Diagnosis, Prognostic Factors and Treatment Considerations for Prostate Cancer

Practice Excellence with a CPOE

A Managed Care Perspective on Prostate Cancer

Investigational Agents for Prostate Cancer
A KEY TARGET IN ANDROGEN SIGNALING IN ADVANCED PROSTATE CANCER

While the focus has been on reducing androgens, androgen receptor (AR) signaling inhibition may be an important approach in controlling advanced prostate cancer. Activation of the AR leads to nuclear translocation and binding to DNA, with subsequent effects that promote tumor growth and progression.

Despite low or even undetectable levels of androgens, AR signaling remains active and continues to drive disease.

Potent AR signaling inhibition may be an important approach to control advanced prostate cancer.

References:

HAVE WE BEEN GETTING ONLY HALF THE STORY?
While the focus has been on reducing androgens, androgen receptor (AR) signaling inhibition may be an important approach in controlling advanced prostate cancer.1,2

- AR signaling is a key driver of disease in advanced prostate cancer (APC). Activation of the AR leads to nuclear translocation and binding to DNA, with subsequent effects that promote tumor growth and progression.2,3

- Despite low or even undetectable levels of androgens, AR signaling remains active and continues to drive disease.2

Potent AR signaling inhibition may be an important approach to control advanced prostate cancer.2

Get the other half of the story at www.TargetAR.com

features

9 Industry Thought Leaders
A Discussion with Patrick Gill and William Noorigian of Horizon Blue Cross Blue Shield of New Jersey
ManagedCare Oncology recently sat down with Patrick Gill, Pharm.D., and William Noorigian, Pharm.D., of Horizon Blue Cross Blue Shield of New Jersey for a unique perspective on their plan’s outlook and current initiatives for managing quality and cost of care in oncology.

14 Letter to the Editor
Economic Evaluations of Bortezomib-Based Regimens in Relapsed and Previously Untreated Multiple Myeloma Compared with Other Approved Therapies
by Si-Tien Wang, M.Sc.; Kristina Chen, Pharm.D., M.S.; Mei Sheng Duh, M.P.H., Sc.D.; Hui Huang, Ph.D., M.B.A.; Abbie Ba-Mancini, B.S., M.B.A.; and Deyanira Corzo, M.D.

18 Improving Value
Moving to Practice Excellence with a CPOE
by Michele Feehily, director of professional services, IntrinsiQ, an AmerisourceBergen Specialty Group company
This paper discusses how oncology practice leaders can accelerate the adoption and benefit of a CPOE system with a step-by-step approach — and ultimately, use the implementation as a catalyst to improve the overall standard of care and clinical workflow.

24 Drug Therapy Reviews
A Managed Care Perspective on the Diagnosis, Evaluation and Treatment of Prostate Cancer
by Tanya Dorff, M.D., assistant professor of clinical medicine, University of Southern California Norris Comprehensive Cancer Center
As the most frequently diagnosed cancer in men and the second-leading cause of male cancer deaths, prostate cancer remains a high priority in managed care oncology.

3 Calendar of Events
Dates and locations of upcoming meetings, workshops and conferences of interest to managed care oncology professionals.

4 Correspondence
by Kjel A. Johnson, Pharm.D., publisher, ManagedCare Oncology

5 Facts & Figures
Data and accompanying graphics regarding prostate cancer.

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Investigational Agents for Prostate Cancer
by Howard “Skip” Burris, M.D., director of drug development, Sarah Cannon Research Institute

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Prostate Cancer: Not Just Your Grandfather’s Disease
by Denise K. Pierce, president, DK Pierce & Associates, Inc.
This article demonstrates the breadth of impact that prostate cancer has and how this has changed perspectives for employers and payors.

39 Drug & Administration Compendia
Coding, reimbursement and available therapies in the treatment of prostate cancer.

47 Clinical Trial Update
by John W. Mucenski, B.S., Pharm.D., director of pharmacy operations, UPMC Cancer Centers
A review of recent clinical trials in the treatment of prostate cancer, including the methods, results, conclusions and managed care implications of each trial reviewed.

54 Resources & References
A comprehensive list of prostate cancer sources relevant to managed care oncology professionals.
Tell us what you think about *ManagedCare Oncology* and ICORE Healthcare's *Medical Pharmacy and Oncology Trend Report™*. Your feedback will help us improve both publications. Please complete this survey and return it by May 31, 2012. In return, we'll send you a $5 Starbucks gift card.

### ManagedCare Oncology

1. What is your overall opinion of *ManagedCare Oncology*?
   - [ ] Very Positive
   - [ ] Positive
   - [ ] Negative
   - [ ] Very Negative

2. How valuable did you find the information in each of the 2011 *ManagedCare Oncology* journals?
   - [ ] Colon Cancer (Q1 2011)
   - [ ] Lung Cancer (Q2 2011)
   - [ ] Multiple Myeloma (Q3 2011)
   - [ ] Lymphoma (Q4 2011)

3. How valuable do you find each of the following features?
   - [ ] Advertisements
   - [ ] Calendar of Events
   - [ ] Clinical Trial Update
   - [ ] Drug & Administration Compendia
   - [ ] Drug Therapy Reviews
   - [ ] Facts & Figures
   - [ ] Improving Value
   - [ ] Industry Thought Leaders
   - [ ] Pipeline Report
   - [ ] Regulatory & Reimbursement
   - [ ] Resources & References

4. How important will each of the following be to you as a source of information on chemotherapy trends in 2012?
   - [ ] Printed journals
   - [ ] Electronic journals or e-newsletters
   - [ ] Websites
   - [ ] Mailings from professional associations
   - [ ] Pharmaceutical company representatives

5. What topics would you like to see addressed more, or added to, *ManagedCare Oncology*?

6. What do you do with *ManagedCare Oncology* after reading it?
   - [ ] Keep it for reference.
   - [ ] Pass it along to another person.
   - [ ] Discard or recycle it.

### Medical Pharmacy and Oncology Trend Report

7. What is your overall opinion of the *Trend Report*?
   - [ ] Very Positive
   - [ ] Positive
   - [ ] Negative
   - [ ] Very Negative

8. What is the main reason you give this rating?

9. Overall, do you find the information in the *Trend Report* to be:
   - [ ] Very Useful
   - [ ] Somewhat Useful
   - [ ] Not too Useful
   - [ ] Not Useful at All

10. Would you purchase additional trend data, if made available via the web?
    - [ ] Yes
    - [ ] No
    - [ ] Not sure (why?)

11. What statistics, topics, facts or other improvements would you like to see in next year's report?

12. What statistics, topics, facts or other information should be removed from the report (if any)?

13. What do you do with the *Trend Report* after reading it?
    - [ ] Keep it for reference.
    - [ ] Pass it along to another person.
    - [ ] Discard or recycle it.

14. Do you prefer to receive the *Trend Report* as a:
    - [ ] Printed copy
    - [ ] Electronic copy
    - [ ] Both

### Professional Role

15. Which position or type of organization most closely matches your role?
    - [ ] Consultant
    - [ ] Health plan management
    - [ ] Oncologist
    - [ ] Pharmaceutical company
    - [ ] Practice or office manager
    - [ ] Other, please specify
Your opinions about ManagedCare Oncology are essential to our planning. Return this survey, and you will receive a $5 Starbucks gift card. Simply complete the survey, detach, fold, seal and mail. NO POSTAGE IS REQUIRED. We’ll use your responses to plan future issues of the journal.

Name

Address

City  State  ZIP

Telephone

Email
The list of events that follows provides the dates and locations of upcoming meetings, workshops and conferences of interest to managed care oncology professionals.

April
18-20 Academy of Managed Care Pharmacy's 24th Annual Meeting and Expo
San Francisco, California

May
1-4 8th Annual Armada Specialty Pharmacy Summit
Las Vegas, Nevada
15-17 Pinsonault’s Managed Care Account Management Training
Bonita Springs, Florida

June
1-5 American Society of Clinical Oncology’s Annual Meeting
Chicago, Illinois
20-22 America’s Health Insurance Plans’ Institute 2012
Salt Lake City, Utah
Last week, I had the opportunity to present at a specialty drug program during the Pharmacy Benefit Management Institute’s 2012 Drug Benefit Conference in Phoenix. My colleagues were keenly focused on evaluating the most appropriate benefit design for specialty products and in particular for medical injectables used for oncology and rheumatology, since no clear guidelines exist on what designs strike the balance between incentives for using cost-effective therapies and appropriate levels of demand — also known as compliance.

In ICORE Healthcare’s 2011 Medical Pharmacy & Oncology Trend Report™, we showed that for provider-administered injectable products (those paid under the medical benefit), the average copay has drifted modestly over the past three years from $43 to $46 to $64, resulting in about a 50 percent increase.1 Coinsurances, on the other hand, have averaged 17 percent, 20 percent and 22 percent over the same period, for a 30 percent increase in the same period. While at first glance the coinsurance increase seems to trend less quickly, a fast study proves that the impact to member contribution can be tremendous. In a study published a few years ago, my colleague Pat Gleason found that “abandonment rate,” which he defined as the reversal of an adjudicated claim with no evidence of a subsequent adjudicated claim in the following 90 days, was just 6 percent in members who pay less than $100 — basically the copay for the average provider-administered injectable used for cancer care according to our Trend Report.2 However, the abandonment rate rose to 26 percent for those members who paid a coinsurance consistent with what the average payor has implemented — that 22 percent coinsurance, or approximately $500 per claim. Wow — we may be doing a lot more harm than good with our most recent benefit designs.

What’s a plan to do? Take a look at some of the references below and understand that more than $150 in member out-of-pocket expenses per claim and more than approximately $2,500 annually will lower the likelihood our patients actually take the lifesaving drugs that have been prescribed.3,4 We are studying the 2013 payor benefit designs now, and I sure hope this increase in coinsurances is stemmed.

Here is to spring coming around the corner. I look forward to seeing you soon.

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

References
1. ICORE Healthcare’s 2011 Medical Pharmacy & Oncology Trend Report™
In every issue, Facts & Figures provides snapshots of information key to managed care oncology professionals. This installment features data regarding prostate cancer. We hope you find these facts and figures of value as you review your own health plan data.

ICORE Healthcare analyzed paid medical claims for calendar year 2010 with a prostate cancer diagnosis (Primary ICD-9 Diagnosis Code 185). The following table illustrates these claims across Medicare and commercial lines of business (LOBs), with an average of $9.8 million in allowed drug claims per 1 million member lives for those with a prostate cancer diagnosis code. However, consistent with the average age at the time of diagnosis of 67 years, these allowed dollars are heavily weighted toward the Medicare LOB at $18.3 million versus only $1.3 million in the commercial line.

**Medical Claims for Diagnosis Code 185 per 1M Lives — Line of Business (LOB) View**

<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>Medicare</td>
<td>$18,370,095.01</td>
<td>393,150</td>
<td>24,568</td>
<td>7,369</td>
</tr>
<tr>
<td>Commercial</td>
<td>$1,332,405.35</td>
<td>32,530</td>
<td>1,353</td>
<td>524</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>$19,702,500.36</strong></td>
<td><strong>425,680</strong></td>
<td><strong>25,921</strong></td>
<td><strong>7,893</strong></td>
</tr>
</tbody>
</table>

**Notes:**
1. Population includes eight commercial plans, one Medicaid plan, six Medicare plans, total eight plans
2. Data calendar year 2010
3. Based on primary diagnosis of 185
4. Outliers excluded
5. All LOB included

Using the same claims data, ICORE 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 this setting tends to be one of the more economical sites of care for all stakeholders.

**Medical Claims for Diagnosis Code 185 per 1M Lives — Site of Service (SOS) View**

<table>
<thead>
<tr>
<th>SOS</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>
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</thead>
<tbody>
<tr>
<td>Physician</td>
<td>$12,743,526.37</td>
<td>319,281</td>
<td>22,138</td>
<td>6,255</td>
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<tr>
<td>HI/Specialty pharmacy providers</td>
<td>$5,163,710.70</td>
<td>19,216</td>
<td>1,821</td>
<td>733</td>
</tr>
<tr>
<td>Hospital</td>
<td>$1,627,076.42</td>
<td>64,286</td>
<td>1,442</td>
<td>436</td>
</tr>
<tr>
<td>Other</td>
<td>$168,186.87</td>
<td>22,897</td>
<td>520</td>
<td>470</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>$19,702,500.36</strong></td>
<td><strong>425,680</strong></td>
<td><strong>25,921</strong></td>
<td><strong>7,894</strong></td>
</tr>
</tbody>
</table>

**Notes:**
1. Data calendar year 2010
2. Based on primary diagnosis of 185
3. Outliers excluded
4. All LOB included
Of the top 10 drugs on these prostate cancer claims, agents classified as androgen deprivation therapy (ADT) were the most common, followed by supportive care agents (i.e., erythropoietin-stimulating agents [ESAs], colony-stimulating factors [CSFs] and antiemetics). Chemotherapy agents appeared twice in the top 10, including Taxotere as the second most highly utilized drug in prostate cancer. Zometa, which is employed to treat bone damage from metastatic disease, was the third most highly utilized therapy.

### Prostate Cancer Drug Spend — Average Allowed Claims per 1M Lives for Diagnosis Code 185

<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>Eligard</td>
<td>$9,827,673.33</td>
<td>29,832</td>
<td>8,639</td>
<td>3,760</td>
</tr>
<tr>
<td>Taxotere</td>
<td>$3,750,542.46</td>
<td>200,778</td>
<td>1,400</td>
<td>299</td>
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<tr>
<td>Zometa</td>
<td>$1,618,743.95</td>
<td>7,106</td>
<td>2,000</td>
<td>416</td>
</tr>
<tr>
<td>Neulasta</td>
<td>$1,067,042.96</td>
<td>403</td>
<td>386</td>
<td>88</td>
</tr>
<tr>
<td>Unclassified</td>
<td>$812,741.41</td>
<td>1,271</td>
<td>228</td>
<td>93</td>
</tr>
<tr>
<td>Trelstar depot</td>
<td>$599,477.52</td>
<td>2,449</td>
<td>961</td>
<td>507</td>
</tr>
<tr>
<td>Zoladex</td>
<td>$571,996.26</td>
<td>1,854</td>
<td>645</td>
<td>262</td>
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<tr>
<td>Vantas</td>
<td>$367,171.73</td>
<td>121</td>
<td>140</td>
<td>121</td>
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<tr>
<td>Procrit</td>
<td>$223,869.03</td>
<td>22,754</td>
<td>519</td>
<td>61</td>
</tr>
<tr>
<td>Novantrone</td>
<td>$166,114.36</td>
<td>1,073</td>
<td>161</td>
<td>22</td>
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<tr>
<td>Aloxi</td>
<td>$129,550.17</td>
<td>6,903</td>
<td>790</td>
<td>130</td>
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<tr>
<td>Neupogen</td>
<td>$99,069.49</td>
<td>312</td>
<td>312</td>
<td>48</td>
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<tr>
<td>Firmagon</td>
<td>$80,561.22</td>
<td>23,102</td>
<td>214</td>
<td>58</td>
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<tr>
<td>Aranesp</td>
<td>$47,659.86</td>
<td>15,301</td>
<td>83</td>
<td>14</td>
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<tr>
<td>Avastin</td>
<td>$36,780.56</td>
<td>599</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td>Dacogen</td>
<td>$30,239.64</td>
<td>999</td>
<td>20</td>
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<tr>
<td>Abraxane</td>
<td>$20,041.95</td>
<td>2,137</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Lupron implant</td>
<td>$17,644.98</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Gemzar</td>
<td>$17,503.08</td>
<td>111</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Low osmolar contrast material</td>
<td>$15,352.51</td>
<td>28,521</td>
<td>267</td>
<td>249</td>
</tr>
<tr>
<td>Aredia</td>
<td>$13,394.64</td>
<td>720</td>
<td>298</td>
<td>44</td>
</tr>
<tr>
<td>Leukine</td>
<td>$10,825.09</td>
<td>418</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Anzemet</td>
<td>$9,878.56</td>
<td>2,301</td>
<td>209</td>
<td>45</td>
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<tr>
<td>Taxol</td>
<td>$9,629.13</td>
<td>589</td>
<td>73</td>
<td>11</td>
</tr>
<tr>
<td>Theracys</td>
<td>$8,726.19</td>
<td>68</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>Navelbine</td>
<td>$7,706.34</td>
<td>735</td>
<td>253</td>
<td>31</td>
</tr>
<tr>
<td>Orthovisc</td>
<td>$7,571.82</td>
<td>32</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Velcade</td>
<td>$7,436.62</td>
<td>187</td>
<td>11</td>
<td>11</td>
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<tr>
<td>Reclast</td>
<td>$6,747.53</td>
<td>29</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Carboplatin</td>
<td>$5,138.48</td>
<td>605</td>
<td>139</td>
<td>18</td>
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<tr>
<td>Heparin</td>
<td>$5,032.66</td>
<td>27,111</td>
<td>748</td>
<td>116</td>
</tr>
<tr>
<td>Aristra</td>
<td>$3,426.62</td>
<td>549</td>
<td>44</td>
<td>4</td>
</tr>
</tbody>
</table>
## Prostate Cancer Drug Spend

