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IBC .......................................................... ICORE Healthcare
BC .......................................................... Amgen
The list of events that follows provides the dates and locations of upcoming meetings, workshops and conferences of interest to managed care oncology professionals.

May
7-10  9th Annual Armada Specialty Pharmacy Summit
Las Vegas, Nevada
31-June 4 American Society of Clinical Oncology’s Annual Meeting
Chicago, Illinois

June
12-14 America’s Health Insurance Plans’ Institute 2013
Las Vegas, Nevada
17-18 Institute for International Research’s Collaborative Summit for Oncology Management
Chicago, Illinois
20-22 Canadian Orthopaedic Association’s Annual Meeting
Winnipeg, Manitoba

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Thanks, and we hope you find the magazine useful.
ManagedCare Oncology has, in the past, reviewed various human habits and behaviors associated with an increased risk of cancers, including smoking, obesity and diet. Last month, a new study was published that prompted us to review yet another common preventable risk factor. You need to brace yourself if you like wine with dinner; you are not going to like the findings. In a forthcoming American Journal of Public Health article published online on February 14, 2013, David E. Nelson, M.D., M.P.H., and colleagues published “Alcohol-Attributable Cancer Deaths and Years of Potential Life Lost in the United States.”

It should be noted that Dr. Nelson is the director of the Cancer Prevention Fellowship Program at the National Cancer Institute. The study was a meta-analysis (basically, a study of previously published studies, in the event you are not a statistics geek) of other alcohol and cancer studies, and used a 2009 survey of U.S. citizens and other epidemiologic studies to evaluate alcohol use. The goal of this project was to provide up-to-date estimates of alcohol-attributable cancer mortality and the years of potential life lost (YPLL) if you developed such a cancer in the United States. By the way, the YPLL was new to me, but I like the concept a lot — sort of like number needed to treat.

The researchers found approximately 20,000 cancers per year associated with alcohol use, which represents roughly 3.5 percent of total annual cancers in our country. Most alcohol-attributable cancer deaths in women were from breast cancer (about 60 percent), while men most commonly suffered upper airway and esophageal cancer (also about 60 percent). The researchers estimated that if you did die of alcohol-related cancer, your life was shortened by about 18 years (this is the YPLL statistic).

Much of this was not new; we have known for a while now that alcohol is associated with an increased risk of developing cancer, and that smokers who also drink face an even greater risk of cancer. A recent study graphically shows that these risks are almost completely due to heavy alcohol use, as seen in Figure 1. These historical studies have associated alcohol use with oral, esophageal, laryngeal, pharyngeal, breast, colorectal and certainly liver cancers. Here is the new part: Previous studies associated heavy alcohol consumption with increased cancer risks, but Dr. Nelson’s study found consumption of ≤ 1.5 drinks per day accounted for 26 to 35 percent of alcohol-attributable cancer deaths!

We must remember that meta-analysis is a somewhat controversial study approach. (Remember the use of hormone replacement therapy in women to prevent heart disease? That was a meta-analysis recommendation until a randomized controlled trial was performed and discredited the findings.) Regardless, this is more confirmation that moderation matters. Nonetheless, it’s Sunday evening and I was going to have a chenin blanc–viognier... darn.

I am raising my glass of green tea to a warm spring!

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

Figure 1. Types of Cancer Associated with Alcohol Use and Overuse

Graph showing the proportion of different types of cancer estimated to be attributable to alcohol overall, and to drinking more than the recommended limits

References
Magellan Pharmacy Solutions analyzed paid medical claims for health plan members for calendar year 2011 with a malignant neoplasm of the pancreas (primary ICD-9 diagnosis codes 157.0 through 157.4, 157.8 and 157.9). The following table illustrates these claims across Medicare and commercial lines of business (LOBs), with an average of $9.7 million in allowed drug claims per 1 million member lives for those with a pancreatic cancer diagnosis code. In keeping with the increased incidence in aging populations, allowed dollars for pancreatic cancer are more heavily weighted toward the Medicare LOB.

### Medical Claims for Diagnosis Codes 157.0 through 157.4, 157.8 and 157.9 per 1M Lives — Line of Business (LOB)

<table>
<thead>
<tr>
<th>LOB Description</th>
<th>Average Allowed per 1M</th>
<th>Average Units per 1M</th>
<th>Average Claims per 1M</th>
<th>Average Members per 1M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial</td>
<td>$5,676,030.10</td>
<td>328,489</td>
<td>10,502</td>
<td>2,237</td>
</tr>
<tr>
<td>Medicare</td>
<td>$13,640,453.33</td>
<td>938,316</td>
<td>26,999</td>
<td>6,288</td>
</tr>
<tr>
<td>Grand total</td>
<td>$19,316,483.43</td>
<td>1,266,805</td>
<td>37,501</td>
<td>8,525</td>
</tr>
</tbody>
</table>

**Notes:**
1. Population includes plans with commercial and Medicare members
2. Data calendar year 2011
3. Based on primary diagnosis of 157.0 through 157.4, 157.8, 157.9
4. Outliers excluded

Using the same data, Magellan Pharmacy Solutions analyzed these claims by site of service (SOS), revealing that drug administration services for pancreatic cancer — in terms of average units, claims and members per 1 million — were received in the physician’s office in the majority of cases. This follows the fact that this setting tends to be one of the more economical sites of care for all stakeholders. The SOS analysis confirms this assertion, with the hospital outpatient setting carrying a significantly higher average cost per claim than other settings.

### Medical Claims for Diagnosis Codes 157.0 through 157.4, 157.8 and 157.9 per 1M Lives — Site of Service (SOS)

<table>
<thead>
<tr>
<th>SOS</th>
<th>Average Members per 1M</th>
<th>Average Allowed per 1M</th>
<th>Average Units per 1M</th>
<th>Average Claims per 1M</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI/SPP</td>
<td>1,064</td>
<td>$628,009.72</td>
<td>110,071</td>
<td>3,783</td>
</tr>
<tr>
<td>Hospital OP</td>
<td>2,329</td>
<td>$6,563,010.01</td>
<td>177,549</td>
<td>7,157</td>
</tr>
<tr>
<td>Other</td>
<td>642</td>
<td>$1,256,114.95</td>
<td>94,078</td>
<td>727</td>
</tr>
<tr>
<td>Physician</td>
<td>4,490</td>
<td>$10,869,348.75</td>
<td>885,108</td>
<td>25,834</td>
</tr>
<tr>
<td>Grand total</td>
<td>8,525</td>
<td>$19,316,483.43</td>
<td>1,266,805</td>
<td>37,501</td>
</tr>
</tbody>
</table>

**Notes:**
1. Population includes plans with commercial and Medicare members
2. Data calendar year 2011
3. Based on primary diagnosis of 157.0 through 157.4, 157.8, 157.9
4. Outliers excluded
Of the leading drugs on these pancreatic cancer claims, a nucleoside analog indicated for locally advanced or metastatic adenocarcinoma of the pancreas (Gemzar) featured the highest average allowed claims per 1 million lives, with the platinum-based chemotherapy Eloxatin carrying the next highest average. The supportive care agent Neulasta (a colony-stimulating factor) carried the third-highest average allowed claims per 1 million lives, followed by Sandostatin (a synthetic analog of the hormone somatostatin indicated as palliative treatment for carcinoid syndrome and used off-label in pancreatic cancer). Next was another off-label agent, Camptosar, which is approved for metastatic colorectal cancer. Supportive care agents round out the list, with Neupogen (a colony-stimulating factor), Aloxi (an antiemetic), Aranesp (an erythropoiesis-stimulating agent) and Emend (an antiemetic) having higher average allowed claims per 1 million lives than Taxotere in the 10th spot.

