57.7-91.4) with a Val600Glu BRAF-mutant melanoma responded and 15 (56 percent; 95 percent CI, 35.3-74.7) had a confirmed response. Those patients with the Val600 BRAF mutations had durable responses with 17 patients (47 percent) on treatment for more than six months. Nine of 10 patients (90 percent) with melanoma and untreated brain metastases had a reduction in the size of their brain lesions. For patients with other solid tumors, responses were also noted. In patients with BRAF-mutant papillary thyroid cancer, three of nine (33 percent) patients achieved a partial response, as did the lone patient with BRAF-mutant non-small cell lung cancer. Stable disease was noted in patients with BRAF-mutant gastrointestinal stromal disease and ovarian cancer.

Conclusion: Dabrafenib is safe in patients with solid tumors and an active inhibitor of Val600-mutant BRAF with responses noted in patients with melanoma, brain metastases and other solid tumors.

Managed Care Implications: Dabrafenib shows activity in a number of disease states, even in this phase 1 study. Its ability to cross the blood-brain barrier and treat brain metastases, as well as being oral, makes it an interesting molecule for further study.
This resource guide features links and websites on melanoma that may be of use to the reader in daily practice.*

American Cancer Society (ACS). The ACS is a national, community-based volunteer health organization that offers programs for education, patient service, advocacy and rehabilitation. This detailed guide provides information on risk factors, diagnosis, staging and treatment of melanoma. www.cancer.org/cancer/skincancer-melanoma/index

American Society of Clinical Oncology (ASCO). This nonprofit organization is committed to improving cancer care and prevention, advancing the education of those caring for cancer patients and supporting cancer research. The website offers clinical practice guidelines, clinical tools and other resources for treating melanoma. http://melanoma.jco.org

Cancer.Net. This website from the ASCO provides peer-reviewed information on melanoma, including clinical trials, staging, treatment and current research. www.cancer.net/cancer-types/melanoma

eMedicineHealth. Owned and operated by WebMD, this consumer health information website contains health and medical articles written by physicians, including information on melanoma. www.emedicinehealth.com/melanoma/article_em.htm

Mayo Clinic. The largest integrated not-for-profit practice group in the world, the Mayo Clinic uses its vast physician expertise to provide information and resources to help consumers manage their health. This website has a section devoted to melanoma. www.mayoclinic.com/health/melanoma/DS00439


National Cancer Institute (NCI). The NCI, part of the U.S. National Institutes of Health, conducts and supports cancer-related research, training and health information dissemination. This online guide provides information on treatment, screening, testing and clinical trials, plus links to published literature and research on melanoma. www.cancer.gov/cancertopics/types/melanoma

National Comprehensive Cancer Network (NCCN). The NCCN publishes clinical practice guidelines that are developed through an evidence-based process, including the current practice guidelines for melanoma. Users must register to access guidelines. www.nccn.org/professionals/physician_gls/f_guidelines.asp#melanoma

OncoLink. OncoLink’s mission is to provide patients, health care professionals and the public with accurate cancer-related information. Started by University of Pennsylvania cancer specialists in 1994, this website provides information on treatment options, clinical trials and other resources for melanoma. www.oncolink.org/types/article.cfm?c=18&s=63&ss=497&id=8600

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ICORE, a Magellan Health Services company, is redefining how health care payors manage specialty pharmaceuticals for complex conditions to ensure clinical excellence, while minimizing costs in one of the fastest growing areas of health care spending.

We draw upon our comprehensive suite of services to deliver solutions that yield powerful results. They include:

- Formulary Management
- Medical Pharmacy Solutions
- Specialty Pharmacy Dispensing

For more specialty pharmacy insights, go to ICOREhealthcare.com or snap the QR code with your smart phone.