### Table: Drug Spend Details

<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>Kytril</td>
<td>$2,534.24</td>
<td>1,257</td>
<td>263</td>
<td>64</td>
</tr>
<tr>
<td>Zofran</td>
<td>$2,179.48</td>
<td>6,478</td>
<td>309</td>
<td>65</td>
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<tr>
<td>Dexamethasone sodium phosphate</td>
<td>$2,115.57</td>
<td>22,038</td>
<td>2,276</td>
<td>239</td>
</tr>
<tr>
<td>Feraheem</td>
<td>$2,050.46</td>
<td>2,358</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Lupron depot</td>
<td>$2,005.79</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Gammagard</td>
<td>$1,906.29</td>
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<td>1</td>
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<tr>
<td>Venofer</td>
<td>$1,699.27</td>
<td>3,892</td>
<td>14</td>
<td>6</td>
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<tr>
<td>Actives</td>
<td>$1,486.97</td>
<td>33</td>
<td>21</td>
<td>5</td>
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<td>Saline solution</td>
<td>$1,229.90</td>
<td>2,291</td>
<td>1,159</td>
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<tr>
<td>Cytoxan</td>
<td>$1,124.51</td>
<td>188</td>
<td>38</td>
<td>6</td>
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<tr>
<td>High osmolar contrast material</td>
<td>$972.10</td>
<td>4,230</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Adriamycin</td>
<td>$767.41</td>
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<td>GlucaGen</td>
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<td>Midazolam</td>
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<td>Benadryl</td>
<td>$584.07</td>
<td>704</td>
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<td>137</td>
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<td>Levaquin</td>
<td>$583.02</td>
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<td>Sublimaze</td>
<td>$482.01</td>
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<td>41</td>
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<td>Zantac</td>
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<td>Novarel</td>
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<td>157</td>
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<td>Ativan</td>
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<td>Leuprolide acetate</td>
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<td>Ketorolac tromethamine</td>
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<td>Rocephin</td>
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<td>26</td>
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<td>Cisplatin</td>
<td>$181.65</td>
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<td>Dextrose</td>
<td>$181.35</td>
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<td>139</td>
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<td>Lactated ringers</td>
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<tr>
<td>5-Flu</td>
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<td>32</td>
<td>5</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>$19,622,766.14</strong></td>
<td><strong>424,788</strong></td>
<td><strong>25,598</strong></td>
<td><strong>7,716</strong></td>
</tr>
</tbody>
</table>

### Notes:

1. Population includes eight commercial plans, one Medicaid plan, six Medicare plans, total eight plans
2. Data calendar year 2010
3. Based on primary diagnosis of 185
4. Outliers excluded
5. All LOB included
In looking at the top chemotherapy regimen (i.e., Taxotere) and injectable supportive care agents for prostate cancer, ICORE analyzed the drug and administration costs according to three different reimbursement schemes (i.e., Medicare, commercial ASP + 15 and commercial AWP - 15), as well as acquisition costs. The total cost of care for all these agents and their administration fees was highest according to the commercial AWP - 15 arrangement, followed by the commercial ASP + 15 arrangement. A similar pattern was observed in terms of patient out-of-pocket costs, which were lowest for Medicare beneficiaries and highest for those covered by a commercial plan employing AWP - 15.

 Costs Associated with the Top Chemotherapy Regimen and Supportive Care Agents for Prostate Cancer

<table>
<thead>
<tr>
<th></th>
<th>Medicare</th>
<th>Avg Commercial Plan (ASP + 15)</th>
<th>Avg Commercial Plan (AWP - 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost of care</td>
<td>$50,669.48</td>
<td>$54,777.99</td>
<td>$64,859.20</td>
</tr>
<tr>
<td>Drug costs</td>
<td>$18,302.70</td>
<td>$19,856.70</td>
<td>$21,546.00</td>
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<tr>
<td>Administration costs</td>
<td>$2,280.32</td>
<td>$2,280.32</td>
<td>$2,280.32</td>
</tr>
<tr>
<td>IV infusion &lt; one hour</td>
<td>$1,171.52</td>
<td>$1,171.52</td>
<td>$1,171.52</td>
</tr>
<tr>
<td>Support med. inj. ESA avg.</td>
<td>$369.60</td>
<td>$369.60</td>
<td>$369.60</td>
</tr>
<tr>
<td>Support med. inj. Aranesep</td>
<td>$184.80</td>
<td>$184.80</td>
<td>$184.80</td>
</tr>
<tr>
<td>Support med. inj. (Procrit)</td>
<td>$554.40</td>
<td>$554.40</td>
<td>$554.40</td>
</tr>
<tr>
<td>Support med. inj. CSF avg.</td>
<td>$554.40</td>
<td>$554.40</td>
<td>$554.40</td>
</tr>
<tr>
<td>Support med. inj. (Neulasta)</td>
<td>$184.80</td>
<td>$184.80</td>
<td>$184.80</td>
</tr>
<tr>
<td>Support med. inj. (Neupogen)</td>
<td>$924.00</td>
<td>$924.00</td>
<td>$924.00</td>
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<tr>
<td>Support med. inj. antiemetics avg.</td>
<td>$82.05</td>
<td>$89.01</td>
<td>$332.48</td>
</tr>
<tr>
<td>Support med. inj. (Zofran)</td>
<td>$24.58</td>
<td>$26.66</td>
<td>$130.56</td>
</tr>
<tr>
<td>Support med. inj. (Kytril)</td>
<td>$139.52</td>
<td>$151.37</td>
<td>$534.40</td>
</tr>
<tr>
<td>ESA costs (average)</td>
<td>$11,141.20</td>
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<td>$13,873.77</td>
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<tr>
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<td>CSF costs (average)</td>
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<tr>
<td>CSF costs (Neupogen)</td>
<td>$15,902.72</td>
<td>$17,252.95</td>
<td>$16,224.00</td>
</tr>
</tbody>
</table>

| Premeds                      |          |                                |                                |

| Antiemetics costs (average)  | $82.05    | $89.01                        | $332.48                        |
| Antiemetics costs (Zofran)   | $24.58    | $26.66                        | $130.56                        |
| Antiemetics costs (Kytril)   | $139.52   | $151.37                       | $534.40                        |

Patient out-of-pocket costs — in network | $10,269 | $11,956 | $13,972
Patient out-of-pocket costs — out of network | $10,269 | $18,933 | $21,958
Deductible — in network | $135 | $1,000 | $1,000
Deductible — out of network | $135 | $2,500 | $2,500
Member contribution in network | 20% | 20% | 20%
Member contribution out of network | 20% | 30% | 30%
As New Jersey’s oldest and largest health insurer, Horizon Blue Cross Blue Shield of New Jersey (BCBSNJ) serves more than 3.6 million members. In 2010, the company processed more than 57.6 million claims totaling more than $13 billion for its members. The company has more than 4,800 employees and is headquartered in Newark, with offices in Harrison, Wall Township, Mt. Laurel and West Trenton. ManagedCare Oncology recently sat down with Patrick Gill, Pharm.D., and William Noorigian, Pharm.D., of Horizon Blue Cross Blue Shield of New Jersey, for a unique perspective on their plan’s outlook and current initiatives for managing quality and cost of care in oncology.

**MCO:** When you think about managing oncology costs, what are your key goals from both a quality-of-care and cost perspective?

**Dr. Gill:** I think the primary focus is in prevention. We invest a lot of time and resources to encourage members to get their appropriate screenings, which in oncology means detecting the disease earlier and improving the chance of better outcomes. We all know it doesn’t always work that way though. Once the patient has a diagnosis and is prescribed treatment, our main focus is making sure the patient is getting the right kind of therapy. It’s really no different in oncology than anything else.
Dr. Noorigian: From a clinical perspective, it all centers on prescribing the right drug for the right patient. All the recent advancements in treatment, including a number of targeted drugs with accompanying genomic tests, definitely help the cause.

MCO: How does your team decide what treatments are targeted for management initiatives?

Dr. Gill: There are many layers to that decision. If there’s a genetic testing component, we will always include it for management. Any drug that has a wide range of uses that aren’t always recognized by compendia is also a potential candidate. With most drugs, our primary concern is that we don’t know exactly how a particular agent will affect a patient in the real world. In clinical trials, you’re dealing with a carefully selected population in a closely monitored environment, but there are a great deal more uncontrolled variables and patient circumstances in actual practice. In addition to these clinical and quality considerations, we’re also looking at the costs. If comparable therapies yield similar outcomes, but one is available at a lower cost, that’s always a factor.

As pharmacists, we’re the last line of defense against unforeseen outcomes. Our goal is to give providers the latitude to operate within an evidence-based framework while maintaining a watchful eye over how treatments unfold in a patient’s everyday life.

Dr. Noorigian: Specifically in oncology and the oncology market, we want to look at any kind of clinical trial data that are available and consider potential adverse events to make sure we have symptom management techniques and supportive care in place before we start using a particular therapy. That’s one specific area where you want to have tighter management interventions established.

MCO: What are the noteworthy quality and cost concerns for 2012?

Dr. Noorigian: I would definitely say — and this goes back to what I previously said — oral oncolytics and the availability of genetic testing for certain agents are an issue. With this more targeted approach, questions are naturally being raised because it’s a new technology. How is it going to be addressed and implemented?

Indications are also a concern. The status of individual agents — whether they be approved, revoked or included in the compendia — are in constant flux. Continual updates to labeling and consensus recommendations make it difficult to effectively manage the class.

Dr. Gill: From a quality standpoint, we’re seeing that things are getting more complicated. We have over 200 oncologists in our network, so treatment variability is definitely a health quality concern. If you pulled five oncologists into a room and asked them to recommend an appropriate course of therapy, you could conceivably have five different yet potentially “correct” answers.

There may not always be good comparative outcome data. This is important not only from a plan perspective but also from a physician and member perspective. And of course the pipeline impact cannot be understated in terms of cost concerns.

MCO: When investing in programs for preventing inappropriate off-label use of chemotherapy and chemotherapy support, what are the main clinical and implementation challenges?

Dr. Gill: The challenges start with medical policy development and the
research that goes into it, after which the new policy must be connected to the provider network through Web-based channels.

We also have a sort of “skunkworks” in-house to pilot our new initiatives. Through our subsidiary company, Horizon Healthcare Innovations, we have a team working on a pathways program, and they’re also considering an accountable care organization (ACO) model for oncology. Implementation challenges come first in that the medical claims systems have not been adapted to integrate important new initiatives. From a clinical perspective, we need more clinical oncology support to help steer collaborative discussions. To Dr. Noorigian’s point, the clinical side is evolving quickly, so it’s a challenge to stay current. Everyone is talking about pathways, and we have a pilot under way to evaluate the program and measure the results. Quality will obviously come first, but we’re also going to be looking at costs and getting feedback from participating providers. The biggest challenge in the industry is that there are multiple pathway programs out there from different organizations, so it’s going to be difficult to get everyone to agree on a single pathway, both clinically and operationally.

**MCO:** How have your providers responded to these and other management initiatives? What can be done to minimize any disruption that may occur from these initiatives?

**Dr. Gill:** Thus far, the providers have given positive feedback on the clinical pathways initiative. The feedback we get from our collaboration allows us to refine and advance our efforts.

**MCO:** What are some of the challenges your plan has experienced in implementing its clinical pathways program?

**Dr. Gill:** We’ve only enacted the clinical pathways initiative with a handful of practices and only in a pilot capacity. At this point, it’s been very transparent as a means of better understanding the merit of using this type of program. That aspect has helped significantly, but down the road, when both sides aren’t freely exchanging information, we may see some contention. Now we’re challenged with next steps: Do we test multiple pathways? Do we develop pathways with physicians in our network? How do we support physicians in using the pathways?

Early signs look encouraging, and it looks like we’re saving a modest amount of money, but these savings may become more pronounced over time. Still, even if the pathways initiatives end up being cost-neutral, they may be worthwhile if they allow us to deliver a higher level of quality care. Specifically, if pathways can help to improve the quality of treatment up front, that could lead to significantly better outcomes as well as help to curb some end-stage costs in the long run. If and when pathways become the norm, the challenge then becomes how practices differentiate themselves. If everyone is using the same treatment protocols, will offices turn to reporting outcomes to set themselves apart from the rest? This all remains to be seen.

**MCO:** What is the concern with site-of-service changes? How should payors measure site-of-service changes?

**Dr. Gill:** We prefer to see drugs administered in the physician’s office
because it’s a more convenient and cost-effective means of delivering care. Clearly, there will always be situations where patients need to be in the hospital to receive treatment. That said, when clinically appropriate, we believe patients are well served when receiving care in the company of their own physicians in the physician’s office setting.

**MCO:** Some cancer care is provided through home health care. In your experience with this distribution channel, what are the opportunities?

**Dr. Gill:** Home care is not fully realizing its potential. The main reason for this is that home health care agencies haven’t yet demonstrated a strong competency for the intensive management necessary in oncology. For the most part, chemotherapy is too complicated and/or risky for home infusion, and few companies in the industry have demonstrated the clinical prowess necessary to manage these types of agents. For this same reason, providers generally are not fully comfortable with sending their patients to home health agencies to receive treatment.

**MCO:** Many new treatments for cancer are oral products. Does this present a different management strategy than traditional injectables?

**Dr. Noorigian:** The genetic testing component available with some of these newer targeted oral therapies creates a unique opportunity for management. Beyond this, there’s a more robust level of management that you can apply with regard to utilization management on the pharmacy side, where these agents are covered. I think the biggest challenge with the oral oncolytics is that patients are being left on their own now. With injectables, you have guaranteed compliance; you can monitor the patient and keep a close eye on tolerability and potential toxicities. With the orals, this intensive level of provider oversight isn’t there, which means that compliance and side effects become the issues. In some cases, you have oral treatments without an IV counterpart and in some cases you have both: That’s where cost will come into play. While we may want an oral therapy, the physician may want an IV therapy for various reasons. Taking this into consideration, I think it’s important that providers aren’t penalized for choosing an oral agent.

Another challenge that comes into play with oral agents is how the drug should be supplied. With an injectable, you have a single infusion or a cycle, versus an oral given every day. This opens up a whole host of questions surrounding quantity limits.

**MCO:** Can you comment on how benefits are changing as a tool to manage injectable costs?
Dr. Gill: In our market, thus far we have not seen changes in benefit designs specific to oncology.

MCO: How do you view the movement to consumer-directed health plans and the role this trend will play in the injectable management? Have you seen any examples with your membership today?

Dr. Gill: It’s interesting, but what we normally see is that patients who select this option tend to be healthy with low utilization and low costs.

MCO: If you could fix one thing to improve your ability to manage oncology costs, what would you want to change?

Dr. Gill: The most difficult part of managing oncology costs stems from the very nature of cancer as a disease: You have a patient who’s very sick with an often dire outlook and a physician who wants to do anything he or she can to help that patient. At one point, there’s nothing left to do and the prospect of ceasing treatment must be discussed. It’s extremely difficult for a health plan to insert itself into this conversation without seeming insensitive, so some means of approaching end-of-life care would be valuable. Clinical pathways may provide a potential solution, but only if end-of-life care is a consideration built into the design of the program.

MCO: Speaking to that point, studies have shown that approximately one-third of patients with cancer receive chemotherapy in the last several weeks of their life. So what is the best strategic approach to optimizing the use of hospice?

Dr. Gill: Clinical pathways programs may offer some sort of assistance, but only if the pathways actually contemplate end-of-life care. Most often, these programs are focused on the right course of treatment but not necessarily the point at which to initiate hospice discussions. If you’re incenting physicians to move patients into hospice, it suggests that you’re incenting them to end their care of patients. It would be nice if there was some kind of guideline from the American Society of Clinical Oncology or the National Comprehensive Cancer Network advising when to have these discussions. A neutral third party directing hospice care would certainly be advantageous from a payor perspective.

MCO: There has been a lot of discussion in the past regarding reimbursement strategies for oncologists and other providers who administer injectable drugs. What is the next horizon for payors who wish to optimize the use of high-quality, cost-efficient chemotherapy?

Dr. Gill: I think it all comes down to making sure that reimbursement is reasonable for both parties. It has to be adequate enough for the provider to acquire the drug and pay their bills. Something on the cusp between a pathway program and an ACO model would be ideal. The consolidation of practices in alignment with hospitals is evidence of the reimbursement pressures that physicians are experiencing right now. More than ever, we need to work collaboratively with these practices and really see where each other is coming from.
Economic Evaluations of Bortezomib-Based Regimens in Relapsed and Previously Untreated Multiple Myeloma Compared With Other Approved Therapies


by Si-Tien Wang,1 M.Sc.; Kristina Chen,1 Pharm.D., M.S.; Mei Sheng Duh,1 M.P.H., Sc.D.; Hui Huang,2 Ph.D., M.B.A.; Abbie Ba-Mancini,2 B.S., M.B.A.; and Deyanira Corzo,2 M.D.

AFFILIATIONS:
1. Analysis Group, Inc., Boston, Mass., USA
2. Millennium Pharmaceuticals, Inc., Cambridge, Mass., USA

In the Quarter 3, 2011, issue of ManagedCare Oncology, Dr. Gary Owens discussed the important issue of assessing the value of multiple myeloma (MM) therapies.1 We thank Dr. Owens for addressing this topic and agree that high-quality economic assessments are required to inform payors of the cost-effectiveness of the different treatment options available. We would like to offer comments on the issues raised by Dr. Owens.