### Pancreatic Cancer Drug Spend — Average Allowed Claims per 1M Lives for Diagnosis Codes 157.0 through 157.4, 157.8 and 157.9

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average Allowed per 1M</th>
<th>Average Units per 1M</th>
<th>Average Claims per 1M</th>
<th>Average Members per 1M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemzar</td>
<td>$9,315,393.80</td>
<td>73,709</td>
<td>9,469</td>
<td>1,562</td>
</tr>
<tr>
<td>Eloxatin</td>
<td>$5,173,461.01</td>
<td>504,134</td>
<td>1,726</td>
<td>533</td>
</tr>
<tr>
<td>Neulasta</td>
<td>$1,267,155.45</td>
<td>465</td>
<td>465</td>
<td>299</td>
</tr>
<tr>
<td>Sandostatin</td>
<td>$766,991.43</td>
<td>7,083</td>
<td>298</td>
<td>65</td>
</tr>
<tr>
<td>Camptosar</td>
<td>$538,281.33</td>
<td>12,492</td>
<td>223</td>
<td></td>
</tr>
<tr>
<td>Neupogen</td>
<td>$487,351.06</td>
<td>1,319</td>
<td>761</td>
<td>382</td>
</tr>
<tr>
<td>Aloxi</td>
<td>$440,691.25</td>
<td>16,170</td>
<td>1,735</td>
<td>285</td>
</tr>
<tr>
<td>Aranesp</td>
<td>$388,904.73</td>
<td>114,073</td>
<td>240</td>
<td>119</td>
</tr>
<tr>
<td>Emend</td>
<td>$233,035.60</td>
<td>101,701</td>
<td>745</td>
<td>165</td>
</tr>
<tr>
<td>Taxotere</td>
<td>$182,639.68</td>
<td>8,745</td>
<td>103</td>
<td>51</td>
</tr>
<tr>
<td>Activease</td>
<td>$106,299.43</td>
<td>2,648</td>
<td>557</td>
<td>338</td>
</tr>
<tr>
<td>Procrit</td>
<td>$92,362.66</td>
<td>9,025</td>
<td>226</td>
<td>93</td>
</tr>
<tr>
<td>Fusilev</td>
<td>$80,789.71</td>
<td>47,707</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>S-FU</td>
<td>$72,338.87</td>
<td>27,748</td>
<td>3,452</td>
<td>676</td>
</tr>
<tr>
<td>Kytril</td>
<td>$35,169.68</td>
<td>10,233</td>
<td>1,061</td>
<td>226</td>
</tr>
<tr>
<td>Zofran</td>
<td>$24,480.00</td>
<td>94,727</td>
<td>2,898</td>
<td>428</td>
</tr>
<tr>
<td>Velcade</td>
<td>$16,950.40</td>
<td>177</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Heparin</td>
<td>$14,857.04</td>
<td>137,504</td>
<td>3,144</td>
<td>774</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>$12,439.47</td>
<td>4,736</td>
<td>1,499</td>
<td>164</td>
</tr>
<tr>
<td>Glucagen</td>
<td>$8,655.32</td>
<td>67</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Zometa</td>
<td>$7,897.61</td>
<td>30</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Presc script, generic (Price could not be determined)</td>
<td>$6,033.63</td>
<td>1,257</td>
<td>46</td>
<td>15</td>
</tr>
<tr>
<td>Dexamethasone sodium phosphate</td>
<td>$5,320.60</td>
<td>52,160</td>
<td>4,738</td>
<td>706</td>
</tr>
<tr>
<td>Low osmolar contrast material</td>
<td>$5,090.45</td>
<td>2,074</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Venofer</td>
<td>$4,263.89</td>
<td>12,232</td>
<td>61</td>
<td>31</td>
</tr>
<tr>
<td>Midazolam</td>
<td>$4,051.71</td>
<td>1,091</td>
<td>227</td>
<td>209</td>
</tr>
<tr>
<td>Cipro</td>
<td>$3,440.66</td>
<td>38</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Dextrex</td>
<td>$3,242.21</td>
<td>225</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Atropine sulfate</td>
<td>$2,994.99</td>
<td>13,505</td>
<td>368</td>
<td>73</td>
</tr>
<tr>
<td>Leukine</td>
<td>$2,956.12</td>
<td>113</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Sublimaze</td>
<td>$2,054.27</td>
<td>1,400</td>
<td>206</td>
<td>187</td>
</tr>
<tr>
<td>Platinol</td>
<td>$1,357.16</td>
<td>516</td>
<td>215</td>
<td>17</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>$1,093.18</td>
<td>1,216</td>
<td>72</td>
<td>57</td>
</tr>
<tr>
<td>Gad-base MR contrast NOS, 1 ml</td>
<td>$882.42</td>
<td>75</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mefoxin</td>
<td>$815.98</td>
<td>15</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Invanz</td>
<td>$798.55</td>
<td>22</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>$733.85</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Levaquin</td>
<td>$718.03</td>
<td>46</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>$716.76</td>
<td>694</td>
<td>363</td>
<td>70</td>
</tr>
<tr>
<td>Zantac</td>
<td>$658.88</td>
<td>783</td>
<td>391</td>
<td>79</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>$499.80</td>
<td>84</td>
<td>49</td>
<td>42</td>
</tr>
</tbody>
</table>
Pancreatic Cancer Diagnosis — Average Allowed Claims per 1M Lives for Diagnosis Codes 157.0 through 157.4, 157.8 and 157.9

<table>
<thead>
<tr>
<th>Diagnosis Code</th>
<th>Average Allowed per 1M</th>
<th>Average Units per 1M</th>
<th>Average Claims per 1M</th>
<th>Average Members per 1M</th>
</tr>
</thead>
<tbody>
<tr>
<td>157.0 Malignant neoplasm of head of pancreas</td>
<td>$4,324,747.37</td>
<td>287,396</td>
<td>7,568</td>
<td>1,674</td>
</tr>
<tr>
<td>157.1 Malignant neoplasm of body of pancreas</td>
<td>$1,931,932.17</td>
<td>174,552</td>
<td>5,410</td>
<td>731</td>
</tr>
<tr>
<td>157.2 Malignant neoplasm of tail of pancreas</td>
<td>$1,221,186.94</td>
<td>51,468</td>
<td>3,008</td>
<td>629</td>
</tr>
<tr>
<td>157.3 Malignant neoplasm of pancreatic duct</td>
<td>$1,855,483.62</td>
<td>15,375</td>
<td>947</td>
<td>640</td>
</tr>
<tr>
<td>157.4 Malignant neoplasm of islets of Langerhans</td>
<td>$53,329.25</td>
<td>300</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>157.8 Malignant neoplasm of other specified sites of pancreas</td>
<td>$1,692,372.39</td>
<td>51,774</td>
<td>2,563</td>
<td>368</td>
</tr>
<tr>
<td>157.9 Malignant neoplasm of pancreas, part unspecified</td>
<td>$8,237,431.71</td>
<td>685,940</td>
<td>17,974</td>
<td>4,455</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$19,316,483.43</strong></td>
<td><strong>1,266,805</strong></td>
<td><strong>37,501</strong></td>
<td><strong>8,525</strong></td>
</tr>
</tbody>
</table>

Notes:
1. Population includes plans with commercial and Medicare members
2. Data calendar year 2011
3. Based on primary diagnosis of 157.0 through 157.4, 157.8, 157.9
4. Outliers excluded

In looking at claims by diagnosis code, Magellan Pharmacy Solutions found that malignant neoplasms of the islets of Langerhans carried the lowest average allowed claims per 1 million lives among all pancreatic cancer claims. Conversely, malignant neoplasms of unspecified parts of the pancreas carried the highest average allowed claims per 1 million lives. These various diagnosis codes also generally followed suit in terms of average units, claims and members per 1 million, with malignant neoplasms of the islets of Langerhans being far less prevalent and unspecified sites in the pancreas being the most commonly coded.