Our response addresses two distinct aspects of Dr. Owens’ article:

1. We focus on the methodology of the health economic analyses critiqued by Dr. Owens to explain the study design rationale with regard to accounting for differences in patient populations and follow-up lengths. Selecting an appropriate time period to evaluate health economic outcomes is critical. A 20-year lifetime horizon is more clinically meaningful versus a one-year time period. Additionally, it is essential to base assumptions on the treatment protocol to reflect the real-world clinical practice setting. For example, bortezomib is dosed for a finite time period compared with lenalidomide, which is given until disease progression. These differences have significant clinical relevance and are important considerations in the model design. Using too short a time period will incorrectly minimize overall plan expenses and lead to incorrect conclusions regarding total costs.

2. We address Dr. Owens’ statements about the specific assumptions made in the Markov model reported by Wang and colleagues2 regarding the comparability of MP dosing between studies and evidence supporting lack of survival benefit with MPR-R. Valid methodologies using assumptions based on viable clinical evidence are required for appropriate economic comparisons. The Markov model represents such a methodology by accounting for individual patient variability and between-study differences in treatment duration, endpoints and follow-up.

In order to address fully the concerns raised by Dr. Owens in the article, we must break it down into three key methodological discussion points. First, with regard to the budget impact...
models as reported by Fullerton and colleagues, the article states, “The selection of duration of therapy as an endpoint for product comparison raises questions since … it introduces a bias in favor of the less tolerable therapy”; shorter treatment duration cannot be inferred to be solely indicative of poorer tolerability as length of therapy is affected by the protocol. The purpose of these models was to compare on-treatment costs for one treatment course based on median duration, which is one of the most commonly used methods in the field. The overall survival (OS) benefit was similar between therapies based on one course of treatment (bortezomib hazard ratio [HR] of 0.57 [p = 0.001]; lenalidomide-dexamethasone HRs of 0.66 [p = 0.03] in MM-009 and 0.44 [p < 0.001] in MM-010). This approach provides payors with an opportunity to evaluate the budget impact of one course of treatment in light of the clinical benefit in the corresponding period as well as the flexibility to determine costs over different time periods.

The second methodological discussion point presented is that cost estimates for patients treated with bortezomib should be provided for the 18- to 44-week time period to make the comparison with lenalidomide-dexamethasone more meaningful. Following the prescribed resolve suggested in the article would not be in accordance with the prescribing information for bortezomib. Patients treated with bortezomib receive a finite treatment course (median 18 weeks5), typically followed by a treatment-free interval prior to receiving subsequent therapy.6 The median time to next therapy is 10.6 months (approximately 46 weeks).6 As a result, the majority of patients would not continue on bortezomib therapy and thus would not incur medical or adverse event (AE) costs during the treatment-free interval. In contrast, patients receiving lenalidomide-dexamethasone are treated until progression and initiation of subsequent therapy.7,8 Therefore, patients receive treatment over a longer period, with the median duration of therapy being 44 weeks8 and median progression-free survival 11.1 months (approximately 48 weeks).9 This difference in average length of therapy has a direct and significant impact on total cost of therapy. In fact, drug cost is the number one variable in contributing to total cost of MM treatment.1 Dr. Owens’ suggestion introduces bias in favor of lenalidomide-dexamethasone.

To overcome differences in treatment protocols, such as different durations of treatment and lengths of follow-up, the article referenced a poster presented by Durie and colleagues at the International Myeloma Working Group 2011,11 comparing bortezomib with lenalidomide-dexamethasone, as an example of an analysis that used common time periods and validated endpoints for comparison purposes. However, for this methodology to provide accurate and meaningful comparisons, it is critical that the assumptions used reflect the essential differences in protocols between the two treatments, which does not appear to be the case in this analysis. Drug costs of bortezomib and lenalidomide-dexamethasone were comparable as Durie’s model assumed that patients received the same therapy at relapse/progression. This introduces a bias against bortezomib because this does not account for the treatment-free interval with bortezomib and incorrectly incurs drug costs for two full courses within the 12-month horizon. The reality is that patients receiving bortezomib would require only a median of 1.4 months subsequent therapy. In support of this point, other analyses have suggested two- or threefold higher drug costs with lenalidomide-dexamethasone compared with bortezomib, yet these articles were not included or discussed.3,4,12 In addition, the model assumes that treatment-related medical and AE costs were incurred every day during the 12-month horizon, which
is incorrect. This assumption biases the model against bortezomib because patients would have incurred such costs for a median of 18 weeks only and would not have incurred further costs until starting subsequent therapy (at a median of 46 weeks from start of treatment). This clearly reduces the overall cost of bortezomib-based treatment.

The third discussion point concerns the methodology of the Markov model reported by Wang and colleagues. This method compares the cost-effectiveness of bortezomib-melphalan-prednisone (VMP, phase 3 VISTA study) and lenalidomide-melphalan-prednisone followed by lenalidomide maintenance (MPR-R, phase 3 MM-015 study). Dr. Owens notes that the studies involved different treatment populations with varying lengths of follow-up. The Markov model methodology is more rigorous than the simple cost comparison conducted by Durie et al. as it accounts for interpatient variability in treatment course by using an indirect comparison method to compare patients’ baseline characteristics. It should be noted that applying data from different studies in Markov models is a common practice for this methodology. Furthermore, in order to overcome differences in follow-up, data were applied to the model on the basis of survival distribution, which is a common and well-respected approach for models simulating a 20-year horizon.

Dr. Owens also questioned some of the assumptions made in the Markov model reported by Wang and colleagues. First, the assumption of comparability between the MP dosing regimens used in VISTA and MM-015 is valid; thus, this issue would not affect the metrics as suggested in the article. The MP regimens comprised melphalan 9 mg/m² and prednisone 60 mg/m² on days one to four, every six weeks, in VISTA, and melphalan 0.18 mg/kg and prednisone 2 mg/kg on days one to four, every four weeks, in MM-015, both for a maximum of nine cycles. Converting the doses into the same units based on average body surface area and weight suggests that MP dosing is, in fact, very similar between studies. Supporting this, the progression-free survival with MP also appears similar between studies (15.2 months in VISTA and 13.2 months in MM-015). Second, the article questioned why the HR for OS with MPR-R versus MP was set to 1.0, suggesting that this is not consistent with the available evidence and predetermines the outcomes. Data presented to date indicate no significant difference in OS between MPR-R and MP,
as compared with 3.4 on MPR-R, but these were not model inputs, rather the outcomes of the analysis. The finding of the Wang et al. study that VMP provided 0.8 additional life years compared with MPR-R indicates a notable survival benefit.

The evidence regarding economic assessments of MM therapies is currently limited, and cost-effectiveness analyses are most useful if comparisons are transparent, accurate and credible. As discussed above, valid methodologies employing accurate assumptions, based on clinical evidence, are required for appropriate comparisons between treatments. This is of particular importance for those involving different treatment protocols. In this regard, the Markov model reported by Wang and colleagues represents a valid methodological approach that overcomes the critical issues highlighted in the article through the use of patient-level data to account for individual patient variability, and the use of probabilities of transitioning from one health state to another during a lifetime horizon to overcome differences in treatment duration, study endpoints and follow-up between studies.

## References

12. Cook R. "An Economic Perspective on Treatment Options in Multiple Myeloma." *Managed Care Oncology.* 2007; Quarter 1:10-12.
MOVING TO Practice Excellence with a CPOE

There’s been a lot written about the benefits — and challenges — of implementing and cultivating adoption of a computerized physician order entry (CPOE) solution since the technology was introduced nearly 40 years ago.

For oncology practices, there’s a lot to gain from a CPOE solution in terms of better patient care and a more efficient practice. The key to a successful implementation and ongoing consistent use of an oncology CPOE system by all stakeholders — physicians, nurses, pharmacists and practice managers — lies in change management that recognizes the three pillars of any effective solution: people, process and technology.

This paper discusses how oncology practice leaders can accelerate the adoption and benefit of a CPOE system with a step-by-step approach — and ultimately, use the implementation as a catalyst to improve the overall standard of care and clinical workflow. Drawing from best practices used in hundreds of CPOE solution implementations in oncology practices of many shapes and sizes, the paper discusses:

- Key benefits for a practice’s primary stakeholders
- Five steps for ensuring implementation and adoption success
- Key questions to evaluate and choose an implementation partner to achieve success quickly and cost-efficiently
KEEP YOUR EYES ON THE BIGGER GOAL

No matter where you are on the path toward implementing a CPOE solution, you can use the framework here to achieve your goals.

In the middle of change, all too often, it’s easy to lose sight of the reason the change is being made in the first place. For every practice, the reasons behind moving to a CPOE system will be unique, but to navigate the road ahead, keeping your eyes — and everyone in the practice — on the endgame will make it easier to overcome any obstacles.

BLUEPRINT FOR A SUCCESSFUL IMPLEMENTATION

Step #1: Define Your Vision for the CPOE

The many reasons for leveraging technology — efficiency, accuracy, compliance, visibility, etc. — are not necessarily the same as a vision. Working with your key stakeholders, understand and articulate what the organization expects and requires from the implementation:

- What will the practice look like or how will it function differently once the CPOE solution is in use?
- What opportunities does the team expect to realize with the solution?
- What challenges will be eliminated with the solution?
- How will it interact with or enhance existing information technology systems?

Once the vision is in place, communicate it early, and often, reminding everyone why they got on board.

Step #2: Choose an Internal Project Champion

Having a single point of contact for advocating, planning for and shepherding the change required to embrace a technology-driven solution is a critical step. The ideal project champion:

- Embraces change
- Communicates well with all levels of the clinic
- Has deep insight into practice processes, clinical knowledge and provider preferences and differences
- Has the ability to problem solve, prioritize and delegate
- Can align resources to accommodate project deadlines
- Engenders respect that translates into influence to keep things moving
- Is able to facilitate conversations among key stakeholder groups

WHO BENEFITS?

In any organization, there are different audiences with widely varying needs — even when everyone is working toward the same goal. Oncology practices are no different; physicians, nurses, pharmacists and practice managers share the common goal for excellence in patient care, but each stakeholder sees the path to achieving that goal based on his or her role in the practice.

What’s critical to cultivating the consistent use of a CPOE system is understanding what matters most to each audience and communicating the value of the solution based on that audience’s unique needs.

For physicians: CPOEs can be a strong catalyst for standardization of care and decision support, engendering clinical best practices from a drug and treatment perspective.

For nurses: CPOEs reduce the time required for administrative work — e.g., transcribing physician orders or clarifying the instructions — thereby giving them more time to focus on patient safety and excellent care.

For pharmacists: CPOEs can be a tool to ensure accurate dosage calculations and provide structured practice treatment policies and guidelines. Clear and concise physician orders standardized with detailed drug and hydration instructions are essential to the safety and efficiency of pharmacy practice.

For practice managers: CPOEs streamline and ensure accuracy in capturing charges, lowering the risk for reimbursement rejection. These systems can also automate alignment of care plans with managed care guidelines.

REASONS CITED BY HOSPITALS FOR NOT HAVING A CPOE:

- 32 percent resistance from physicians
- 32 percent unclear on return on investment
- 30 percent lack the information technology expertise

Step #3: Create a Team and Training Program That Accelerates Adoption

Make sure all key stakeholder groups are included as part of the core team. Identify your “super-users”: those individuals who, along with the project champion, are going to be the vanguard for using the software. Involve them in the process as early as possible. This will allow them to become early advocates of the solution and they can become peer trainers as the implementation moves along.

It is important to understand your practice’s resource constraints, as the software rollout will require time from every group at some point during implementation. It is also important to understand your practice’s culture. Is it open to change, or does it tend to resist it? Know the answer before you start, because it takes only one person to derail an implementation.

Role-based training is the most efficient use of resource time. Training plans need to be flexible and individualized to meet the needs of all diverse practices — using a mix of online videos, hands-on webinar sessions and on-site classroom training. Reflect on previous training experiences for other systems (if applicable) and ask yourself what worked well. What didn’t? Use this information to customize the training to best suit your practice.

Step #4: Design the CPOE Solution to Meet Your Needs With Clinical Foundation Building

The implementation is not “one-size-fits-all” — every practice operates differently. On the same note, technology is most effective when it maps to the specific needs of the environment in which it is deployed.

WORKFLOW: LITTLE WAYS TO MAKE A BIGGER IMPACT

With any major change, there are often seemingly small areas where improvement — in the aggregate — can deliver powerful results. When designing the program for use, look at all areas of the practice and workflow to identify those opportunities, including:

- How are orders managed through the clinic: Who preps the order, signs the order and manages the order going forward?
- Do you have all the necessary nursing documentation? Is it consistent across staff and locations?
- How are new drugs and therapies introduced into the practice? Is there a committee to review them?
- Is there a consistent organized authorization process?
- How are treatment plans currently created, reviewed and edited?
- How do you capture, review and modify charge codes from patient infusion through the billing process?

Start with a self-assessment: Analyze your patient population, prescriber preferences and treatment plan utilization. From there, design custom treatment plans based on what you currently utilize. Leverage building blocks, but adapt them to your practice preferences. Provide training to key...
amount of fortitude needed to facilitate the change that brings the true benefits.

Partnering with an expert in CPOE solutions, implementation and adoption can significantly improve the likelihood of success — the first time. When evaluating a potential partner to help you with the implementation, here are some things to consider:

- How knowledgeable is the team about the unique requirements of an oncology practice?
- What other practices similar to yours have they worked with?
- How knowledgeable is the team about integration of the CPOE solution with other electronic health record systems?

THE TIME FOR CPOE ADOPTION IS NOW

Administrative, clinical and efficiency improvements are some of the workflow benefits that an oncology CPOE solution provides. Regulatory requirements for CPOE systems are beginning to extend beyond hospitals to clinics.

As you move toward implementation, you are likely to encounter obstacles to the change required. Skepticism is normal. Your practice is busy. Change is uncomfortable.

You can achieve your goals for practice and patient care excellence with a thoughtful and careful process that:

- Encompasses the benefits for all participants
- Ensures that the solution reflects your practice's unique needs
- Empowers key users to discover the benefits and then become advocates for the solution

Step #5: Stay Engaged to Stay on Track

Clinical and technical kickoff meetings turn into a series of weekly meetings, involving representatives from major areas impacted by the software: physicians, nurses, pharmacists and practice managers. Establish goals to achieve and metrics to measure progress and success.

Effective agendas for these meetings include progress updates and milestone reviews in three key areas:

- Project, including reviews of scope of work, resource requirements and phases of project
- Clinical, including treatment plan design, workflow consulting and analysis, software customization based on clinical workflow, and Web-based and on-site training
- Technical, including system specifications, technical timeline and interface testing discussions

EXPERT PARTNERS BRING BEST PRACTICES TO YOU

Investing in a CPOE solution is more than the price of the hardware and software. It’s also about the time, human resources and immeasurable

PROVENGE is the first in a new class of therapy that is designed to activate a patient's own antigen-presenting cells to stimulate an immune response against prostate cancer.

- Extends median survival beyond 2 years—25.8 months compared with 21.7 months for patients in the control* group (P = .032)
- Reduction in risk of death—22.5% (HR=0.775, 95% CI: 0.614, 0.979)
- Therapy completed in 3 cycles—3 infusions, at approximately 2-week intervals †
- Most common adverse events are primarily mild or moderate—chills, fatigue, fever, back pain, nausea, joint ache, and headache

*Control was nonactivated, autologous, peripheral blood mononuclear cells.
†The dosing interval ranged from 1 to 15 weeks in controlled clinical trials.


INDICATION: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

IMPORTANT SAFETY INFORMATION: PROVENGE is intended solely for autologous use and is not routinely tested for transmissible infectious diseases.

In controlled clinical trials, serious adverse events reported in the PROVENGE group include acute infusion reactions (occurring within 1 day of infusion) and cerebrovascular events. Severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

The most common adverse events (incidence ≥15%) reported in the PROVENGE group are chills, fatigue, fever, back pain, nausea, joint ache, and headache.

Please see Brief Summary of full Prescribing Information on the adjacent page.
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A Managed Care Perspective on the Diagnosis, Evaluation and Treatment of Prostate Cancer

by Tanya Dorff, M.D., assistant professor of clinical medicine, University of Southern California Norris Comprehensive Cancer Center

Despite ranking as only the fifth-leading cancer in terms of direct treatment costs at $11.85 billion in 2010, increasing survivorship and the accompanying need for long-term management makes prostate cancer a growing concern among plan stakeholders and clinicians alike. In fact, prostate cancer leads all cancer types with a projected 36 percent increase in survivors between 2010 and 2020, with mortality steadily declining since the 1990s. While these data are promising and indicative of increased screening efforts and advances in treatment modalities, they also signal a pronounced need for ongoing care and intensive management in the disease state.

It is estimated that 241,740 men will be diagnosed with prostate cancer in 2012, and 28,170 will die of the disease. Incidence rates are significantly higher among African-American males than in whites, with mortality rates also being more than two times higher for the former demographic than the latter. In addition to race/ethnicity, age and family history of the disease are the other well-established risk factors for prostate cancer. Approximately 62 percent of cases are diagnosed in men ages 65 and older, and 97 percent of cases occur in men ages 50 and older. An increased risk for prostate cancer has also been linked to a diet high in processed meat and dairy foods, while obesity has only been correlated with an increased risk for aggressive disease.

Although some debate exists regarding the value of routine testing for early prostate cancer detection with the
prostate-specific antigen (PSA) test, the aforementioned risk factors play a role in considerations and current recommendations for screening. The American Cancer Society recommends that — beginning at age 50 — men who are at average risk for prostate cancer and have a life expectancy of at least 10 years receive information about the potential benefits and known limitations of testing for early prostate cancer detection. Those at high risk, including African-Americans and men with a close relative diagnosed with prostate cancer before age 65, should have this discussion with their health care provider beginning at age 45. If screening via the PSA test or digital rectal exam (DRE) results in suspicion of prostate cancer, clinicians have several different means of diagnosing and characterizing the disease before selecting the appropriate course of treatment.

**DIAGNOSIS AND EVALUATION**

Whether employed as screening methods or for further investigation of telltale symptoms, the PSA test and the DRE represent the initial measures in the diagnostic process for prostate cancer. In fact, since early-stage disease is often asymptomatic, a PSA test and a DRE may be the only means of detecting the disease outside of more invasive analyses. Patients with advanced disease may present with symptoms such as a slowed or weakened urinary stream, an urge to urinate more often and/or hematuria. In addition to initial detection, the DRE can likewise be used to further characterize the disease prior to biopsy and imaging studies, including whether the cancer is unilateral or bilateral or whether it has likely spread beyond the prostate gland to nearby tissue. Similarly, results from a PSA test may also be predictive of disease severity, with higher PSA levels indicating more advanced disease and a higher potential that the cancer has spread.

To confirm a diagnosis of prostate cancer, a biopsy must be performed to collect tissue for cytologic analysis. This is most often a core needle biopsy of the prostate guided by transrectal ultrasound, in which the clinician collects anywhere between eight and 18 core samples. Upon identification of cancerous cells, the pathologist who analyzed the prostate tissue samples typically assigns a Gleason grade (or pattern) to the most common tumor pattern and — since prostate cancers often have areas with different grades — a second grade to the next most common tumor pattern. These grades range from one to five, with five indicating the poorest prognosis (Table 1). The two grades are then added together to calculate the Gleason score (or sum) of the patient’s prostate cancer. This system is adjusted in special scenarios: If the highest grade comprises ≥ 95 percent of the biopsy, the grade for that area is counted twice in the Gleason score. Conversely, if three grades are present in a biopsy core, the highest grade is always included in the Gleason score, even if most of the core is taken up by areas of cancer with lower grades. The Gleason score ranges from two to 10, with 10 indicating the poorest prognosis and highest likelihood of metastasis. Cancers with a Gleason score of ≤ six are considered low grade or well differentiated, while those with Gleason scores of seven are considered moderately differentiated or intermediate grade. When a patient’s prostate cancer has a Gleason score of ≥ eight, it is considered poorly differentiated or high grade.

Unlike other cancers, prostate cancer patients frequently do not require imaging for staging purposes, because PSA-detected cancers are typically very early stage. However, for men with a high Gleason score or PSA (> 20 ng/mL is a typical cutoff), the risk for metastasis is high enough that imaging should be performed to be certain the disease is localized before curative therapy is applied. Since prostate cancer has a strong predilection for spread to the bones, a radionuclide bone scan may be among the first imaging studies ordered. Another common imaging study, computed tomography (CT), is useful in determining whether the prostate cancer has spread into nearby lymph nodes. A CT scan may clarify abnormalities seen on the bone scan, helping to differentiate uptake related to osteoarthritis from that associated with blastic or lytic abnormalities, which would be more suspicious for metastatic involvement. CT scans are also employed at the time of PSA recurrence to ascertain the involvement of other organs or structures in the pelvis.

<table>
<thead>
<tr>
<th>Grade/Pattern</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Tissue closely resembles normal prostate tissue; glands are small, well-formed and closely packed.</td>
</tr>
<tr>
<td>2</td>
<td>Tissue still has well-formed glands, but they are larger and have more tissue between them.</td>
</tr>
<tr>
<td>3</td>
<td>Tissue still has recognizable glands, but the cells are darker; at high magnification, some of these cells have left the glands and are beginning to invade the surrounding tissue.</td>
</tr>
<tr>
<td>4</td>
<td>Tissue has few recognizable glands; many cells are invading the surrounding tissue.</td>
</tr>
<tr>
<td>5</td>
<td>Tissue does not have recognizable glands; there are often just sheets of cells throughout the surrounding tissue.</td>
</tr>
</tbody>
</table>
and categorize men into either the biochemically recurrent (i.e., PSA-only but no imaging abnormalities) or metastatic stage. Although used less frequently, magnetic resonance imaging (MRI) scans can produce a more distinct image of the prostate than CT scans and reveal whether the cancer has spread outside of the prostate into surrounding structures such as the seminal vesicles or bladder.

**TREATMENT CONSIDERATIONS**

Given that most men diagnosed with prostate cancer are not destined to die from the disease, placing the cancer in the context of the patient’s comorbidities and general health status is critical to avoid overtreatment. For elderly patients or those with low-grade and early-stage disease, there is a paucity of evidence demonstrating that treating slow-growing prostate cancer with surgery or radiation will actually prolong survival. For such men, active surveillance is an important consideration. As opposed to so-called “watchful waiting,” active surveillance involves close monitoring to identify cancers that will behave aggressively enough to warrant treatment and then provide curative therapy for those men while continuing to monitor the indolent cancers, sparing those men from the potentially permanent adverse consequences of curative therapy.

However, in younger, healthier men or in those with aggressive forms of the disease, surgery or radiation serves as definitive therapy and provides a high potential for cure. Among surgical options, radical prostatectomy can be performed laparoscopically, with robotic assistance, or via a traditional open approach. As cure is the ultimate goal of this procedure, the entire prostate gland and some of the surrounding tissue, including the seminal vesicles, are removed. Similar to surgery, radiation therapy comes in several different forms, with the two main categories being external beam radiation therapy (EBRT) and brachytherapy. Advances in radiation therapy include intensity modulated radiation therapy (IMRT) and proton therapy, which are designed to deliver a higher dose of radiation to kill cancer cells but hopefully with fewer and generally minimal gastrointestinal and genitourinary side effects. Randomized data are not available to compare these treatments, and decision making is therefore complicated. Patients with intermediate- and high-grade cancers will typically receive androgen deprivation as part of their radiation treatment plan for up to three years. Despite being potentially curative, both radiation therapy and surgery can have significant side effects. Surgery is associated with a risk for incontinence and/or impotence, while radiation therapy is more often associated with gastrointestinal issues and impotence.

In situations where surgery and radiation therapy are not appropriate, androgen-deprivation therapy (ADT) is used. ADT agents exert their effect through the inhibition of androgens such as testosterone and dihydrotestosterone, which stimulate prostate cancer cell growth under normal conditions. The classes of agents include luteinizing hormone-releasing hormone (LHRH) analogs (e.g., leuprolide, goserelin, triptorelin and histrelin), LHRH antagonists (e.g., degarelix) and antiandrogens (e.g., flutamide, bicalutamide and nilutamide). Orchiectomy, or surgical castration, is also considered a form of ADT since > 90 percent of the androgens in males are produced in the testicles. While orchiectomy is likely the least expensive and simplest way to reduce androgen levels in the body, it is irreversible and often viewed as an undesirable procedure by patients.

Although ADT is extremely effective and the majority of men will respond to treatment, the cancer inevitably develops resistance, yielding the lethal castration-resistant form of the disease. Chemotherapy is primarily used in this setting. The standard first-line
chemotherapy regimen is docetaxel and prednisone, which has been shown to palliate cancer symptoms and prolong survival for an average of approximately three months compared with mitoxantrone in patients with advanced prostate cancer that is no longer responding to ADT. For those patients whose hormone-refractory prostate cancer has progressed after treatment with docetaxel and other chemotherapy regimens, cabazitaxel was recently approved in combination with prednisone after a survival benefit was documented in comparison with prednisone alone. Similarly, abiraterone has demonstrated increased survival in this setting when administered in combination with prednisone and was approved by the U.S. Food and Drug Administration (FDA) in April 2011.

A truly innovative therapy, sipuleucel-T, was approved by the FDA in April 2010 for the treatment of advanced hormone-refractory prostate cancer. Described as a personalized therapeutic vaccine, sipuleucel-T is an autologous cellular immunotherapy designed to activate the patient's own immune defenses against hormone-refractory prostate cancer. The vaccine is produced by taking antigen-presenting cells from the patient via leukapheresis and then processing the cells with fusion protein of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) to sensitize them to prostate cancer cells. The cells are then reintroduced to the patient to provoke an immune response against the tumor. In clinical trials, sipuleucel-T improved median survival time by > four months compared with placebo (p < 0.01) in patients with asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer. In addition to bolstering the therapeutic armamentarium, this and similar immune-based therapies that eventually follow may have the potential to offer a more durable treatment response in contrast to the eventual development of resistance experienced with current therapies.

Supportive care is provided in prostate cancer centers upon relieving the pain associated with bone metastases in advanced disease. Beyond nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid painkillers, bisphosphonates (primarily zoledronic acid, but also pamidronate) and RANK-ligand inhibitors (denosumab) are often employed for this purpose. Denosumab, a fully human monoclonal antibody against RANK-ligand, was approved in November 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors and may also be useful to prevent ADT-induced loss of bone mineral density. EBRT is frequently employed for relief of pain associated with bone metastases, and radiopharmaceuticals such as strontium-89 and samarium-153 are sometimes used when diffuse metastases or multiple sites of pain are present. Even in end-stage disease, these treatments may be used as part of a palliative care program.

A PROSPECTIVE VIEW IN MANAGED CARE
A relatively diverse array of therapies is available for the treatment of prostate cancer, and the list of FDA-approved agents continues to grow. In addition to the recent approvals of cabazitaxel and abiraterone, sipuleucel-T ushered in a new era of immune-based therapies, which offers significant promise for the future. Specific to the area of bone metastases in prostate
cancer, samarium, may be replaced by radium-223, a radiopharmaceutical that has shown not only palliative benefits but also a survival advantage in a randomized phase 3 trial. This experimental agent, which uses alpha radiation, naturally self-targets to bone metastases via its calcium-mimetic properties. Furthermore, alpha radiation has a very short range when compared with the beta or gamma radiation used in current therapies, making it less likely to significantly damage surrounding healthy tissues, which is critical in the bone marrow to minimize myelosuppression. The short half-life and rapid clearance/excretion of the agent also make it ideal for targeted cancer treatment while minimizing adverse effects.

Despite growth in the field of genomic testing for targeted agents directed at other high-profile cancers such as breast and colon, developmental advances have been sparse with regard to biomarkers for prostate cancer therapies. While this needs to change, especially given the increasing number of therapeutic choices, the long-term survival associated with prostate cancer will make genomic testing more costly and difficult to develop. Due to the differences in side-effect profiles and geographic differences in the availability of therapies, randomized trials of localized therapies are untenable. Effective treatments for the disease have always been developed in parallel, leaving clinicians with a menu of viable options. As all these treatments are costly, and long-term survival with side effects can be costly as well, the optimal means of controlling prostate cancer costs would be prevention. Unfortunately, positive data from phase 3 prevention trials have been greeted with limited enthusiasm.

While prostate cancer screening has been the virtual norm for several years, the United States Preventive Services Task Force (USPSTF) recently published draft recommendations against PSA-based screening for prostate cancer in asymptomatic men. After previously stating there was insufficient evidence to make a definitive judgment in the 2008 guidelines, the USPSTF gave the draft guidance a D recommendation in late 2011, indicating moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; furthermore, the task force discourages use of the service. Meanwhile, the American Cancer Society stands by its recommendation for screening in men at average risk who are age 50 and older (45 and older for high-risk men), so payors will be faced with their own decision to make based on the available evidence. Certainly, men at high risk due to ethnicity or family history will continue to receive screening. Acknowledging the more positive data in support of PSA screening from the European study and applying screening sensibly, PSA testing remains our best current tool for detecting and characterizing prostate cancer. Mitigating our reaction to PSA results, applying more expensive imaging studies judiciously and optimizing treatment selection in the future will help ensure high value for cost in managing this disease. As health plans have become more accepting of even high-cost clinical tools as valuable for effectively staging and treating the disease, it is likely that insurers will stay the course with clinically sound means of management.

References
The past two years have marked an interesting and exciting time in the development of new therapies for advanced prostate cancer. Docetaxel’s approval for the treatment of castrate-resistant prostate cancer (CRPC) in 2004 was the first new therapy approved since the gonadotropin-releasing hormone agonists and antiandrogen therapies in the 1980s.

Docetaxel was previously the only modern chemotherapy agent to demonstrate an overall survival advantage in CRPC, and now we’ve had three new medical therapies recently approved in the past two years on the basis of prolonged overall survival: sipuleucel-T (Provenge), cabazitaxel (Jevtana) and abiraterone acetate (Zytiga).

Sipuleucel-T was approved in April 2010 for use in CRPC that is asymptomatic or minimally symptomatic. It is uniquely classified as an autologous cellular immunotherapy. After the collection of the patient’s peripheral blood mononuclear cells, they are delivered to a central manufacturing site and processed with recombinant fusion proteins, containing both prostate acid phosphatase and granulocyte-macrophage colony-stimulating factor elements. The product is then sent back to the patient and physician to infuse three times over a four-week period. Sipuleucel-T was initially tested in a phase 2 trial of 127 patients assessing time to progression as a primary endpoint, which was found to be insignificant, but a surprisingly significant overall survival difference of 25.9 versus 21.4 months compared with placebo was observed. A larger phase 3 trial then randomized 512 subjects with metastatic CRPC to sipuleucel-T versus placebo in a 2:1 design. Once again, overall survival of 25.8 months versus 21.7 months was noted in favor of sipuleucel-T. In addition, 64 percent of the patients on placebo received the immunotherapy on crossover. Toxicity centered mostly on chills, fever and headache, although few of these were found to be difficult to manage. The primary debate around the use of
this exciting new therapy has been its $93,000 price tag for a standard course and the fact that many of these patients are in the Medicare population.

Cabazitaxel was approved by the U.S. Food and Drug Administration in 2010 for the treatment of metastatic CRPC after failure of docetaxel chemotherapy. It is a noncross-resistant microtubule-targeted agent, and it was tested in an international phase 3 trial of 775 men, randomized to either cabazitaxel 25 mg/m² or mitoxantrone 12 mg/m² given intravenously every three weeks. Both treatment arms received prednisone. Overall survival of 15.1 versus 12.7 months in favor of cabazitaxel (p < 0.0001) was observed. Febrile neutropenia at 8 percent was the primary toxicity of concern in the cabazitaxel group, although diarrhea, including a grade 3 rate of 6 percent, was also noted.

Abiraterone acetate received approval in April 2011 for the treatment of CRPC patients who had received prior docetaxel. This oral inhibitor of CYP17, a lyase and a key driver of testosterone production, abiraterone acetate directly suppresses extragonadal testosterone production, resulting in testosterone levels near zero. Phase 2 trials revealed prostate-specific antigen (PSA) responses, reductions of more than 50 percent, ranging from 36 percent to 67 percent. Interestingly, patients who had previously been treated with ketoconazole showed little treatment responses and were excluded from the phase 3 trial.

An international, randomized phase 3 study of abiraterone acetate randomized patients to the investigational therapy plus prednisone versus best supportive care plus prednisone in a 2:1 fashion. Median overall survival for abiraterone acetate was 14.8 months compared with 10.9 months in the placebo arm (p < 0.001). In addition, an improvement in PSA progression of 10.2 months versus 6.6 months was noted, as well as a PSA response rate of 29 percent versus 6 percent, all favoring abiraterone acetate. Toxicities were mild and manageable, including fluid retention (31 percent), hypokalemia (17 percent) and hypertension (10 percent). Phase 3 studies in chemo-naive patients are under way with accrual completed and results anticipated.

MDV3100 is an oral androgen receptor signaling inhibitor (ARSI) in development for the treatment of early-stage and advanced prostate cancer. The novel mechanism of action is distinct from other hormonal therapies, including bicalutamide and abiraterone. MDV3100 competitively inhibits androgen binding to the receptor, inhibits movement of the receptor to the nucleus of prostate cancer cells and inhibits binding to DNA. The pivotal phase 3 AFFIRM trial completed enrollment in 2010 for advanced prostate cancer previously treated with docetaxel. In November 2011, a planned interim analysis showed that MDV3100 significantly improved survival compared with placebo. Specific results documented an 18.4 months versus 13.6 months median survival (hazard ratio 0.63) favoring MDV3100. The trial was thus stopped, and the placebo patients were allowed to receive MDV3100. Side effects were modest, and a favorable risk-benefit ratio for the new therapy was observed. The phase 3 PREVAIL trial is enrolling patients with advanced prostate cancer who have not received prior chemotherapy. Studies in earlier stages of this disease comparing MDV3100 with bicalutamide, as well as evaluating monotherapy, are now under way. Medivation is partnering with Astellas in a comprehensive drug development program for MDV3100.