Pancreatic Cancer Drug Spend — Average Allowed Claims per 1M Lives for Diagnosis Codes 157.0 through 157.4, 157.8 and 157.9
Managing the Quality and Cost of Medical Injectable Utilization:

A PAYMENT DENIAL PROGRAM BASED ON APPROPRIATE DIAGNOSES AND UNITS

Based in Massachusetts, Harvard Pilgrim Health Care (HPHC) is an independent, not-for-profit health benefits company serving members throughout New England and beyond. An innovator in managed care, the plan offers a myriad of coverage options designed to offer premium savings and exceptional choice without sacrificing quality. In fact, Harvard Pilgrim consistently ranks among the leading plans in the country in terms of health care quality, and recently topped the list of America’s Best Health Plans for the ninth year in a row. ManagedCare Oncology recently sat down with Andrea Grande, R.Ph., director of pharmacy operations, Harvard Pilgrim Health Care, to discuss how one of the most highly regarded payors in the nation began addressing the management of medical injectables.

MCO: What was the impetus at Harvard Pilgrim for initiating the management of medical injectables?

Ms. Grande: Even though we have an open formulary, we manage our drugs aggressively on the pharmacy side. Infusible drugs on the medical benefit side had really not been managed, though the capability was available. With that, we wanted to be appropriately cautious on how we identified programs to help mitigate costs while supporting our provider community. For this reason, we wanted to look at some innovative programs for medical infusible drug utilization management.

Last fall, I served on our Clinical Savings Strategy Committee (CSSC) and chaired the Oncology Strategy Work Group, which was charged with delivering a program that continued to ensure the highest quality of care for Harvard Pilgrim members who were diagnosed with cancer, while simultaneously reducing the high cost associated with infusible/injectable oncology and other selected infusible drugs. The focus of the Oncology Strategy Work Group was to implement a drug intervention program to address appropriate diagnoses and use for drugs paid under the medical benefit, which as I mentioned before, had not previously been managed.
MCO: Did you use an outside vendor to assist you in this process? Can you describe that interaction?

Ms. Grande: ICORE, one of our limited network specialty pharmacies, provided a cost-savings solution for medical injectable drugs that projected an annual savings of 10 to 15 percent. Most of the program focused on oncology infusibles; a lesser portion, 44 percent, was other targeted injectable drugs paid under our medical benefit. So they essentially did an analysis on specific medical injectables, and there was a lot of money that could be saved if we implemented a payment denial program based on ICORE’s criteria, as they use the National Comprehensive Cancer Network as one of their primary references, well known across the health care industry as a dependable compendia source, among others, for appropriate diagnosis and units.

MCO: What factors played into your decision to move forward with a payment denial program based on ICORE’s criteria?

Ms. Grande: The projected cost savings along with the supporting documentation presented to us by ICORE is what really made us move forward and say, “Let’s do this.” Upon reviewing these projected savings, it was agreed that this was a win-win situation, especially since most of the edits for eligible diagnoses and units were being implemented by ICORE at CMS [Centers for Medicare and Medicaid Services] in the spring of 2012. Being a CMS-approved initiative legitimized this action in the eyes of providers and gave the support to the physician groups to move forward. It’s a cost-savings measure, but it’s a quality initiative as well, in that we’re trying to ensure that these high-cost medical injectables are being appropriately prescribed and administered. As such, the quality of ICORE’s data also played into our decision. Their clinical claims edit program, which is based on nationally recognized sources, including published literature and compendia, includes a comprehensive list of medical injectable drugs for which ICORE has developed a set of post-service claim edits that evaluates for medically eligible diagnoses and maximum units supported by clinical medical policy.

MCO: Can you describe the steps necessary in operationalizing the program?

Ms. Grande: The program consisted of Harvard Pilgrim implementing ICORE’s Claim Payment edit criteria as an adjunct to our internal claims payment platform, iCES. As part of the post-service claims edit process, 30-plus medical injectable/infusible drugs are reviewed. Again, the goal of this process is to reduce clinically unnecessary medical infusible drug claim costs. So we deployed ICORE’s clinical information via edits directly in our system. To start, Clinical Policy, with Medical Management, reviewed ICORE’s policies and created HPHC Medical Clinical Policy in our own custom format. In May 2012, after these policies were approved, providers were notified through Harvard Pilgrim’s electronic communication, Network Matters. Beginning on August 1, 2012, HPHC went live with ICORE’s proprietary drug claims edit program. Medical drug claims submitted by providers on or after this date, for those selected medical injectable drugs, were subjected to claim payment edits for eligible diagnoses and allowed units.
Payment Policy coded all the claims edits and Clinical Policy/UM [Utilization Management] created the medical policies based on the information provided by ICORE. It’s a payment denial rather than a prior authorization, so it either pays or it doesn’t pay. If it doesn’t pay, we obviously allow the providers to appeal, and we’re working in partnership with ICORE to do the extra review work in the appeals process, whether it is providing extra documentation, or compendia, or a peer-to-peer consultation. That said, experience has shown that there has been minimal push-back, as again these edits are used by CMS and are in place to support appropriate utilization while promoting critical cost savings in this area. If there are appeals, this will be reviewed by Utilization Management with support from ICORE.

**MCO:** What are some of the obstacles you faced when implementing the program?

**Ms. Grande:** Operationally, most of this was done outside of the pharmacy department, so I had to work with different business areas to actually get it to go live. It was a great team and we met all the project management deadlines that were set forth when we kicked things off. Importantly, there were coding edits that needed to get done. We had UM clinicians and clinical policy staff helping to write all the policies with the supporting documentation that ICORE provided to us. We have two different policy committees that oversee all of medical policy, so these new payment policies had to get vetted through each of them before we actually got the OK to go live. So like any health plan, there are many different committees and different operational impacts, but we worked through it and it was a great team effort internally — we met the deadlines. ICORE was a great partner throughout the entire process.

**MCO:** Can you describe the extent to which ICORE is involved in the program on a day-to-day basis?

**Ms. Grande:** Obviously, since we used ICORE’s proprietary information as the criteria on which our payment denials for medical injectables are based, their involvement was crucial in the very early stages. Beyond that, the program essentially runs itself through our own internal processes. However, the appeals process is the one area where there’s ongoing involvement on the part of ICORE. It’s our appeal process and it’s still being conducted in-house, but when there’s a request by a physician where he or she thinks a drug is appropriate for a specific patient despite not having the particular diagnosis associated with it, we’ll reach out to ICORE for their opinion. As our partner in this process, we might ask what their benchmark data show, or ask for our clinician to speak with their clinician. We’re much different from a lot of other health plans in that we essentially manage everything ourselves. Even on the pharmacy side, where we employ the services of a PBM [pharmacy benefit manager], it’s still our formulary, our P&T [pharmacy and therapeutics committee], and we manage those components in-house. Likewise, with the injectables on the medical side, even though ICORE has assisted us with their information, we’re managing it in-house. There are no ICORE systems or transfers of files going on. In addition, we receive quarterly updates regarding existing edits or new edits. If there are uses that are outside of what ICORE’s criteria consider appropriate diagnoses, that would be considered “off-label.” That’s when we’d go through a reconsideration review or appeals process. Again, it’s
not a prior authorization. We’re not doing these reviews before, but rather after, payment gets denied.

**MCO:** Have your relationships with provider networks been impacted with these programs?

**Ms. Grande:** As I mentioned before, there has been virtually no push-back from our provider networks. I can tell you that there have been inquiries for off-label uses, and we have included ICORE in their review; however, we haven’t heard any negative feedback that the foundation of the program is not appropriate. There have been some inquiries and some interactions with clinicians concerned about their patients continuing on a medication that may not be part of these approved diagnoses, but we’ve worked through such concerns with the providers. You certainly don’t want to interfere with a member’s treatment if it has been proven effective thus far, and we have the ability to provide authorization on a case-by-case basis.

**MCO:** What has your success been? What was the “secret” to this success? Will you change any component of the program based on what you’ve seen so far?