Orteronel (TAK-700), a novel nonsteroidal lyase inhibitor, is also in development from Millennium Takeda. Its selectivity may be associated with less mineralocorticoid excess, potentially leading to an improved side-effect profile. Randomized phase 3 trials with TAK-700 are under way in advanced prostate cancer.

It is clear that we are closer to making advanced prostate cancer a chronic disease. With this abundance of new therapies, understanding the appropriate sequence of utilizing these agents will require well-conducted clinical trials.
Indication

YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.1

J-code for YERVOY2

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
<th>Effective</th>
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</thead>
<tbody>
<tr>
<td>J9228a</td>
<td>Injection, ipilimumab, 1 mg</td>
<td>January 1, 2012</td>
</tr>
</tbody>
</table>

*Replaces J9999, J3490, J3590, and C9284.

Important Safety Information

**WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

YERVOY can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs) and thyroid function tests at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Please see Important Safety Information, including Boxed WARNING regarding immune-mediated adverse reactions, continued on adjacent page.

REFERENCES
Recommended Dose Modifications
Withhold dose for any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving <7.5 mg prednisone or equivalent per day.

Permanently discontinue YERVOY for any of the following:
• Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day
• Failure to complete full treatment course within 16 weeks from administration of first dose
• Severe or life-threatening adverse reactions, including any of the following
  – Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (≥7 over baseline), stool incontinence, need for intravenous hydration for >24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
  – AST or ALT >5 × the upper limit of normal (ULN) or total bilirubin >3 × the ULN
  – Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full-thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations
  – Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  – Severe immune-mediated reactions involving any organ system
  – Immune-mediated ocular disease which is unresponsive to topical immunosuppressive therapy

Immune-mediated Enterocolitis:
• In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 (5%) patients
• Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis
• Infliximab was administered to 5 of 62 (8%) patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids
• Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms
• Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients
• Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent)

Immune-mediated Hepatitis:
• In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5× the ULN or total bilirubin elevations >3× the ULN; Grade 3–5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%
• 13 (2.5%) additional YERVOY-treated patients experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations >2.5× but ≤5× the ULN or total bilirubin elevation >1.5× but ≤3× the ULN; Grade 2)
• Monitor LFTs (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring until resolution
• Permanently discontinue YERVOY in patients with Grade 3-5 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids
• Withhold YERVOY in patients with Grade 2 hepatotoxicity

Immune-mediated Dermatitis:
• In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5) occurred in 13 (2.5%) patients
  – 1 (0.2%) patient died as a result of toxic epidermal necrolysis
  – 1 additional patient required hospitalization for severe dermatitis
• There were 63 (12%) YERVOY-treated patients with moderate (Grade 2) dermatitis
• Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated
• Permanently discontinue YERVOY in patients with severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY in patients with moderate to severe signs and symptoms
Important Safety Information (cont)

- Treat mild to moderate dermatitis (e.g., localized rash and pruritus) symptomatically. Administer topical or systemic corticosteroids if there is no improvement within 1 week.

**Immune-mediated Endocrinopathies:**
- In the pivotal Phase 3 study in YERVOY-treated patients, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported.
- Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.
- Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré–like syndromes.
- Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe endocrinopathies. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities).

**Immune-mediated Neuropathies:**
- In the pivotal Phase 3 study in YERVOY-treated patients, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported.
- Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.
- Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré–like syndromes.
- Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe endocrinopathies. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities).

**Other Immune-mediated Adverse Reactions, Including Ocular Manifestations:**
- In the pivotal Phase 3 study in YERVOY-treated patients, clinically significant immune-mediated adverse reactions seen in <1% were: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.
- Across the clinical development program for YERVOY, immune-mediated adverse reactions also reported with <1% incidence were: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclasis, retinitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.
- Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions.
- Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy.

**Pregnancy & Nursing:**
- YERVOY is classified as pregnancy category C. There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Human IgG1 is known to cross the placental barrier and YERVOY is an IgG1; therefore, YERVOY has the potential to be transmitted from the mother to the developing fetus.
- It is not known whether YERVOY is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from YERVOY, a decision should be made whether to discontinue nursing or to discontinue YERVOY.

**Common Adverse Reactions:**
- The most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

Please see brief summary of Full Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions, on the following spread.
YERVOY™ (ipilimumab) Injection, for intravenous infusion

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY (ipilimumab) can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), nephropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe, life-threatening or severe immune-mediated adverse reactions. [See Dosage and Administration (2.2) in Full Prescribing Information]

Assess patients for signs and symptoms of enterocolitis, dermatitis, nephropathy, and endocrinopathy and evaluate clinical chemistry including liver function tests and thyroid function tests at baseline and before each dose. [See Warnings and Precautions]

INDICATIONS AND USAGE

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert. [See Warnings and Precautions]

CLINICAL STUDIES

In Study 1, severe, life-threatening, or fatal diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3–5 immune-mediated enterocolitis occurred in 34 (7%) YERVOY-treated patients, and moderate diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2 enterocolitis occurred in 28 (6%) YERVOY-treated patients. Across all YERVOY-treated patients (n=511), 5 (1%) patients developed intestinal perforation, 0.8% patients died as a result of complications, and 26 (5%) patients were hospitalized for severe enterocolitis.

The median time to onset was 7.4 weeks (range 1.6–13.9) and 6.3 weeks (range 0.3–18.9) after the initiation of YERVOY for patients with Grade 3–5 enterocolitis and with Grade 2 enterocolitis, respectively.

Twelve (2%) patients with Grade 3–4 enterocolitis were treated with high-dose (≥140 mg prednisone equivalent per day) corticosteroids, with a median dose of 80 mg/day of prednisone or equivalent; the median duration of treatment was 2.3 weeks (ranging up to 13.9 weeks) followed by corticosteroid taper. Of the 28 patients with moderate enterocolitis, 46% were not treated with systemic corticosteroids, 29% were treated with <40 mg prednisone or equivalent per day for a median duration of 5.1 weeks, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 of the 62 patients (8%) with moderate, severe, or life-threatening immune-mediated enterocolitis, resulting in inadequate response to corticosteroids.

Of the 34 patients with Grade 3–5 enterocolitis, 74% experienced complete resolution, 3% experienced improvement to Grade 2 severity, and 24% did not improve. Among the 28 patients with Grade 2 enterocolitis, 79% experienced complete resolution, 11% improved, and 11% did not improve.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid tapering and continue to taper over at least 4 weeks. In a clinical trial of high-dose corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients.

Withhold YERVOY dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than one week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent. [See Dosage and Administration (2.2) in Full Prescribing Information]

Vaccine Administration

Vaccination with YERVOY followed by gp100 peptide vaccine was not evaluated in Study 1, and is not recommended due to increased incidence of all-grade immune-mediated side effects following gp100 vaccination. A gp100 peptide vaccine may be administered before YERVOY if the benefit outweighs the increased risk of developing immune-mediated adverse reactions.

Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as needed based on clinical course of the event.

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatitis to characterize the clinical course of this event.

There were insufficient numbers of patients with biopsy-proven hepatitis to evaluate the risk of severe hepatitis.

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients in Study 1: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.

Across the clinical development program for YERVOY, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angioedema, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Admit steroid-resistant eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. [See Dosage and Administration (2.2) in Full Prescribing Information]

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

• Immune-mediated enterocolitis [see Warnings and Precautions]
• Immune-mediated hepatitis [see Warnings and Precautions]
• Immune-mediated dermatitis [see Warnings and Precautions]
• Immune-mediated nephropathy [see Warnings and Precautions]
• Immune-mediated endocrinopathies [see Warnings and Precautions]
• Immune-mediated dermatitis [see Warnings and Precautions]
• Immune-mediated adverse reactions, including ocular manifestations [see Warnings and Precautions]
Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared with rates in other clinical trials or experience with therapeutics in the same class and may not reflect the rates observed in clinical practice.

The clinical development program excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Exposure to YERVOY (ipilimumab) 3 mg/kg for four doses given by intravenous infusion in previously treated patients with unseetable or metastatic melanoma was assessed in a randomized, double-blind clinical study (Study 1). (See Clinical Studies (14) in Full Prescribing Information.) One hundred thirty-one patients (median age 57 years, 60% male) received YERVOY as a single agent, 360 patients (median age 56 years, 61% male) received YERVOY with an investigational gp100 peptide vaccine (gp100), and 132 patients (median age 57 years, 54% male) received gp100 peptide vaccine alone. Patients in the study received a median of 4 doses (range 1 to 4 doses). YERVOY was discontinued for adverse reactions in 10% of patients.

The most common adverse reactions (>5%) in patients who received YERVOY at 3 mg/kg were fatigue, diarrhea, pruritus, rash, and colitis.

Table 1 presents selected adverse reactions from Study 1, which occurred in at least 5% of patients in the YERVOY-containing arms and with at least 5% increased incidence over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3–5 events.

Table 1: Selected Adverse Reactions in Study 1

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>YERVOY 3 mg/kg (n=131)</th>
<th>YERVOY 3 mg/kg+gp100 (n=360)</th>
<th>gp100 (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32% 5/35</td>
<td>37% 4/35</td>
<td>40% 1/1</td>
</tr>
<tr>
<td>Colitis</td>
<td>8% 5/6</td>
<td>5% 3/6</td>
<td>3% 2/0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>31% 0/3</td>
<td>21% &lt;1/2</td>
<td>11% 0/0</td>
</tr>
<tr>
<td>Rash</td>
<td>29% 2/2</td>
<td>25% 2/2</td>
<td>8% 0/0</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>41% 7/35</td>
<td>34% 5/35</td>
<td>31% 3/3</td>
</tr>
</tbody>
</table>

Table 2 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from Study 1.

Table 2: Severe to Fatal Immune-mediated Adverse Reactions in Study 1

<table>
<thead>
<tr>
<th>Any Immune-mediated Adverse Reaction</th>
<th>YERVOY 3 mg/kg (n=131)</th>
<th>YERVOY 3 mg/kg+gp100 (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Immune-mediated Adverse Reaction</td>
<td>15% 2/13</td>
<td>12% 0/15</td>
</tr>
<tr>
<td>Enterocolitis/abdominal pain</td>
<td>7% 1/13</td>
<td>7% 1/35</td>
</tr>
<tr>
<td>Hepatotoxicity/abdominal pain</td>
<td>1% 1/13</td>
<td>2% 2/35</td>
</tr>
<tr>
<td>Dermatitis/abdominal pain</td>
<td>2% 2/13</td>
<td>3% 3/35</td>
</tr>
<tr>
<td>Neutropathy/abdominal pain</td>
<td>1% 1/13</td>
<td>&lt;1% 0/0</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>4% 1/13</td>
<td>1% 1/35</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4% 1/13</td>
<td>1% 1/35</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>0% 0/13</td>
<td>1% 1/35</td>
</tr>
<tr>
<td>Other</td>
<td>0% 0/13</td>
<td>&lt;1% 0/0</td>
</tr>
</tbody>
</table>

a Including fatal outcome.
b Including intestinal perforation.
c Underlying etiology not established.

Across clinical studies that utilized YERVOY doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence less than 1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Based on the experience in the entire clinical program for melanoma, the incidence and severity of enterocolitis and hepatitis appear to be dose dependent.

Immunogenicity

In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusion reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed in the dose cohort with the lowest trough levels. In this analysis, 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to YERVOY with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted with YERVOY (ipilimumab).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a combined study of embryo-fetal and peri- and postnatal development, severe toxicities including increased incidences of threethrd trimester abortion, stillbirth, premature delivery, low birth weight, and infant mortality occurred following intravenous administration of ipilimumab to pregnant cynomolgus monkeys every 21 days from the onset of organogenesis through parturition at doses of 3.6 or 7.2 times the recommended human dose of 3 mg/kg (by AUC). (See Nonclinical Toxicology (13.2) in Full Prescribing Information.)

In genetically engineered mice in which the gene for CTLA-4 has been deleted (a “knockout mouse”), offspring lacking CTLA-4 were born apparently healthy, but died within 3–4 weeks due to multi-organ infiltration and damage by lymphocytes.

Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus.

Nursing Mothers

It is not known whether ipilimumab is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from YERVOY, a decision should be made whether to discontinue nursing or to discontinue YERVOY, taking into account the importance of YERVOY to the mother.

Pediatric Use

Safety and effectiveness of YERVOY have not been established in pediatric patients.

Geriatric Use

Of the 511 patients treated with YERVOY at 3 mg/kg, 28% were 65 years and over. No overall differences in safety or efficacy were reported between the elderly patients (65 years and over) and younger patients (less than 65 years).

Renal Impairment

No formal studies of YERVOY in patients with renal impairment have been conducted. (See Clinical Pharmacology (12.3) in Full Prescribing Information)

Hepatic Impairment

No formal studies of YERVOY in patients with hepatic impairment have been conducted. (See Clinical Pharmacology (12.3) in Full Prescribing Information)

OVERdosAGE

There is no information on overdosage with YERVOY.

PATIENT COUNSELING INFORMATION

See MEDICATION GUIDE in Full Prescribing Information.

Withdraw patients of the potential risk of immune-mediated adverse reactions.

Advise patients to read the YERVOY Medication Guide before each YERVOY infusion.

Advise women that YERVOY may cause fetal harm.

Advise nursing mothers not to breast-feed while taking YERVOY.

Manufactured by: Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Bristol-Myers Squibb
Princeton, NJ 08543 U.S.A.

128155802 IP-B0001A-03-11 Issued: March 2011
Societal convention regards prostate cancer as a disease of the elderly. Comments such as “If you live long enough, you’ll get prostate cancer” seem to only further emphasize that.

This article will demonstrate the breadth of impact that prostate cancer has and how this has changed perspectives for employers and payors. Prostate cancer is, in most cases, slow-growing and symptom-free. Elderly patients diagnosed with early, localized disease may commonly die of other causes rather than of the cancer. More aggressive prostate cancers, however, account for the greatest cancer-related mortality, second only to lung cancer. To provide perspective on these implications for the health system, prostate cancer registry data from 2001 to 2007 indicated that only about 4 percent of patients were diagnosed with distant disease. So the consensus is that initial diagnosis of aggressive disease is relatively small. This data does not, however, include patient progression from other less-aggressive stages. What may be more telling is that the total cost of prostate cancer care was calculated at $11.85 billion in mid-year 2010 (see Table 1), which makes it the fifth most costly cancer. This is influenced by the fact that prostate cancer is the most common cancer in men, second only to skin cancer. In addition, it may represent the long-term nature of this disease, with the potential to integrate a variety of treatment options across different stages of disease for a given patient. This data could easily be considered understated, having been compiled prior to market entry of newer treatment options such as Provenge (sipuleucel-T), Jevtana (cabazitaxel) and Zytiga (abiraterone acetate) — all providing clinical benefit for prostate cancer patients, but also adding increased cost. Trending the data to create potential costs in 2020 (applying a 2 percent inflation rate), the estimated costs would be in the $18 billion range — again, likely

### Table 1. Direct Health Care Costs, by Cancer Type

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Direct Costs (in billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>$124.57</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>$16.50</td>
</tr>
<tr>
<td>Colorectal</td>
<td>$14.14</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>$12.14</td>
</tr>
<tr>
<td>Lung</td>
<td>$12.12</td>
</tr>
<tr>
<td>Prostate</td>
<td>$11.85</td>
</tr>
<tr>
<td>Leukemia</td>
<td>$5.44</td>
</tr>
</tbody>
</table>
understated. These estimates assume constant incidence and survival as estimated from 2002 to 2005. With the growing population, possibility of earlier and more definitive diagnosis, and market entry of new clinical treatments, both incidence and survival trends could be affected.

A TREND TO YOUNGER DIAGNOSIS
Since the advent of prostate-specific antigen (PSA) testing in 1986, the age at diagnosis has continued to decrease. Age curves comparing the period prior to PSA availability (1980 to 1985) with the PSA era (1990 to 1995) indicate a decrease in mean age at diagnosis of 1.7 years in whites and 1.3 years in blacks. To continue the chronological trend analysis, the mean age at diagnosis over the past four decades, as seen in Table 2, has dropped a total of six years. Based on the last period’s data (2004 to 2008), it’s age 67.3,6,7 With more prostate cancer screening efforts, the evolution of genetic DNA microarray technology, color Doppler ultrasound and enhanced magnetic resonance imaging, it is anticipated that prostate cancer may likely continue to be diagnosed at increasingly earlier points in a man’s life. This challenges the perception that prostate cancer is only for the elderly, especially with statistics demonstrating that 40.4 percent of the total new diagnoses occur between ages 35 and 64 — affecting the working-age population.6

Revisiting the health care costs discussed earlier, if we carve out only those costs associated with prostate cancer patients younger than age 65 by phase of treatment (initial, continuing and last), there is an expected 51.9 percent increase in costs by 2020 during the initial treatment period (Table 3).8 The initial treatment phase currently includes options such as surgery, radiation (brachytherapy and intensity-modulated radiation therapy), hormonal therapies or no therapies (watchful waiting/active surveillance). Future options will include novel vaccines, enhanced hormonal therapies and newer biologics over time, based on current or planned clinical trials.