**Ms. Grande:** We’re definitely seeing savings and we should hit the projection that we were originally presented by ICORE. We took a quick look to see where we were at in November, but it takes a greater amount of time to see paid claims on the medical side, so there will be a run-out time frame. We also did another analysis in January, so we’re actively tracking it and it’s projecting very close to what we had hoped to save.

In terms of ensuring success, I would say that buy-in from providers and communication in general to all constituents are key; we’re very careful about communicating any changes before we roll them out. Before enacting this payment denial process, for example, we met with the major provider groups and made sure we had their buy-in. After that, we maintained the lines of communication so that we were available to answer any questions or address any concerns. Listening to any feedback you receive and responding accordingly is a very important part of the process. You also have to work collaboratively in different business groups with one common priority: the member. However, you want to support the providers that deliver the care and be cost-conscious for the benefit of everyone. It’s all about appropriate utilization, which ultimately is in the best interest of everyone involved, including the providers and the members.

**MCO:** Will you change any component of the program based on the results you’ve seen so far?

**Ms. Grande:** It’s a work in progress. Our expectations for the program were based on real data from 2011 that we filtered through all the edits to come up with projected savings. With that in mind, we moved forward with the program. We are actively looking to add additional edits to the program to further control the rising costs of these injectable drugs. That’s what we’ve been doing so far; every three months we apply new edits as information and ICORE suggest. If there’s new information that we can apply and create a new policy, that’s our focus — to build upon what we already have and continue to strive for improvement. There may be a time when we will need to move to a prepayment edit, such as prior authorization, to continue improving upon this critical initiative.
On November 1, 2012, the Centers for Medicare and Medicaid Services (CMS) issued the CY 2013 MPFS final rule, which softened the proposed rule published in July to some degree. The MPFS affects payment to all physicians and clinics. The proposed rule called for the estimated impact on total allowed charges for radiation oncology to be -14 percent and for radiation therapy centers to be -18 percent. The final rule calls for the estimated impact for radiation oncology and radiation therapy centers to be -7 percent and -9 percent, respectively. Figures in Table 1 are selected from the CY 2013 proposed and final rules issued by CMS.

The majority of these negative impacts on the MPFS stem from the practice expense (PE) relative value units (RVUs). Medicare physicians are reimbursed on a resource-based relative value scale (RBRVS) and under this system, medical procedures are ranked according to the relative costs of resources required to perform the procedures. There are relative value units for physician work, practice expense and malpractice expense, and CMS establishes physician work RVUs for new and revised codes based, in part, on its review of recommendations received from the American Medical Association/Specialty Society Relative Value Scale Update Committee (AMA RUC).

The PE RVUs are a significant focus for CY 2013, as the AMA RUC has been
revisiting the accuracy of available data related to the procedure times that are used to value physician work RVUs. Historically, physician surveys have estimated procedure time assumptions used in developing nonfacility PE RVUs, and frankly the procedure time assumptions are thought by CMS to be inflated. Physician intraservice time is one basis for allocating the appropriate number of minutes within the service period to account for the time used in care provided to patients. The number of intraservice minutes is allocated to both the clinical staff and equipment that assists the physician in providing a service. Some codes do not contain physician work; thus CMS has assumed that the nonphysician clinical staff performs the procedure in place of the physician. Consequently, codes without physician work are now going to be examined thoroughly.

There were two codes of serious concern regarding the PE proposed reductions. These are the intensity modulated radiation therapy (IMRT) treatment delivery (CPT® code 77418) and stereotactic body radiation therapy (SBRT) treatment delivery (CPT code 77373) codes. There is nophysician work associated with CPT codes 77418 and 77373. In addition, IMRT treatment delivery is on CMS’s list for close review because of rapid growth, high payment and frequent utilization. While significant attention is directed to the two aforementioned codes, there was a long list of radiation oncology codes that had proposed PE RVU reductions, such as the treatment device, special treatment procedure, image guidance and simulation codes.

CMS proposed to adjust the procedure time assumption for IMRT from 60 minutes to 30 minutes and the procedure time assumption for SBRT from 90 minutes to 60 minutes. Typically, centers have time allotments in the 15-30 minute range for IMRT patients. This is only for the actual time spent in the room, but clearly there is more time allotted for patient questions, time spent in the department and additional RT services outside the room.

In the final rule, CMS finalized its proposal to adjust the procedure times for IMRT and SBRT. CMS took into consideration the blaze of comments addressed to this proposal and is incorporating items that positively affect the PE RVUs for CY 2013 (Table 2). These are the finalized adjustments affecting the PE RVUs:

- Incorporating a second radiation therapist, 30 minutes of allocated service time, for CPT code 77418
- New equipment item, “IMRT accelerator”
- Radiation treatment vault and water chiller (incorporated in both 77418 and 77373)
- Updating price of the laser diode for patient positioning
- Reinstating seven pieces of equipment that were incorrectly removed from 77418 in CY 2012

<table>
<thead>
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<td>54 — Physician assistant</td>
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<td>1%</td>
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<td>3%</td>
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</tbody>
</table>

| MP RVU = malpractice relative value units; PE RVU = practice expense relative value units

### Table 2. CY 2012 and CY 2013 PE RVUs for CPT Codes 77418 and 77373

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>2012 PE RVU</th>
<th>Proposed 2013 PE RVU</th>
<th>Final 2013 PE RVU</th>
</tr>
</thead>
<tbody>
<tr>
<td>77418</td>
<td>IMRT treatment delivery</td>
<td>13.98</td>
<td>8.41</td>
<td>11.91</td>
</tr>
<tr>
<td>77373</td>
<td>SBRT treatment delivery, per fraction to 1 or more lesions, including image guidance, maximum of 5 sessions per course</td>
<td>46.82</td>
<td>33.66</td>
<td>37.22</td>
</tr>
</tbody>
</table>
Figure 1 demonstrates the overall impact to most radiation oncology codes’ ‘nonfacility practice expense’ RVUs for CY 2013. Figure 2 presents the CY 2013 radiation oncology nonfacility practice expense decreases, extrapolated from Figure 1.

The actual mechanism of the cut is related to adjustments in the conversion factor (CF). The CY 2013 final rule conversion factor is $25.0008, roughly a 26 percent reduction from last year, and this reduction to the CF affects every physician and freestanding practice in the country that accepts Medicare enrollees. Since the publication of the final rule, the legislature has stepped in once again with the American Taxpayer Relief Act of 2012 (H.R. 8) and averted the conversion factor reduction. The conversion factor for CY 2013 effective January 1 is $34.0230. Here is the equation for determining payment rates under the MPFS:

\[
\text{MPFS Payment Equation} = \left[ (\text{Work RVU} \times \text{Work GPCI}) + (\text{PE RVU} \times \text{PE GPCI}) + (\text{MP RVU} \times \text{MP GPCI}) \right] \times \text{Conversion Factor}
\]
The conversion factor converts every RVU into an actual dollar figure per geographic region of the United States and territories. The unstable CF has an impact on our industry in numerous ways; e.g., physicians and clinics may hold out on building cancer centers, hiring staff or purchasing equipment, software and other operational clinic supplies. Clearly, action must be taken to stabilize MPFS payments in the coming years.

Significantly, the RVU calculation includes the interest rate assumption and has also been reduced.

Equipment cost per minute is calculated as:

\[
(\frac{1}{\text{minutes per year} \times \text{usage}}) \times \text{price} \times \left(\frac{\text{interest rate}}{1-(1/((1+\text{interest rate})^{\text{life of equipment}}))}\right) + \text{maintenance}
\]

To expand on this topic, the calculation addresses the following:

- Minutes per year = maximum minutes per year if usage were continuous (that is, usage = 1); generally 150,000 minutes
- Usage = 0.5 is the standard equipment utilization assumption; 0.75 for certain expensive diagnostic imaging equipment
- Price = price of the particular piece of equipment
- Interest rate = sliding scale
- Life of equipment = useful life of the particular equipment
- Maintenance = factor for maintenance; 0.05

Historically, a single interest rate (of 11 percent) was applied across all equipment. Now CMS will apply a varying rate approach and since radiation oncology is capital intensive, the change will have a significant impact.