EMPLOYER CONSIDERATIONS FOR PROSTATE CANCER
Numerous factors have piqued employer desire to manage prostate cancer. There is a lack of definitive data to confirm the best treatment option for localized prostate cancer, the stage at which younger men would most likely be diagnosed. In addition, there is concern that temporary or permanent side effects from specific treatments could affect employee work productivity and quality of life.9

Another factor is the employer’s increasing endeavor to help employees manage health care costs, since the employee is carrying more of the cost responsibility. A 2011 Towers Watson/National Business Group on Health Survey6,10 indicated that the average employee annual premium payment increased from $2,379 to $2,660 — an 11.8 percent increase in one year (Table 4). This survey also identified a 45 percent greater premium contribution from five years prior. Add to this any significant deductible responsibility or high coinsurance for medical and/
Cancer Network (NCCN), selected four primary cancers, including clinically localized prostate cancer, for which to provide CER guidance.\(^\text{12}\) As a result, they created a prostate cancer guide for employers, providing tools to develop employee patient decision aids using information from the Agency for Healthcare Research and Quality, the Foundation for Informed Medical Decision Making and NCCN.\(^\text{13}\)

### INFLUENCE OF FUTURE TREATMENTS

The prostate cancer population is large and will likely continue to expand, so it is a prime target for clinical development. In 2011, the Pharmaceutical Research and Manufacturers of America published a report documenting that a total of 80 biopharmaceuticals and vaccines are in development targeting prevention, diagnosis and treatment of prostate cancer.\(^\text{14}\) Some agents are already approved by the U.S. Food and Drug Administration for other indications, with the intent to expand into treatment for prostate cancer. Examples are Gleevec (imatinib), Halaven (eribulin), Revlimid (lenalidomide), Sprycel (dasatinib) and Zaltrap (aflibercept). Other late-stage candidates include custirsen and MDV3100. Add to that prostate cancer vaccines, additional diagnostic methodologies, treatments for bone metastases and therapeutic radiopharmaceuticals, and there will be quite an armamentarium for clinical decision making.

Prostate cancer is increasingly a concern for working-age males and their employers and is already an identified issue for the elderly. A growing number of employers will be forming initiatives to guide employees to appropriate resources for treatment decisions, using CER approaches and education. Payors may likely align with those employer initiatives by integrating CER/pathways for the disease should the investment warrant that. No matter what the approach, more emphasis will be placed on managing the cost of care associated with prostate cancer, whether for Medicare-eligible or commercial/employer-benefit-eligible beneficiaries.

### Table 4. Annual Employee Health Care Benefit Premium Increase 2010 to 2011

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>$2,379</td>
<td>$2,660</td>
<td>$2,660</td>
</tr>
</tbody>
</table>

### References

TREATMENT OF Prostate Cancer

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.

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:

185 Malignant neoplasm of prostate
   Excludes seminal vesicles (187.8)
## FDA-Approved Medications Currently Available to Treat Prostate Cancer

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code — Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 2/1/12</th>
<th>Medicare Allowable (ASP + 6%) — Effective 1/1/12-3/31/12</th>
<th>CPT Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>abiraterone acetate (Zytiga)</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>abiraterone acetate (Zytiga)</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>bicalutamide (Casodex)</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>
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<tr>
<td>cabazitaxel (Jevtana)</td>
<td>J9043 — injection, cabazitaxel, 1 mg</td>
<td>$163.22</td>
<td>$135.20</td>
<td>96413</td>
</tr>
<tr>
<td>degarelix (Firmagon)</td>
<td>J9155 — injection, degarelix, 1 mg</td>
<td>$6.07</td>
<td>$2.80</td>
<td>96402</td>
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<tr>
<td>docetaxel (Taxotere, Doceefrez)</td>
<td>J9171 — injection, docetaxel, 1 mg</td>
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<td>estradiol valerate (Delestrogen)</td>
<td>J1380 — injection, estradiol valerate, up to 10 mg</td>
<td>$15.24</td>
<td>$7.44</td>
<td>96372</td>
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<tr>
<td>estramustine (Emcyt)</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>
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<tr>
<td>estradiol (e.g., estradiol, conjugated estrogen, esterified estrogen)</td>
<td>J8499* — prescription drug, oral, nonchemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>flutamide (Eulexin)</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>flutamide (Eulexin)</td>
<td>S0175 — flutamide, oral, 125 mg</td>
<td>$2.09</td>
<td>$0.02</td>
<td>N/A</td>
</tr>
<tr>
<td>goserelin acetate (Zoladex)</td>
<td>J9202 — goserelin acetate implant, per 3.6 mg</td>
<td>$451.19</td>
<td>$176.68</td>
<td>96372, 96402</td>
</tr>
<tr>
<td>histrelin (Vantas)</td>
<td>J9225 — histrelin implant (Vantas), 50 mg</td>
<td>$3,840.00</td>
<td>$3,188.77</td>
<td>11981, 11982, 11983</td>
</tr>
<tr>
<td>leuprolide acetate (Eligard, Lupron Depot)</td>
<td>J9217 — leuprolide acetate (for depot suspension), 7.5 mg</td>
<td>$493.20</td>
<td>$215.04</td>
<td>96402</td>
</tr>
<tr>
<td>leuprolide acetate (Lupron)</td>
<td>J9218 — leuprolide acetate, per 1 mg</td>
<td>$27.52</td>
<td>$4.86</td>
<td>96402</td>
</tr>
<tr>
<td>mitoxantrone (Novantrone)</td>
<td>J9293 — injection, mitoxantrone hydrochloride, per 5 mg</td>
<td>$90.00</td>
<td>$39.57</td>
<td>96409, 96413</td>
</tr>
<tr>
<td>nilutamide (Nilandron)</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>prednisone (Deltasone)</td>
<td>J7506 — prednisone, oral, per 5 mg</td>
<td>$0.08</td>
<td>$0.02</td>
<td>N/A</td>
</tr>
<tr>
<td>sipuleucel-T (Provenge)</td>
<td>Q2043 — sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion (Code price is per 250 ml)</td>
<td>$37,200.00</td>
<td>$32,860.00</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>triptorelin (Trelstar Depot, Trelstar LA)</td>
<td>J3315 — injection, triptorelin pamoate, 3.75 mg</td>
<td>$975.89</td>
<td>$785.09</td>
<td>96372, 96402</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 Casodex) in column 24D and the drug name, strength and NDC (National Drug Code) in box 19 to ensure appropriate reimbursement.
## Compendia-Listed Off-Label Use Medications Currently Available to Treat Prostate Cancer

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code — Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 2/1/12</th>
<th>Medicare Allowable (ASP + 6%) — Effective 1/1/12-3/31/12</th>
<th>CPT Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bacillus Calmette-Guerin (Tice BCG)</td>
<td>90585 — bacillus Calmette-Guerin vaccine (BCG) for tuberculosis, live, for percutaneous use</td>
<td>$169.10</td>
<td>$112.82</td>
<td>50471</td>
</tr>
<tr>
<td>bacillus Calmette-Guerin (Tice BCG, TheraCys)</td>
<td>90586 — bacillus Calmette-Guerin vaccine (BCG) for bladder cancer, live, for intravesical use</td>
<td>$169.10</td>
<td>$115.47</td>
<td>51720</td>
</tr>
<tr>
<td>bacillus Calmette-Guerin (Tice BCG, TheraCys)</td>
<td>J9031 — BCG (intravesical), per installation</td>
<td>$169.10</td>
<td>$115.47</td>
<td>51720</td>
</tr>
<tr>
<td>bevacizumab (Avastin)</td>
<td>J9035 — injection, bevacizumab, 10 mg</td>
<td>$71.61</td>
<td>$61.09</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>cisplatin (Platinol AQ)</td>
<td>J9060 — injection, cisplatin, powder or solution, per 10 mg</td>
<td>$4.33</td>
<td>$1.78</td>
<td>96409, 96413, 96415</td>
</tr>
<tr>
<td>cyclophosphamide (Cytoxan)</td>
<td>J8530 — cyclophosphamide, oral, 25 mg</td>
<td>$2.09</td>
<td>$0.82</td>
<td>N/A</td>
</tr>
<tr>
<td>cyclophosphamide (Cytoxan)</td>
<td>J9070 — cyclophosphamide, 100 mg</td>
<td>$29.70</td>
<td>$14.91</td>
<td>96409, 96413, 96415</td>
</tr>
<tr>
<td>doxorubicin (Adriamycin)</td>
<td>J9000 — injection, doxorubicin hydrochloride, 10 mg</td>
<td>$13.20</td>
<td>$3.88</td>
<td>96409</td>
</tr>
<tr>
<td>epirubicin (Ellence)</td>
<td>J9178 — injection, epirubicin hydrochloride, 2 mg</td>
<td>$5.38</td>
<td>$1.73</td>
<td>96409, 96413</td>
</tr>
<tr>
<td>fluorouracil (Adrucil)</td>
<td>J9190 — injection, fluorouracil, 500 mg</td>
<td>$3.30</td>
<td>$1.43</td>
<td>96409</td>
</tr>
<tr>
<td>hydrocortisone (Solu-Cortef)</td>
<td>J1720 — injection, hydrocortisone sodium succinate, up to 100 mg</td>
<td>$2.42</td>
<td>$4.08</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>ixabepilone (Ixempra)</td>
<td>J9207 — injection, ixabepilone, 1 mg</td>
<td>$75.99</td>
<td>$64.69</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>ketoconazole (Nizoral)</td>
<td>J8499* — prescription drug, oral, nonchemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>medroxyprogesterone (Depo-Provera)</td>
<td>J1051 — injection, medroxyprogesterone acetate, 50 mg</td>
<td>$11.12</td>
<td>$8.23</td>
<td>96402</td>
</tr>
<tr>
<td>megestrol (Megace)</td>
<td>J8499* — prescription drug, oral, nonchemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>megestrol (Megace)</td>
<td>S0179 — megestrol acetate, oral, 20 mg</td>
<td>$0.66</td>
<td>$0.50</td>
<td>96409, 96413</td>
</tr>
<tr>
<td>melphalan (Alkeran)</td>
<td>J8600 — melphalan, oral, 2 mg</td>
<td>$9.29</td>
<td>$7.37</td>
<td>N/A</td>
</tr>
<tr>
<td>melphalan (Alkeran)</td>
<td>J9245 — injection, melphalan hydrochloride, 50 mg</td>
<td>$1,922.50</td>
<td>$1,315.21</td>
<td>96409, 96413</td>
</tr>
<tr>
<td>methylprednisolone (Medrol)</td>
<td>J7509 — methylprednisolone, oral, per 4 mg</td>
<td>$1.43</td>
<td>$0.88</td>
<td>N/A</td>
</tr>
<tr>
<td>methylprednisolone (Depo-Medrol)</td>
<td>J1020 — injection, methylprednisolone acetate, 20 mg</td>
<td>$3.78</td>
<td>$3.12</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>methylprednisolone (Depo-Medrol)</td>
<td>J1030 — injection, methylprednisolone acetate, 40 mg</td>
<td>$5.84</td>
<td>$3.30</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>methylprednisolone (Depo-Medrol)</td>
<td>J1040 — injection, methylprednisolone acetate, 80 mg</td>
<td>$9.52</td>
<td>$7.09</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>methylprednisolone (Solu-Medrol)</td>
<td>J1920 — injection, methylprednisolone sodium succinate, up to 40 mg</td>
<td>$2.32</td>
<td>$1.87</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>methylprednisolone (Solu-Medrol)</td>
<td>J1930 — injection, methylprednisolone sodium succinate, up to 125 mg</td>
<td>$5.50</td>
<td>$2.58</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>paclitaxel (Taxol)</td>
<td>J9265 — injection, paclitaxel, 30 mg</td>
<td>$15.84</td>
<td>$7.55</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>prednisolone (e.g., Orapred, Millipred)</td>
<td>J7510 — prednisolone, oral, per 5 mg</td>
<td>$0.59</td>
<td>$0.02</td>
<td>N/A</td>
</tr>
<tr>
<td>topotecan (Hycamtin)</td>
<td>J9351 — injection, topotecan, 0.1 mg</td>
<td>$18.00</td>
<td>$7.87</td>
<td>96413</td>
</tr>
<tr>
<td>trastuzumab (Herceptin)</td>
<td>J9355 — injection, trastuzumab, 30 mg</td>
<td>$85.52</td>
<td>$72.45</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>vinblastine (Velban)</td>
<td>J9360 — injection, vinblastine sulfate, 1 mg</td>
<td>$3.18</td>
<td>$1.01</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 Casodex) in column 24D and the drug name, strength and NDC (National Drug Code) in box 19 to ensure appropriate reimbursement.
## Ancillary Medications Used in Cancer Treatment

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HPCPCS Code — Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 2/1/12</th>
<th>Medicare Allowable (ASP + 6%) — Effective 1/1/12-3/31/12</th>
<th>CPT Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aprepitant (Emend)</td>
<td>J8501 — aprepitant, oral, 5 mg</td>
<td>$7.62</td>
<td>$6.17</td>
<td>N/A</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>J1626 — injection, granisetron hydrochloride, 100 mcg</td>
<td>$3.93</td>
<td>$0.74</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 the time of chemotherapy treatment, not to exceed a 24-hour dosage regimen — see also S0091</td>
<td>$59.01</td>
<td>$2.51</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>$0.09</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>$0.08</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>
</tr>
<tr>
<td>palonosetron (Aloxi)</td>
<td>J2469 — injection, palonosetron hydrochloride, 25 mcg</td>
<td>$44.52</td>
<td>$18.47</td>
<td>96374</td>
</tr>
</tbody>
</table>

## CPT Administration Code Descriptions

<table>
<thead>
<tr>
<th>CPT Administration Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>90471</td>
<td>Immunization administration (includes percutaneous, intradermal, subcutaneous or intramuscular injections); one vaccine (single or combination vaccine/toxoid) (Do not use 90471 in conjunction with 90473.)</td>
</tr>
<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>
<tr>
<td>11900</td>
<td>Injection, intraslesional; up to and including seven lesions</td>
</tr>
<tr>
<td>11901</td>
<td>Injection, intraslesional; more than seven lesions</td>
</tr>
<tr>
<td>11981</td>
<td>Insertion, nonbiodegradable drug delivery implant</td>
</tr>
<tr>
<td>11982</td>
<td>Removal, nonbiodegradable drug delivery implant</td>
</tr>
<tr>
<td>11983</td>
<td>Removal with reinsertion, nonbiodegradable drug delivery implant</td>
</tr>
<tr>
<td>20600</td>
<td>Arthrocentesis, aspiration and/or injection; small joint or bursa (e.g., fingers, toes)</td>
</tr>
<tr>
<td>20605</td>
<td>Arthrocentesis, aspiration and/or injection; intermediate joint or bursa (e.g., temporomandibular, acromioclavicular, wrist, elbow, ankle, olecranon bursa)</td>
</tr>
<tr>
<td>20610</td>
<td>Arthrocentesis, aspiration and/or injection; major joint or bursa (e.g., shoulder, hip, knee joint, subacromial bursa)</td>
</tr>
<tr>
<td>S1720</td>
<td>Bladder instillation of anticarcinogenic agent (including retention time)</td>
</tr>
</tbody>
</table>

## References
- HCPCS Level II Expert 2012
- FDA-approved indication (product-prescribing information).
- CMS (Centers for Medicare & Medicaid Services) — Medicare-Allowable First Quarter 2012 — Effective Dates 1/1/12-3/31/12.