Figure 3 displays the historical Medicare national average payments for 77418 since CY 2005.

A typical course of IMRT therapy for one patient, the payment rate variance from CY 2012 to 2013, without the conversion factor reduction, is -12 percent.

Figure 4 displays the historical Medicare national average payments for stereotactic body radiation therapy treatment delivery. Note: Even without the conversion factor decrease, expect a large reduction for CY 2013.

Figure 5 is a snapshot of the different modalities of treatment we typically deliver and their CY 2012-2013 effects.
HOPPS RATES
Finally, Table 3 compares the CY 2013 Hospital Outpatient Prospective Payment System (HOPPS) rates for IMRT and stereotactic treatment delivery to the CY 2013 MPFS rates. For your reference, the CY 2012 HOPPS national average payment for IMRT treatment delivery is $475.85. The stereotactic treatment delivery codes that are reported differ based on the hospital outpatient setting versus the freestanding setting. CMS stated in the proposed rule that it would like to align hospital and freestanding payments, but as you can see from the final rule numbers, we are still seeing discrepancies.

Please also note that the American Taxpayer Relief Act of 2012 included a payment reduction on or after April 1, 2013, in a hospital for CPT code 77371, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of one session; multisource Cobalt 60-based. Currently this code is reimbursed under APC 0127 (Medicare national average rate of $7,910.51); however, this code will see a reassignment to APC 0067 (Medicare national average rate of $3,300.64).

Keep in mind that the MPFS CY 2013 final rule includes a laundry list of radiation oncology that CMS has “under review.” The suspect codes are as follows: 77280 — set radiation therapy field; 77285 — set radiation therapy field; 77290 — set radiation therapy field; 77301 — radiotherapy dose plan IMRT; 77338 — design MLC device for IMRT; 77372 — SRS linear-based; 77373 — SBRT delivery; 77402 — radiation treatment delivery; 77403 — radiation treatment delivery; 77404 — radiation treatment delivery; 77406 — radiation treatment delivery; 77407 — radiation treatment delivery; 77408 — radiation treatment delivery; 77409 — radiation treatment delivery; 77412 — radiation treatment delivery; 77413 — radiation treatment delivery; 77414 — radiation treatment delivery; 77416 — radiation treatment delivery; 77418 — radiation TX delivery IMRT; 77600 — hyperthermia treatment; 77785 — HDR brachytx 1 channel; 77786 — HDR brachytx 2-12 channel; 77787 — HDR brachytx over 12 channel; 88358 — electron microscopy.

In summary, the large blow to the radiation oncology codes was avoided under MPFS, but there still will be decreases. Radiation oncology practices have been warned: CMS is watching the industry like a hawk and questioning services, payments and surveys and looking at material distributed to patients. Industry leaders must think of effective ways to help these practices keep their doors open, keep their staffs, keep their patients and keep up with technology. To comment on rulings, speak to your representatives and stay involved in what is going on in Medicare rulings.

Table 3. Hospital and Freestanding IMRT and Stereotactic 2013 Payment Comparison

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>2013 HOPPS Rate</th>
<th>2013 MPFS Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>77418</td>
<td>IMRT treatment delivery</td>
<td>$483.70</td>
<td>$405.55</td>
</tr>
<tr>
<td>77372</td>
<td>Radiation treatment delivery, SRS, complete course of treatment of cerebral lesion(s) consisting of 1 session; linear accelerator-based</td>
<td>N/A</td>
<td>$784.91</td>
</tr>
<tr>
<td>77373</td>
<td>SBRT treatment delivery, per fraction to 1 or more lesions, including image guidance, maximum of 5 sessions per course</td>
<td>N/A</td>
<td>$1,268.72</td>
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<td>G0173</td>
<td>Linac SRS, 1 session course</td>
<td>$3,300.64</td>
<td>N/A</td>
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<tr>
<td>G0251</td>
<td>Linac SRS, per session, maximum of 5 Fxs</td>
<td>$978.25</td>
<td>N/A</td>
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<tr>
<td>G0339</td>
<td>Robotic SRS, 1 session or 1st Fx of SBRT course</td>
<td>$3,300.64</td>
<td>N/A</td>
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<td>G0340</td>
<td>Robotic SRS, per session, Fxs 2-5</td>
<td>$2,354.79</td>
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</table>
Management of Pancreatic Endocrine Cancer
Considerations for Managed Care Decision Makers

by Keith A. Thompson, M.D., partner and medical oncologist, Montgomery Cancer Center

Although this group of cancers is rare, the indolent nature of this family of malignancies and the long survival of patients stricken with this disease make it an important class of diseases for the managed care community.

INTRODUCTION
Pancreatic neuroendocrine tumors (PNETs) are a group of rare neoplasms that arise from the hormone-producing neuroendocrine system of the gut. Because they are derived from cells that produce hormones that typically regulate the function of the gastrointestinal tract, they can sometimes secrete a variety of peptide hormones. These overproduced peptide hormones may include insulin, gastrin, glucagon and vasoactive intestinal peptide (VIP), resulting in myriad clinical syndromes. Modern data suggest that up to 75 percent of PNETs are nonfunctioning: that is, they are not associated with a hormone oversecretion syndrome.

EPIDEMIOLOGY
Historical perception is that pancreatic endocrine cancer is a rare disorder, but this is a family of tumors that has been increasing in frequency in recent decades. An analysis of the Surveillance, Epidemiology and End Results Database shows the historical estimated annual incidence is less than one case per 100,000. Some recent analyses show rates have increased up to 2.2 per 100,000. There is a preponderance of males to females (2.6 to 1.8). More aggressive radiologic imaging behavior by providers may be contributing to this increase. In other words, the tumor was present but was asymptomatic and growing so slowly as to lie undiscovered in the pancreas for a long time.

Autopsy studies show a strikingly different picture compared to the clinical trials, with rates around 10 percent. Hence there are many people that die of other causes who never knew they had a PNET. Interestingly, 19 percent of all pancreatic cancer discovered incidentally on computed tomography (CT) scans done for other reasons are PNETs. This statistic confirms the large number of “silent tumors” in the general population.

ADDITIONAL CLINICAL CONSIDERATIONS
Perhaps more importantly, PNETs are associated with many other significant tumors such as cancers of the ovary, breast, bladder, prostate and esophagus. So when a PNET is
discovered, it should be followed by a diligent search for other malignancies. The PNETs may occur alone but they also may be part of a genetic syndrome such as MEN1, von Hippel-Lindau disease, neurofibromatosis-1 or tuberous sclerosis, as these are syndromes associated with particular genetic abnormalities that predispose the patient to other cancers.

**TUMOR CLASSIFICATION AND HISTOPATHOLOGY**

These tumors typically present with the symptoms of hormone hypersecretion or as a result of the mass effect of the primary cancer. Clinically, therefore, they are separated into “functional” or “nonfunctioning” depending on the presence of the syndrome of inappropriate hormone hypersecretion.

Because they are heterogeneous and rare, designing a prognostic stratification tool has been quite a challenge. The presence or absence of hypersecretion does not provide prognostic information. These tumors are divided pathologically into poorly differentiated or low-grade tumors. While there are differences in terminology and grading for these tumors arising at different sites, all commonly used classification systems reflect a basic separation between more indolent, well-differentiated tumors and far more aggressive, poorly differentiated types that behave clinically more like small-cell carcinoma of the lung.