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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 (AWP-Based Pricing)*</th>
<th>Medicare Allowable (ASP + 6%)*</th>
<th>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 (158.8) Malignant neoplasm of retroperitoneum and peritoneum — peritoneum, unspecified (158.9) Malignant neoplasm of pleura (163.<em>) Malignant neoplasm of thymus, heart and mediastinum — heart (164.1) Myeloid leukemia — acute (205.0</em>) Hereditary hemolytic anemias — other thalassemia (282.49) Sickle-cell disease (282.6_)</td>
<td>$6.18</td>
<td>$5.26</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.<em>) Malignant neoplasm of tongue (141.</em>) Malignant neoplasm of major salivary glands (142.<em>) Malignant neoplasm of gum (143.</em>) Malignant neoplasm of floor of mouth (144.<em>) Malignant neoplasm of other and unspecified parts of mouth (145.</em>) Malignant neoplasm of oropharynx (146.<em>) Malignant neoplasm of nasopharynx (147.</em>) Malignant neoplasm of hypopharynx (148.<em>) Malignant neoplasms of other and ill-defined sites within the lip, oral cavity and pharynx (149.</em>) Malignant neoplasm of colon (153.<em>) Malignant neoplasm of rectum, rectosigmoid junction and anus (154.</em>) Malignant neoplasm of nasal cavities, middle ear and accessory sinuses (160.<em>) Malignant neoplasm of larynx (161.</em>) 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>$59.34</td>
<td>$50.46</td>
<td>96413 96415</td>
</tr>
<tr>
<td>clofarabine (Clolar)</td>
<td>J9027 — injection, clofarabine, 1 mg</td>
<td>Lymphoid leukemia — acute (204.0_) 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></td>
<td>$141.75</td>
<td>$122.19</td>
<td>96413 96415</td>
</tr>
<tr>
<td>generic (Brand) Name</td>
<td>HPCS 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>CPT Admin Code(s)</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td>dactinomycin (Cosmegen)</td>
<td>J9120 — injection, dactinomycin, 0.5 mg</td>
<td>Malignant neoplasm of retroperitoneum and peritoneum — retroperitoneum (158.0) Malignant neoplasm of bone and articular cartilage (170.<em>) Malignant neoplasm of connective and other soft tissue (171.</em>) Malignant neoplasm of placenta (181._) Malignant neoplasm of testis — undescended testis (186.0) Malignant neoplasm of testis — other and unspecified testis (186.9) Malignant neoplasm of kidney and other and unspecified urinary organs — kidney, except pelvis (189.0) Neoplasm of uncertain behavior of genitourinary organs — placenta (236.1)</td>
<td>Malignant melanoma of skin (172.<em>) Kaposi’s sarcoma (176.</em>) Malignant neoplasm of ovary and other uterine adnexa (183.<em>) Malignant neoplasm of other and unspecified female genital organs (184.</em>) Malignant neoplasm of penis and other male genital organs (187.<em>) Malignant neoplasm of eye (190.</em>) Complications of transplanted organ — kidney (996.81) Complications of transplanted organ — heart (996.83)</td>
<td>$684.36 $577.38</td>
<td></td>
<td>96409</td>
</tr>
<tr>
<td>decitabine (Dacogen)</td>
<td>J0894 — injection, decitabine, 1 mg</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)</td>
<td>Lymphoid leukemia — acute (204.0_) Myeloid leukemia — acute (205.0_) Myeloid leukemia — chronic (205.1_)</td>
<td>$39.31 $33.19</td>
<td></td>
<td>96413 96415</td>
</tr>
<tr>
<td>degarelix (Firmagon)</td>
<td>J9155 — injection, degarelix, 1 mg</td>
<td>Malignant neoplasm of prostate (185)</td>
<td>N/A</td>
<td>$6.07 $2.80</td>
<td></td>
<td>96402</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>CPT Admin Code(s)</td>
</tr>
<tr>
<td>---------------------</td>
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<td>------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>fluorouracil (Adrucil)</td>
<td>J9190 — injection, fluorouracil, 500 mg</td>
<td>Malignant neoplasm of esophagus (150_) Malignant neoplasm of stomach (151_) Malignant neoplasm of colon (153_) Malignant neoplasm of rectum, rectosigmoid junction and anus — rectosigmoid junction (154.0) Malignant neoplasm of rectum, rectosigmoid junction and anus — rectum (154.1) Malignant neoplasm of pancreas (157_) Malignant neoplasm of female breast (174_) Malignant neoplasm of male breast (175_)</td>
<td>Vinal warts — condyloma acuminatum (078.31) Malignant neoplasm of lip (140_) Malignant neoplasm of tongue (141.1) Malignant neoplasm of major salivary glands (142_) Malignant neoplasm of gum (143.0) Malignant neoplasm of floor of mouth (144.0) Malignant neoplasm of other and unspecified parts of mouth (145.0) Malignant neoplasm of oropharynx (146.0) Malignant neoplasm of nasopharynx (147.0) Malignant neoplasm of hypopharynx (148.0) Malignant neoplasms of other and ill-defined sites within the lip, oral cavity and pharynx (149.0) Malignant neoplasm of small intestine, including duodenum (152.0) Malignant neoplasm of liver and intrahepatic bile ducts (155.0) Malignant neoplasm of gallbladder and extrahepatic bile ducts — extrahepatic bile ducts (156.1) Malignant neoplasm of gallbladder and extrahepatic bile ducts — ampulla of Vater (156.2) Malignant neoplasm of gallbladder and extrahepatic bile ducts — other specified sites of gallbladder and extrahepatic bile ducts (156.8) Malignant neoplasm of gallbladder and extrahepatic bile ducts — biliary tract, part unspecified (156.9) Malignant neoplasm of nasal cavities, middle ear and accessory sinuses (160.0) Malignant neoplasm of larynx (161.0) Malignant neoplasm of trachea, bronchus and lung (162.0) Other malignant neoplasm of skin (173.0) Malignant neoplasm of cervix uteri (180.0) Malignant neoplasm of body of uterus — corpus uteri, except isthmus (182.0) Malignant neoplasm of ovary and other uterine adnexa (183.0) Malignant neoplasm of other and unspecified female genital organs (184.0) Malignant neoplasm of prostate (185.0) Malignant neoplasm of penis and other male genital organs (187.0) Malignant neoplasm of bladder (188.0) Malignant neoplasm of kidney and other and unspecified urinary organs — kidney, except pelvis (189.0) Malignant neoplasm of brain (191.0) Malignant neoplasm of other endocrine glands and related structures — adrenal gland (194.0) 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) Secondary malignant neoplasm of respiratory and digestive systems — liver, specified as secondary (197.7) Malignant neoplasm without specification of site — disseminated (199.0) Malignant neoplasm without specification of site — other (199.1) Neuroendocrine tumors — malignant carcinoid tumors of the small intestine (209.0) Neuroendocrine tumors — malignant carcinoid tumors of the appendix, large intestine and rectum (209.1) Neuroendocrine tumors — malignant carcinoid tumors of other and unspecified sites (209.2) Neuroendocrine tumors — malignant poorly differentiated neuroendocrine tumors (209.3) Neoplasm of uncertain behavior of other and unspecified sites and tissues — skin (238.2) Other retinal disorders — other proliferative retinopathy — other non diabetic proliferative retinopathy (362.29) Glaucoma — borderline glaucoma (glaucoma suspect) (365.0) Glaucoma — open-angle glaucoma (365.1) Glaucoma — primary angle-closure glaucoma (365.2) Glaucoma — corticosteroid-induced glaucoma (365.3) Glaucoma — glaucoma associated with congenital anomalies, dysostoses and systemic syndromes (365.4) Glaucoma — glaucoma associated with disorders of the lens (365.5) Glaucoma — glaucoma associated with other ocular disorders (365.6) Glaucoma — other specified forms of glaucoma (365.8) Glaucoma — unspecified glaucoma (365.9) Psoriasis and similar disorders — other psoriasis (696.1)</td>
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<td>J9303 — injection, panitumumab, 10 mg</td>
<td>Malignant neoplasm of colon (153.<em>) Malignant neoplasm of rectum, rectosigmoid junction and anus (154.</em>)</td>
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<td>pemetrexed (Alimta)</td>
<td>J9305 — injection, pemetrexed, 10 mg</td>
<td>Malignant neoplasm of trachea, bronchus and lung (162.<em>) Malignant neoplasm of pleura (163.</em>)</td>
<td>Malignant neoplasm of lip (140.<em>) Malignant neoplasm of tongue (141.</em>) Malignant neoplasm of major salivary glands (142.<em>) Malignant neoplasm of gum (143.</em>) Malignant neoplasm of floor of mouth (144.<em>) Malignant neoplasm of other and unspecified parts of mouth (145.</em>) Malignant neoplasm of oropharynx (146.<em>) Malignant neoplasm of nasopharynx (147.</em>) Malignant neoplasm of hypopharynx (148.<em>) Malignant neoplasm of other and ill-defined sites within the lip, oral cavity and pharynx (149.</em>) Malignant neoplasm of stomach (151.<em>) Malignant neoplasm of colon (153.</em>) Malignant neoplasm of rectum, rectosigmoid junction and anus (154.<em>) Malignant neoplasm of pancreas (157.</em>) Malignant neoplasm of nasal cavities, middle ear and accessory sinuses (160.<em>) Malignant neoplasm of larynx (161.</em>) Malignant neoplasm of female breast (174.<em>) Malignant neoplasm of male breast (175.</em>) Malignant neoplasm of cervix uteri (180.<em>) Malignant neoplasm of bladder (188.</em>) Malignant neoplasm of kidney and other and unspecified urinary organs — kidney, except pelvis (189.0) 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) Carcinoma in situ of digestive organs — lip, oral cavity (230.0) Carcinoma in situ of digestive organs — colon (230.3) Carcinoma in situ of digestive organs — rectum (230.4) Carcinoma in situ of respiratory system — larynx (231.0) Carcinoma in situ of breast and genitourinary system — breast (233.0) Carcinoma in situ of breast and genitourinary system — cervix uteri (233.1) Carcinoma in situ of breast and genitourinary system — bladder (233.7)</td>
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* Current code prices are effective as of 2/1/12. 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 1/1/12-3/31/12

**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 First Quarter — Effective Dates 1/1/12-3/31/12.

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Outlooks for patients with chemotherapy-resistant, castration-resistant prostate cancer (CRPC) are not optimal at present. New drug strategies (e.g., abiraterone or combination therapy with sunitinib and eribulin), new drug development (e.g., YM155) and/or personalized vaccine development may hold the key to a longer survival in this patient population.

**Title:** Abiraterone and increased survival in metastatic prostate cancer.  
**Authors:** de Bono J.S., Logothetis C.J., Molina A., et al.  
**Purpose:** The standard of care for men with advanced prostate cancer has been the deprivation of androgens. This results in a reduction in the concentration of prostate-specific antigen (PSA), tumor regression and symptomatic relief in most patients. However, these effects are not durable, with a reactivation of androgen-receptor signaling and an increase in PSA level. Nonhormonal therapies, such as docetaxel (Taxotere), cabazitaxel (Jevtana) and sipuleucel-T (Provenge), have been found to prolong survival. Abiraterone acetate (Zytiga) is a selective inhibitor of androgen biosynthesis that potentially blocks cytochrome P450 c17 (CYP17), an enzyme critical for testosterone synthesis, thereby blocking androgen synthesis by the adrenal gland, testes and within the prostate tumor itself. Early studies with abiraterone acetate as either a single agent or in combination with low-dose prednisone resulted in antitumor activity in patients with progressive CRPC whether or not they had received prior therapy. This study evaluates whether the drug prolongs overall survival (OS) in patients with metastatic CRPC who have received chemotherapy.  
**Methods:** Patients with histologically or cytologically confirmed prostate cancer who had previously been treated with docetaxel and had disease progression as defined by two consecutive increases in PSA over a reference value, radiographic evidence of soft tissue or bone progression with or without PSA increase, and ongoing androgen deprivation with a serum testosterone level of less than 50 ng/dL were eligible. All patients also had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and hematologic and chemistry values that met predefined criteria, including an albumin level of ≥ 3.0. Patients were excluded if aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values were ≥ 2.5 times the upper limit of normal, or if they had serious comorbid nonmalignant disease, viral hepatitis, uncontrolled hypertension and/or previous ketoconazole therapy. Patients were randomized in a 2:1 ratio to receive 1 g of abiraterone acetate or placebo orally once a day and prednisone 5 mg orally twice a day. Active drug or placebo were taken at least one hour prior to or two hours following a meal. Each treatment cycle was 28 days. Treatment continued until disease progression was documented on the basis of rising PSA levels, radiographic imaging and/or clinical findings. The primary endpoint of the study was OS. Secondary endpoints included the PSA response rate, defined as the proportion of patients with a decline of ≥ 50 percent in PSA from baseline, which was confirmed after ≥ four weeks by an additional PSA evaluation. Other secondary endpoints included progression-free survival (PFS) and side effects.  
**Results:** A total of 1,195 patients were randomly assigned to receive abiraterone acetate plus prednisone (n = 797) or placebo plus prednisone (n = 398). Baseline demographics and other characteristics were well-balanced between the two treatment arms. After a median follow-up of 12.8 months, OS was longer in the abiraterone plus prednisone arm...
Eribulin mesylate (Halaven) is a synthetic analogue of the marine sponge-derived natural product halichondrin B, which may overcome such resistance. It has demonstrated preclinical activity against prostate cancer cells that are paclitaxel (Taxol)-resistant due to beta-tubulin mutations. This phase 2 study evaluates the efficacy and safety of eribulin in patients with metastatic CRPC with or without prior taxane exposure.

Methods: Patients were required to have histologically proven metastatic prostate cancer with an ECOG performance status of 0 to 2. PSA progression, defined as a minimum of three serum PSA values taken ≥ one week apart to document two consecutive rises in PSA, with the last value being ≥ 5 ng/mL, was required, despite maintenance of castrate-level testosterone with orchiectomy or luteinizing hormone-releasing analogue and appropriate anti-androgen withdrawal. Patients were required to have adequate end-organ function and to have received no prior chemotherapy (except mitoxantrone [Novantrone] or estramustine [Emcyt] in the taxane-naive cohort), or must have failed no more than one previous chemotherapeutic regimen with a taxane in the taxane-pretreated cohort. Eribulin (1.4 mg/m²) intravenously over two to five minutes was infused on days one and eight of a 21-day cycle. Doses were reduced to 1.1 mg/m² on day one of the subsequent cycle for grade 4 neutropenia lasting for > seven days; grade 3 or 4 neutropenia with fever or infection; grade 4 thrombocytopenia or ≥ grade 3 thrombocytopenia requiring platelet transfusions; any grade 3 or 4 nonhematologic toxicity that returned to ≤ grade 2 within seven days; and delay of treatment by more than seven days due to persistent toxicity. Treatment on day eight was delayed for an absolute neutrophil count (ANC) of < 1.0 x 10⁹/L and/or platelet count of < 75 x 10⁹/L, or nonhematologic toxicity (any grade > 2, except inadequately treated nausea and vomiting). A second dose reduction to 0.7 mg/m² was permitted for grade 3/4 nonhematologic toxicity in patients responding to therapy. Patients continued eribulin until unacceptable toxicity, disease progression, investigator decision or withdrawal of patient consent. The primary endpoint of the study was a PSA response. Secondary endpoints included duration of PSA response, PFS, overall response rate (ORR), OS and toxicity.

Results: A total of 108 patients were enrolled: 58 who were taxane-naive and 50 who had been previously treated with a taxane and could be evaluated for safety and efficacy. The median age of the patients was 71 years. The majority of patients had an ECOG performance status of 0 or 1. Bone and lymph nodes were the most common site of metastatic disease, and visceral metastases were documented in just over 40 percent of those enrolled. The median number of treatment cycles was four (range one to 47) in the taxane-naive group and three (range one to 16) in those patients pretreated with a taxane. The PSA response rate was 22.4 percent (95 percent CI 12.5 to 35.3) for taxane-naive patients and 8.5 percent (95 percent CI 2.4 to 20.4) for taxane-pretreated patients. The ORR in taxane-naive patients was 15.2 percent (95 percent CI 5.1 to 31.9) with stable disease (SD) of ≥ 12 weeks in 75.8 percent of those with measurable disease. In the taxane-pretreated group, there were no partial responses, but 69 percent had SD of ≥ 12 weeks. Median PFS was 2.1 months (range 0.03+ to 32.2+) in the taxane-naive population and 1.9 months (range 0.03+ to 9.9) in those patients previously treated with a taxane.

Conclusion: Inhibition of androgen biosynthesis by abiraterone acetate prolonged OS in patients with metastatic CRPC who had previously received chemotherapy.

Managed Care Implications: Abiraterone acetate offers a well-tolerated oral alternative to patients with CRPC who have received previous chemotherapy. Its exact place in therapy versus additional chemotherapy with cabazitaxel has yet to be defined.

Title: Phase 2 study of eribulin mesylate (E7389) in patients with metastatic CRPC stratified by prior taxane therapy.

Authors: de Bono J.S., Molife L.R., Sonpavde G., et al.

OS was 20.8 months (range 2.2+ to 32.4+) and 15 months (1.0+ to 32.4+) in the respective groups. The most common toxicities seen in both groups included grade 3/4 neutropenia, leucopenia, fatigue and peripheral neuropathy.

**Conclusion:** Eribulin demonstrates activity and a relatively favorable toxicity profile in metastatic CRPC.

**Managed Care Implications:** Additional studies are needed, but eribulin mesylate may be a useful addition for patients with metastatic CRPC.

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**Title:** Long-term efficacy and tolerability of once-yearly histrelin acetate subcutaneous implant in patients with advanced prostate cancer.

**Authors:** Shore N., Cookson M.S., Gittelman M.C.


**Purpose:** Prostate cancer is the most frequently diagnosed cancer in the U.S. In patients with locally advanced or metastatic disease, androgen deprivation therapy (ADT) is commonly used. Testosterone promotes the growth of prostate cancer cells, and a reduction in the androgen level can be achieved by bilateral orchiectomy or medical castration through pharmacologic means by the administration of luteinizing hormone-releasing hormone (LHRH) agonists. The endpoint of ADT is to achieve a serum testosterone level of < 50 ng/dL, or serological castration. Patients with advanced or metastatic prostate cancer routinely receive LHRH agonists for extended periods with multiple administrations throughout the year. Histrelin (Vantas) is delivered via a subdermal hydrogel implant and is the only LHRH agonist approved for once-yearly administration. A dose of 50 mg of the drug, contained in a permeable hydrogel device, is placed subcutaneously in the inner aspect of the upper arm during an office-based procedure. It releases the drug at a rate of 50 µg per day. The drug is then released for approximately 12 months. Efficacy and tolerability of the once-yearly histrelin implant have been shown in the pivotal, open-label, single-arm study in 138 patients with advanced or metastatic prostate cancer. The present study enrolled eligible patients into an extension phase to assess the efficacy and tolerability of the histrelin implant for ≥ 2 years.

**Methods:** Patients ages 45 and older with histologically confirmed stage III or IV adenocarcinoma of the prostate or progressively increasing PSA levels, serum testosterone levels of ≥ 150 ng/mL and a life expectancy of at least one year were included. Patients also had to complete one year of therapy during the pivotal trial, and they received a histrelin implant at week 52 and had a PSA and clinical response at week 60. Implants were replaced at week 104 and every 52 weeks thereafter as long as a clinical benefit was maintained. Evaluation of serum testosterone and PSA levels were made at weeks 78, 91, 104 and every three months thereafter. Disease progression was assessed by measurement of PSA levels and clinical evaluation. The primary efficacy variable was the number and proportion of patients maintaining at least a castration level, < 50 ng/dL, of testosterone. Secondary efficacy variables were PSA status as a marker for disease progression and the patient’s pain level and performance status. The tolerability of the drug was also assessed.

**Results:** A total of 104 patients entered the extension study. The mean age was 74.8 years with more than 90 percent of patients older than age 65. Mean serum testosterone levels upon entry into the study were 15.1 ng/dL (range 8.5 to 41.4). The mean PSA level was 2.4 ng/mL (range 0.0 to 107.3). Long-term histrelin maintained serum testosterone levels well below the acceptable castrate levels of 50 ng/dL. Mean testosterone levels were 13.1, 14.8 and 10.8 ng/dL after two (n = 90, or 86.5 percent), three (n = 79, or 76.0 percent) and four years (n = 59, or 56.7 percent) of treatment, respectively. More than 90 percent of the patients at any observation point showed no worsening of their disease during treatment with the histrelin implant. The vast majority of patients requiring pain medication used non-narcotic analgesics with no
more than 12.1 percent of patients requiring the use of narcotic analgesics at any time during the study. The major toxicity of treatment with histrelin was hot flashes (64.4 percent), which were considered mild in most cases. Other adverse events included fatigue, gynecomastia and constipation.

**Conclusion:** Once-yearly histrelin implants maintain testosterone suppression for repeated cycles in patients with advanced or metastatic prostate cancer and is well-tolerated. It provides patients with another option for long-term androgen deprivation.

**Managed Care Implications:** Now approved by the U.S. Food and Drug Administration, once-a-year histrelin implants may prove to be a more cost-effective means of ADT by allowing for fewer office visits and repeated injections.

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**Title:** Sunitinib in combination with docetaxel and prednisone in chemotherapy-naive patients with metastatic CRPC: a phase 1/2 clinical trial.

**Authors:** Zurita A.J., George D.J., Shore N.D., et al.


**Purpose:** Clinical observations implicate the tumor microenvironment as a critical determinant of prostate cancer progression and therapy resistance. Since prostate cancer metastasizes to bone, therapeutic strategies have looked at bone-relevant stromal- and epithelial-interacting pathways, but single-agent therapy in this area has been disappointing. The drug combination of docetaxel (Taxotere) and prednisone has been identified to improve OS in patients with metastatic castrate-resistant prostate cancer (mCRPC). Combining a stromal-targeted therapy to this regimen may be beneficial, particularly since angiogenic growth factors, such as vascular endothelial growth factor (VEGF) A and C, have been implicated in disease progression and bone metastases. Sunitinib (Sutent) is an oral multitargeted inhibitor of VEGFR platelet-derived growth factor receptor and other cytokines and is currently approved for the treatment of advanced renal cell carcinoma and imatinib-intolerant gastrointestinal stromal tumors. The combination of sunitinib and docetaxel has been shown to inhibit growth of hormone-insensitive human prostate cancer xenographs.

**Methods:** Chemotherapy-naive patients with confirmed progressive mCRPC were enrolled. Progression was defined by either nonmeasurable disease and elevated PSA levels or measurable disease alone. Additional eligibility criteria included an ECOG performance status of 0 or 1, a testosterone level of < 50 ng/mL and adequate end-organ function. Treatment consisted of docetaxel administered intravenously every three weeks; sunitinib given orally on a two-week-on, one-week-off basis (schedule 2/1); and oral prednisone administered continuously at a dose of 5 mg twice a day. The endpoint of the phase 1 portion of the trial was to determine the appropriate dose of docetaxel and sunitinib for the phase 2 portion of the trial. In phase 2, the endpoints were to determine a confirmed PSA response rate, a mean time to PSA progression and toxicity.

**Results:** Thirty-two patients were enrolled in phase 1, of whom 25 were evaluable for dose-limiting toxicity (DLT). The median treatment duration was 5.8 months (range 0.5 to 23.7 months) with half the patients on study for greater than six months. The most common treatment-related grade 3/4 events were neutropenia (34 percent) and fatigue (13 percent). Disease progression was seen in 28 percent of the patients enrolled. The phase 2 dosing of the drugs was docetaxel 75 mg/m² and sunitinib 37.5 mg. Fifty-five patients were enrolled in the phase 2 portion of the trial. The patients had a mean baseline PSA of 57.6 ng/mL (range 7.4 to 417.8); most, 64 percent, had an ECOG
performance status of 0, and a majority, 73 percent, had bone metastases at time of enrollment. The median duration of therapy was 5.4 months (range 0.4 to 11.8) with 75 percent of patients receiving therapy for at least three months. The median number of cycles of chemotherapy was seven (range one to 16) with 12 patients (22 percent) receiving all 16 planned cycles. Confirmed PSA responses occurred in 31 patients (56.4 percent) with a median time to PSA progression of 9.8 months. Of the 33 patients with measurable disease, 14 (42.4 percent) had a confirmed Response Evaluation Criteria in Solid Tumors (RECIST)-defined partial response, and eight (24 percent) had SD. The median PFS was 12.6 months and the median OS was 21.7 months. The one-year survival probability was 85.5 percent and the two-year survival probability was 44.7 percent. The most frequently reported treatment-related adverse events were fatigue/asthenia (80 percent), diarrhea (73 percent) and neutropenia (56 percent). The most common grade 3/4 adverse events were neutropenia (53 percent), fatigue/asthenia (16 percent) and febrile neutropenia (16 percent).

**Conclusion:** The combination of docetaxel, sunitinib and prednisone was moderately well-tolerated with promising response rate and survival benefits in patients with mCRPC. Further investigation is warranted.

**Managed Care Implications:** Drugs with unique mechanisms of action, such as sunitinib, may have an important role to play in combination with standard chemotherapy in patients with mCRPC and overcome some means of therapy resistance.

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**Title:** A phase 2 study of YM155, a novel small-molecule suppressor of survivin, in castration-resistant taxane-pretreated prostate cancer.

**Authors:** Tolcher A.W., Quinn D.I., Ferrari A., et al.


**Purpose:** Survivin is a protein that inhibits apoptosis. Its expression is increased in most solid and hematologic malignancies but is undetectable in normal adult tissue. Survivin has been detected in prostate intraepithelial neoplasia, in both castrate-sensitive and castrate-resistant prostate cancer, and has been associated with a poor prognosis and increased rate of recurrence following local therapy. YM155 is a small-molecule suppressor of the anti-apoptosis protein survivin. It downregulates survivin gene expression at the messenger RNA (mRNA).

In preclinical models including prostate cancer cell lines, YM155 treatment resulted in a dose-dependent and time-dependent reduction in survivin mRNA and protein expression with increased apoptosis and tumor cell kill. A phase 1 study determined the maximum tolerated dose to be 4.8 mg/m²/day for 168 hours by continuous intravenous infusion (CIVI). Two patients with CRPC who had received prior docetaxel (Taxotere) had PSA responses. Based upon these findings, a phase 2 study was initiated.

**Methods:** Male patients with pathologically confirmed prostate cancer that was resistant to standard hormonal therapy and had received one prior taxane-containing chemotherapy regimen were eligible. Initiation of bisphosphonate therapy was not permitted during the study; however, patients were allowed to continue bisphosphonate therapy if it was initiated at least four weeks prior to the first dose of YM155. Other eligibility criteria included age ≥ 18 years old; life expectancy of ≥ 12 weeks; ECOG performance status of 0 to 2; PSA of > 5 ng/mL, with a rising level on at least two prior occasions at least one week apart; castration level of serum testosterone (≤ 50 ng/mL); a new evaluable lesion on imaging or progression of at least a 20 percent increase in objective tumor measurements since last treatment; and adequate end-organ function. YM155 was administered at a dose of 4.8 mg/m²/day by CIVI over 168 hours via a portable infusion pump in the ambulatory setting and repeated every three weeks. Besides blood sampling for population pharmacokinetic profiles, subjects with measurable disease at baseline had radiologic studies for disease status repeated after every other cycle. Study endpoints included PSA response—as defined by a 50 percent decline in PSA without evidence of radiologic...
or clinical progression that was confirmed by a second PSA value at least three weeks later—objective tumor response, safety, PFS and OS.

**Results:** Thirty-five patients with CRPC were enrolled, with 32 evaluable for response. A total of 128 cycles of YM155 was administered with the median number of cycles per patient being three (range one to 16+). Two of 32 patients (6 percent) had a PSA response lasting 21 and 112 days; two other patients had PSA decrements of > 50 percent that were not confirmed, and three additional patients had lesser falls in PSA that did not meet the criteria for response. Of the 16 patients with measurable disease, one (6.2 percent) had a partial response and another 8 (25 percent) had SD following six cycles of therapy. The median PFS was 3.1 months (95 percent CI 2.12 to 6.28 months) and the median OS was 11.2 months (95 percent CI 7.57 to 24.5 months). The most common adverse reactions were fatigue (63 percent), nausea (40 percent), anorexia (31 percent), fever (26 percent) and vomiting (26 percent).

**Conclusion:** YM155 had modest activity as a single agent in patients with CRPC who had been pretreated with a taxane, although 25 percent had at least stable disease for > 18 weeks. The regimen was well-tolerated. Additional studies with docetaxel are planned.

**Managed Care Implications:** New drugs with unique mechanisms of action and potential synergy with established agents used for the treatment of CRPC may offer a therapeutic alternative for patients with this disease.

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**Title:** Phase 2 study of personalized peptide vaccination for CRPC patients who failed docetaxel-based chemotherapy.

**Authors:** Noguchi M., Moriya F., Seukane S., et al.

**Reference:** Prostate. doi 10.1002/pros.21485.

**Purpose:** CRPC is the second-leading cause of cancer deaths in the developed world. Patients with metastatic disease may improve with androgen-deprivation therapy but eventually develop progressive disease. Chemotherapy with docetaxel (Taxotere) showed an improvement in OS and superiority to mitoxantrone (Novantrone)-based therapy. However, survival following progression on a docetaxel-based therapy is not optimal and new treatments are needed. Prostate cancer arises from a unique organ and may express a number of antigens against which an immune response can be generated. Immunotherapy with sipuleucel-T (Provenge) has been approved, but the survival benefit of this form of therapy is still under investigation. Personalized peptide vaccine (PPV) is a multiple peptide vaccine regimen planned according to pre-existing immunity that could prolong OS in patients with advanced cancer. Each patient is tested for immunological reactivity to many different peptides capable of inducing a cytotoxic T-lymphocyte (CTL) response. The purpose of this study was the selection of “personalized” antigen peptides considered ideal for individual patients in consideration of the pre-existing host immunity before vaccination.

**Methods:** Patients were eligible if they had a histological diagnosis of adenocarcinoma of the prostate and progressive disease by clinical, radiological or PSA criteria, despite adequate medical or surgical castration therapy with or without prior docetaxel, and showed a positive humoral response to at least two of 31 different candidate peptides, determined by both human leukocyte antigen (HLA)-class IA types and the titers of IgG against each peptide. Patients had to be at least four weeks past any prior chemotherapy or radiation therapy, or a change in hormonal therapy. Additional criteria included age ≥ 20; ECOG performance status of 0 or 1; positive status for HLA-A2, -A24, -A3 supertype or -A26, and a life expectancy of at least 12 weeks. Patients also needed to have adequate hematologic, hepatic and renal function. The study was a nonrandomized open-label phase 2 study; the primary and secondary endpoints were OS and to evaluate the immunological activity and safety in CRPC patients under treatment with PPV. The selection of
the right peptides for vaccination to individual patients was based upon results of HLA typing and peptide-specific IgG titers to each of 31 different vaccine candidates. Selected peptides were mixed with incomplete Freund’s adjuvant to a maximum of four peptides of 1.5 mL emulsion each, at a dose level of 3 mg/peptide injected into the thigh or armpit area once a week for a total of six doses. After the first cycle of six vaccinations of up to four antigen peptides, the antigen peptides were reselected according to the titers of peptide-specific IgG at every cycle of six vaccinations, and administered at two-, three- or four-week intervals until unacceptable toxicity or withdrawal of consent. Outcomes were assessed by post-therapy changes in serum PSA and computed tomography or magnetic resonance imaging of measurable disease symptoms if present at baseline. Partial response (PR) was defined as a decrease in PSA level of ≥ 50 percent and confirmed by two separate measurements at least four weeks apart. Post-therapy decreases of < 50 percent or increases of < 25 percent from baseline were interpreted as stable disease. For measurable disease symptoms, RECIST was used.

**Results:** A total of 42 patients with CRPC were enrolled in the study. Twenty had received prior docetaxel therapy and 22 had not. The median number of docetaxel cycles was 6.5. All patients received ADT prior to study enrollment. The median number of vaccinations was 13.5 (range five to 26) for patients previously treated with docetaxel and 14 (range six to 30) for those not previously treated with the drug. A PSA decrease by ≥ 50 percent was observed in 15 percent of patients with prior docetaxel exposure and 9 percent in patients who were docetaxel-naïve. There were no objective responses observed during the study period. After a median follow-up of 11.1 months, the median OS was 14.8 months (95 percent CI 9.7 to 22.2 months) in the patients with prior docetaxel treatment and not reached in patients without prior docetaxel therapy (p = 0.07). To assess the usefulness of PPV for patients with prior docetaxel exposure, the investigators compared the median OS for the date of progressive disease after docetaxel chemotherapy was treated by PPV with historical data in patients not receiving PPV following docetaxel therapy. During a median follow-up of 15.5 months, the median OS was 17.8 months (95 percent CI 14.9 to 20.6 months) in patients with PPV and 10.5 months (95 percent CI 7.1 to 14.0 months) in patients treated with docetaxel alone. Cox proportional hazard analysis to identify prognostic factors significantly associated with OS found that IL-6 in prevaccination samples was the only one significantly associated with OS (p = 0.0012). There were no grade 4 toxicities and no treatment-related deaths. The most frequent adverse events were dermatologic reactions at the injection site (n = 39), lymphopenia (n = 15), increased AST (n = 12), hypoalbuminemia (n = 11) and bone pain (n = 9).

**Conclusion:** Further clinical study of PPV is recommended for docetaxel-resistant CRPC patients. The therapy is safe and possibly prolongs survival time. Control of elevated IL-6 by combined therapy may provide a much better clinical outcome.

**Managed Care Implications:** OS for patients with chemotherapy-resistant CRPC is not optimal. New therapies, such as vaccines and other types of immunotherapy, may improve the outlook for this patient population.
This resource guide features links and websites specific to prostate cancer 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 prostate cancer.

www.cancer.org/Cancer/ProstateCancer/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. This website includes a portal for prostate cancer; it offers resources on new research.

http://prostate.jco.org

**CancerNet.** This website from the ASCO provides peer-reviewed information on prostate cancer, including clinical trials, staging, treatment, illustrations and current research.

www.cancer.net/patient/Cancer+Types/Prostate+Cancer

**Centers for Disease Control and Prevention (CDC).** The CDC funds efforts to improve the awareness, diagnosis, understanding and treatment of prostate cancer.

www.cdc.gov/cancer/prostate/index.htm

**eMedicineHealth.** Owned and operated by WebMD, this consumer health information website contains health and medical articles written by physicians, including information regarding prostate cancer.

www.emedicinehealth.com/prostate_cancer/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 section is devoted to issues about prostate cancer.

www.mayoclinic.com/health/prostate-cancer/DS00043

**MedlinePlus.** A service of the U.S. Library of Medicine and U.S. National Institutes of Health, this website offers links to peer-reviewed articles and abstracts on prostate cancer, clinical trial information, glossaries, statistics and more.


**National Cancer Institute (NCI).** The NCI conducts and supports cancer-related research, training and health information dissemination. This online guide provides patient information plus links to published literature, clinical trials and research on prostate cancer.

www.cancer.gov/cancertopics/types/prostate

**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 prostate cancer.

www.nccn.org/professionals/physician_gls/f_guidelines.asp

**OncoLink Information and Resources.** 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 includes information on treatment, clinical trials and other resources for prostate cancer.

www.oncolink.org/types/article.cfm?c=16&s=57&ss=608&id=8039

**Prostate Cancer Foundation (PCF).** Founded in 1993, the PCF focuses on finding better treatments and a cure for prostate cancer. The foundation is a world leader in funding prostate cancer research. The PCF website includes information on diagnosis, treatment, clinical trials and grants.

www.prostatecancerfoundation.org

*Note: iCORE Healthcare does not endorse or verify the information presented.*
Oncology continues to be the summit’s primary focus. However, since many payor management techniques are transferable across other specialty products, we are excited to extend our summit to include other therapies, including autoimmune and neurological conditions. This discussion will be held the day after on September 14th.

For more details, visit icorehealthcare.com or call us at 866-664-2673.
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