**DIAGNOSIS AND MANAGEMENT**

The initial steps involved in the management of PNETs are based upon surgical resection of the primary tumor. Optimal management includes assessment for biologically active hormones, localization of the primary tumor, determination of the involvement of the lymph nodes, search for metastatic disease, thorough family history looking for patterns of malignancy, histologic review of the tumor and, when applicable, search for other malignancy.

The best management of a PNET is to surgically resect the lesion. However, only about 40 percent of tumors are resectable. Patients with unresectable disease have a wide variety of choices for therapy, ranging from somatostatin analogs to aggressive chemotherapy to peptide receptor radionuclide therapy.

**Symptoms and Diagnosis**

Patients present typically as asymptomatic but may present with diarrhea due to obstruction of the pancreatic duct resulting in the

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**References**

disruption of delivery of pancreatic digestive enzymes to the gut. Patients may also present with obstruction of the bile duct producing jaundice, or with pain in the upper abdomen simply related to the size and space-occupying nature of the tumor. Rarely, patients may present with gastric outlet obstruction.

The initial diagnostic workup focuses on determining whether a mass in the pancreas is a pancreatic adenocarcinoma or a PNET. CT scanning of a PNET often produces an image that is hyperdense, giving an important clue prior to needle or endoscopic biopsy.

The surgical resection should be carried out by a surgeon experienced in management of this type of tumor and should include a careful search for hidden other malignancy in the affected organs.

Management of Advanced Disease

Cytotoxic chemotherapy using streptozocin and doxorubicin or streptozocin and fluorouracil is an important component of managing advanced disease and had a response rate in the range of 45 to 69 percent. So despite their toxicity, these drugs remain in common use today.

Sunitinib and other tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF) receptors are active in patients with advanced disease. These agents offer modest and consistent responses in multiple clinical trials. One large trial comparing sunitinib to placebo showed a progression-free survival of 11.4 months versus 5.5 months on placebo.

Everolimus is also active in this disease and when used in chemotherapy failures had a 9 percent response rate and disease control rate of 72 percent.

There is also substantial evidence that PNETs, unlike carcinoid tumors, are sensitive to alkylation agents. The best use of these has yet to be defined but may include temozolomide alone or in combination.

Liver-Directed Therapy

Because the liver is often the initial and most serious site of advancing disease and because of the indolent nature of PNETs, this tumor is an ideal candidate for hepatic-related therapy. Therapeutic options include local ablation with surgical resection, radiofrequency ablation, cryotherapy, chemoembolization and radioembolization.

While the optimal sequence of many ablative, embolic and pharmacologic interventions remains unclear, it is certain that the first

References continued

therapies may be appropriate. The targeted therapies everolimus and sunitinib could be considered for use before or after conventional chemotherapy. Orthotopic liver transplantation may be pursued in special circumstances but is not considered standard treatment.

Special consideration for functional tumors requires a multidisciplinary team approach with careful glucose management (insulinoma) and aggressive antacid therapy (gastrinoma) as examples.

**Monitoring After Resection**

After successful resection, monitoring should include checking chromogranin A levels and hepatic imaging, yearly in most cases. The level of monitoring is directed by the original histology (indolent versus aggressive), the initial stage of the disease and the presence or absence of a hypersecretion syndrome.

**SUMMARY**

PNETs are a family of rare tumors that are often silent. Management involves surgical resection followed by monitoring for advanced disease. The liver is the most common site of advanced disease, and management includes a wide array of therapeutic options. The rarity of the tumor has not allowed development of clear guidelines on how to apply this myriad of therapies, so multidisciplinary teams with experience in PNets should manage those with advanced disease.

References continued

Employers face challenges similar to those of payors when it comes to navigating the vast and complex landscape of cancer treatment options and costs. Cancer is expected to cost American employers more than $264 billion in health care expenditures and lost productivity annually, including a share of the estimated $104 billion in yearly direct medical costs attributed to the disease. In addition, the costs associated with absenteeism and "presenteeism" (i.e., being present but not productive at work) are likely to be four times greater than spending on medical care. Cancer is among the leading causes of short-term disability in employees. Employers often find that the impact of a cancer treatment on an employee extends beyond the patient himself or herself, but also to the productivity of his or her co-workers, who may find themselves serving as caregivers. Furthermore, a cancer diagnosis adversely affects long-term employment patterns, with studies estimating that 36 percent of employees do not return to work after receiving treatment. Conversely, among those employees aged < 55 years, nearly 90 percent will return to work within a year of their diagnosis, representing a distinct challenge for employers who want to support these patients at work.

Despite the employer-specific impact and overwhelming magnitude of the indirect costs associated with cancer, direct medical expenditures linked to the disease remain a significant concern for both managed care and employer stakeholders alike. Cancer is the leading condition in terms of medical and pharmacy costs.
among employers, topping even the costs associated with cardiovascular conditions, diabetes and arthritis. This comes as no surprise considering that oncology therapies often fall into the category of speciality drugs, which typically undergo rigorous development and manufacturing processes and accordingly come with a high price tag. As such, while cancer-related disease accounts for only 1 percent of a typical employer’s health care claims, it often equates to >10 percent of health care costs.

Driven by agents for the treatment of cancer and other conditions such as rheumatoid arthritis and multiple sclerosis, speciality drugs are garnering attention from employers and payors as spending on these biologics continues to grow at an exponential rate. After years of double-digit growth, the annual yearly cost trend for speciality pharmaceuticals already represents 17 percent of drug spending by conservative estimates and is predicted to experience a tremendous boom in the near future. Specifically, by 2018, the speciality drug spend is expected to surpass that of traditional agents and account for 45 percent of pharmaceutical manufacturer sales.

Coupled with the growing ubiquity of cancer diagnoses, this growth in the speciality drug spend has given cause for employers to take notice and begin taking the necessary steps towards more effectively managing the disease. At least a third of Americans will be diagnosed with some form of cancer over the course of their lifetimes, and innovative — albeit costly — advances in diagnosis and treatment have shaped the course of the disease to resemble that of a chronic condition rather than the terminal illness it once was. This combination of factors, in addition to humanistic concerns such as the incidence of depression among those diagnosed with the disease, requires careful consideration on the part of employers. As they look for ways to address cancer and its related costs and worksite considerations, many employers are seeking guidance and information. In different areas of the country, employer coalitions serve to provide such knowledge and leverage necessary for understanding and managing this crucial and often sensitive subject.

**THE MIDWEST BUSINESS GROUP ON HEALTH EXPERIENCE**

Employers join business coalitions for a variety of reasons: networking with peers, learning about innovative health benefit strategies and industry trends, participating in group purchasing for benefits and services, and improving the quality and safety of the health care delivery system. There are more than 50 coalitions in the country, offering various services and programs addressing the unique or demonstrated needs of the public and private purchasers in their geographic areas.

Some coalitions focus primarily on the purchasing of health benefits or acquiring better discounts from providers in the community, while others focus on the sharing of knowledge and best practices. The Midwest Business Group on Health (MBGH) falls into this latter category, with a member base seeking practical knowledge on trends in the industry, sharing employer best practices and identifying new ways to save money on health care in a manner that ultimately benefits the employees and increases productivity for the employer.

One role MBGH serves for its members is as a filter through which national health care perspectives and issues may pass. MBGH supports its members — who come from >120 large public and private organizations representing >4 million lives — and helps them determine how they can get more value from their health care benefits and get more employees engaged in health-based initiatives.

MBGH examines, analyzes and reports on the health benefits management activities of public and private employers and the impact on the health of their covered populations. In addition, MBGH provides education through high-quality programming and activities that foster collaboration and networking among members and other health care stakeholders. Through its community initiatives, MBGH also participates in
Choosing Wisely®

The American Board of Internal Medicine (ABIM) and the Consumer Reports, in collaboration with the ABIM Foundation (ABIMF), have partnered to identify the right tests, procedures, and/or treatments whose common use and clinical value are not supported by available evidence (Table 1). According to ASCO, these specific test and treatment options should not be administered unless the physician and patient have carefully considered whether their use is appropriate in the individual case.

<table>
<thead>
<tr>
<th>Table 1. Five Categories of Tests, Procedures and/or Treatments Whose Common Use and Clinical Value in Oncology Are Not Supported by Available Evidence, as Designated by ASCO for the Choosing Wisely® Campaign</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Don’t use cancer-directed therapy for solid tumor patients with the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial and no strong evidence supporting the clinical value of further anticancer treatment.</td>
</tr>
<tr>
<td>• Studies show that cancer-directed treatments are likely to be ineffective for solid tumor patients who meet the above-stated criteria.</td>
</tr>
<tr>
<td>• Exceptions include patients with functional limitations due to other conditions resulting in a low performance status or those with disease characteristics (e.g., mutations) that suggest a high likelihood of response to therapy.</td>
</tr>
<tr>
<td>• Implementation of this approach should be accompanied with appropriate palliative and supportive care.</td>
</tr>
<tr>
<td>2. Don’t perform PET, CT and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.</td>
</tr>
<tr>
<td>• Imaging with PET, CT or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival.</td>
</tr>
<tr>
<td>• In breast cancer, for example, there is a lack of evidence demonstrating a benefit for the use of PET, CT or radionuclide bone scans in asymptomatic individuals with newly identified ductal carcinoma in situ (DCIS) or clinical stage I or II disease.</td>
</tr>
<tr>
<td>• Unnecessary imaging can lead to harm through unnecessary invasive procedures, overtreatment, unnecessary radiation exposure and misdiagnosis.</td>
</tr>
<tr>
<td>3. Don’t perform PET, CT and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.</td>
</tr>
<tr>
<td>• Imaging with PET, CT or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival.</td>
</tr>
<tr>
<td>• In prostate cancer, for example, there is a lack of evidence demonstrating a benefit for the use of PET, CT or radionuclide bone scans in asymptomatic individuals with low risk for metastasis.</td>
</tr>
<tr>
<td>• Unnecessary imaging can lead to harm through unnecessary invasive procedures, overtreatment, unnecessary radiation exposure and misdiagnosis.</td>
</tr>
<tr>
<td>4. Don’t perform surveillance testing (biomarkers) or imaging (PET, CT and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.</td>
</tr>
<tr>
<td>• Surveillance testing with serum tumor markers or imaging has been shown to have clinical value for certain cancers (e.g., colorectal). However, for breast cancer that has been treated with curative intent, several studies have shown there is no benefit from routine imaging or serial measurement of serum tumor markers in asymptomatic patients.</td>
</tr>
<tr>
<td>• False-positive tests can lead to harm through unnecessary invasive procedures, overtreatment, unnecessary radiation exposure and misdiagnosis.</td>
</tr>
<tr>
<td>5. Don’t use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20 percent risk for this complication.</td>
</tr>
<tr>
<td>• ASCO guidelines recommend using white cell stimulating factors when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen, is approximately 20 percent and equally effective treatment programs that do not require white cell stimulating factors are unavailable.</td>
</tr>
<tr>
<td>• Exceptions should be made when using regimens that have a lower chance of causing febrile neutropenia if it is determined that the patient is at high risk for this complication (due to age, medical history or disease characteristics).</td>
</tr>
</tbody>
</table>
Other clinical issues that employers are concerned about include advance directives (e.g., end-of-life care) and pharmacogenomic testing. Too often, patients may be given aggressive third- and even fourth-line therapy mere months before their eventual deaths, for which little or no clinical benefit can likely be expected. According to one study, > 20 percent of Medicare beneficiaries at different regional hospitals received treatment within one month of death. In these situations, hospice care is recommended as a means of sustaining optimal quality of life for patients and represents an opportunity for cost-savings. Along with this underutilization of hospice care, available pharmacogenomic tests that predict response to treatment with costly agents such as trastuzumab and cetuximab are required by approximately 70 percent of health plans, representing a missed opportunity for appropriate care and cost-savings.

On the business side, in terms of specialty drug benefit design, a lack of effective knowledge on the part of employers has proven to be a crucial issue. National employer surveys conducted by MBGH in 2011 and 2012 demonstrated that employers have a general lack of knowledge regarding biologic specialty drugs and that they continue to offer traditional pharmacy benefit designs for specialty benefits.

Specifically, 25 percent of employers had little to no understanding of specialty or biologics coverage, while 53 percent had a moderate understanding of this benefit. At the time of the survey, the vast majority of employers (71 percent) still used a traditional benefit design (e.g., tiered formularies, copayments and coinsurance) instead of value-based or innovative benefit designs that may be more appropriate for biologic/specialty pharmacy medications.

Furthermore, while vendor costs were the most important criteria employers cited when contracting with a specialty pharmacy, only 13 percent used a specialty pharmacy provider.

MBGH has been working to address these issues via an employer toolkit to support employers in more effectively managing their specialty pharmacy benefits. The toolkit offers ways that employers can better partner with their vendors, health plans, pharmacy benefit managers and specialty pharmacies, as well as offer more effective communications on specialty pharmacy benefits to their employees.

In addition, MBGH has worked to educate its members about the pros and cons of patient cost-sharing and the potential barriers to adherence that may exist. Discussions in this particular area have centered around the impact of cost-sharing and out-of-pocket maximums on treatment. The related concept of value-based programs for specialty drugs that encourage employees to remain adherent to costly therapies has likewise been explored.

The Evolving Role of Health Care Coalitions

While placing any sort of limitation on the coverage of cancer care was once considered taboo, the economic environment and dwindling financial resources available to employers have given rise to such discussions with payors in recent years. At one point not long ago, employers would pay for whatever the health plan recommended or allowed — from screening to treatment to hospice. However, employers are becoming increasingly savvy with regard to national trends, the available literature and the nuances of benefit design, and are having discussions with their health plans as well as employers. A valuable comprehensive resource for employers is the “Cancer Continuum of Care,” developed by the National Business Group on Health, at www.businessgrouphealth.org/cancer. This website offers employers a variety of information on strategies, benefit design, health, wellness and productivity programs related to cancer. Also, health care coalitions can be valuable partners in working with health plans, hospitals and physicians in assisting employers and their covered populations to address the key issues in cancer care and the treatment of other serious and chronic conditions.

References

Pancreatic cancer is also considered among the most lethal of cancers, ranking fourth as the most common cause of cancer death. Nearly 38,000 Americans are expected to die from pancreatic cancer this year — almost as many deaths as from breast cancer — according to the American Cancer Society. Yet there are only 45,000 new cases of pancreatic cancer a year compared with more than 230,000 new breast cancer cases.

The potent cytotoxic nab-paclitaxel (Abraxane, Celgene) has shown promising activity against advanced pancreatic cancer in combination with gemcitabine. Encouraging results from a phase 2 study led to a randomized phase 3 comparison of nab-paclitaxel plus gemcitabine versus gemcitabine alone. The results of the study, which involved 861 patients, were presented by Daniel Von Hoff, M.D., FACP, at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium in San Francisco in January 2013. In this trial, patients who received nab-paclitaxel plus gemcitabine, the standard drug for pancreatic cancer, lived a median of 8.5 months compared with 6.7 months for those receiving gemcitabine alone. At the end of one year, 35 percent of those receiving the combination were alive compared with 22 percent of those being treated with gemcitabine only; after two years, the figures were 9 percent for the doublet versus 4 percent for the single agent. Toxicities were modest and centered on reversible myelosuppression and peripheral neuropathy. A pivotal question around the uptake of nab-paclitaxel plus gemcitabine usage in pancreatic cancer could be that its median survival was almost three months less than that of FOLFIRINOX, a combination of four generic cancer drugs. Results of a phase 3 French clinical trial published in 2011 showed that pancreatic cancer patients treated with FOLFIRINOX had a median survival of 11.1 months compared with 6.7 months for those receiving gemcitabine. It is difficult to draw conclusions since nab-paclitaxel and FOLFIRINOX were not compared directly in the same trial, but nonetheless physicians are going to make treatment decisions based on the separate results. In addition, to decrease side effects most physicians are now utilizing a modified FOLFIRINOX regimen that drops the bolus dosing and has not been formally studied. The simplicity
of the nab-paclitaxel plus gemcitabine regimen along with the more modest side effect profile may be attractive to both oncologists and their patients.

In 2005 the Food and Drug Administration approved erlotinib (Tarceva, Roche and Astellas) to treat pancreatic cancer. In a randomized phase 3 clinical trial, those who received erlotinib plus gemcitabine had a six-week increase in time to tumor progression, but median survival was only 12 days longer than for those who received a placebo plus gemcitabine.

The experimental drug TH-302 (Threshold) will be combined with gemcitabine in a phase 3 study (MAESTRO) of 660 patients with previously untreated, locally advanced unresectable or metastatic pancreatic cancer. TH-302 targets oxygen-deprived regions of tumors — so-called “hypoxic domains” — that are tough for drugs to reach effectively without serious side effects. Those regions are more prevalent in fast-growing and aggressive cancers like pancreatic cancer. A phase 2b trial showed that a combination of TH-302 and gemcitabine helped patients live a median of 2.4 months longer, a 63 percent improvement, without their disease progressing, compared to patients who were given only chemotherapy. Patients receiving gemcitabine alone were allowed to cross over to the combination therapy if their disease progressed, which possibly affected the lack of statistical difference in overall survival. TH-302 is also in a phase 3 trial in patients with soft tissue sarcoma.

Trametinib (GSK2110212) is a reversible, allosteric inhibitor of MEK1/MEK2. An open-label, single-arm study was conducted to evaluate the safety, pharmacokinetics (PK) and antitumor activity of trametinib plus gemcitabine, and to determine the recommended phase 2 regimen in patients with advanced solid tumors. The maximum tolerated dose and recommended phase 2 dose was 2 mg trametinib orally daily plus 1,000 mg/m² of gemcitabine intravenously on days one, eight and 15, q 28 days. The most common side effects were rash and fatigue. Trametinib plus gemcitabine was tolerable with evidence of promising clinical activity in pancreatic cancer. A randomized phase 2 study in previously untreated patients with metastatic pancreatic cancer was then performed to investigate the clinical activity of this combination. Unfortunately, the results of that trial showed no difference with the addition of the MEK inhibitor. The median overall survival was 8.4 months in the trametinib plus gemcitabine arm and 6.7 months in the placebo plus gemcitabine arm (hazard ratio [HR] 0.98; p = 0.453). The median progression-free survival, based on radiologic progression, was similar between the treatment arms: 16.1 weeks in the combination arm and 15.1 weeks in the single-agent arm (HR 0.93; p = 0.349). The unconfirmed objective response rate was similar between the treatment arms (22 percent vs. 18 percent in T + G and P + G, respectively).

There are no approved therapies for patients with metastatic pancreatic cancer who fail treatment with gemcitabine. Potentially brightening the prospects for these patients, MM-398 (Merrimack Pharmaceuticals) has shown some promise in a mid-stage study with plans to usher the nanodrug into a phase 3 trial. MM-398 is a formulation of the chemotherapy drug irinotecan encapsulated in tiny liposomal particles to improve its activity and safety profile. In a recent
single-arm phase 2 trial, 40 pancreatic cancer patients on the drug had a median overall survival of 22.4 weeks with one in five surviving for more than a year. The phase 3 trial is expected to enroll 250 patients with metastatic pancreatic cancer and compare MM-398 with an existing treatment for this population that includes the drugs 5-FU and leucovorin.

Clovis’ CO-101 is a novel, lipid-conjugated form of gemcitabine developed to benefit pancreatic cancer patients with low levels of a protein known as hENT1. Previous research suggested low hENT1 levels prevented ordinary gemcitabine from getting into pancreatic tumor cells. CO-101 was designed to enter pancreatic cancer cells independently of a patient’s hENT1 status. Once inside the cell, CO-101 was converted to the active form of gemcitabine. A phase 3 randomized trial of advanced pancreatic cancer patients comparing CO-101 to gemcitabine failed to show any difference in the planned end points of progression-free or overall survival. In addition, tissue was collected on all patients and hENT1 status had no impact on survival for pancreatic cancer patients on gemcitabine.

A randomized phase 3 trial of adjuvant chemotherapy with the oral agent known as S-1 (Taiho Pharmaceutical) significantly increased overall survival in pancreatic cancer patients compared with gemcitabine, which is the current postsurgery treatment standard. However, the implications of the study, which involved only Japanese patients, may be limited to Asian populations. Other studies have shown that, in Caucasians, diarrhea related to S-1 treatment was problematic. Additional studies are needed, in which adjustments in dose and schedule might alleviate this adverse event. In the current study, the investigators randomized 385 patients with stages I-III pancreatic cancer to postoperative treatment with S-1 or gemcitabine. The two-year survival rates were 70 percent and 53 percent for S-1 and gemcitabine, respectively, in an interim analysis (scheduled after 180 deaths; P < .0001 for superiority). This difference translated to 44 percent lower risk for death for the S-1 patients compared with the gemcitabine patients. Relapse rates were also better in the S-1 arm. The two-year relapse-free survival rates were 49 percent and 29 percent for S-1 and gemcitabine, respectively. S-1 is taken orally as a single agent, but has three components including tegafur, a prodrug of 5-fluorouracil (5-FU). Thus S-1, once in the blood, is converted into 5-FU. S-1 is currently available in several Asian countries and most of Europe, but is not yet approved in the United States.

The lack of proven biomarkers and novel targets continues to slow advances in the treatment of pancreatic cancer. The majority of these patients have aberrations in KRAS, but an effective agent against this pathway in the clinical setting has yet to be identified. For now, the choice of very aggressive chemotherapy with FOLFIRINOX, a more modest approach with nab-paclitaxel plus gemcitabine, or a simple regimen of single-agent gemcitabine will be made by physicians and their patients based on performance status and risk/benefit assessments.
Incidence of the disease has consistently increased through this past decade (see Figure 1), with current estimates indicating more than 43,920 new cases of pancreatic cancer in 2012. Even though the incidence numbers are small compared to other tumors, such as breast or colon cancer, the mortality statistics are what make pancreatic cancer a disease to be feared, as more than 37,390 deaths are expected from the disease in 2012 alone. The prognosis is that from diagnosis, most pancreatic cancer patients will die within two years. In fact, the overall five-year relative survival for 2002-2008 from a Surveillance and Epidemiology and End Results (SEER) analysis was only 5.8 percent.²

Even if the cancer is detected at an early stage, when surgical removal of the tumor is possible, the five-year survival rate is an estimated 22 percent. The increasing frustration is that, despite making incremental survival outcome inroads with other tumor types, pancreatic cancer presents an elusive enigma on how to change the current path of its dismal prognosis.
**Drivers of Poor Prognosis**

Late diagnosis is a primary root cause that may affect how long a patient lives, and to what level aggressive interventions, such as surgery and chemotherapy, can be integrated as treatment options. Symptomology associated with pancreatic cancer mirrors many other potential gastrointestinal conditions, such as diseased gallbladder, irritable bowel syndrome and celiac disease, so clear-cut indicators that present both to the physician and the patient are not necessarily immediate. Therefore, patients may simply self-manage some of the symptoms until they are intolerable, or they will undergo a battery of tests to rule out other conditions before considering or identifying evidence of pancreatic cancer.

Late diagnosis, however, may not be the only culprit. A recent study conducted in Australia, as part of the International Cancer Genome Consortium (ICGC) repository, sheds light on what may actually prompt a possible new definition for pancreatic cancer. The study obtained diseased tissue from 100 pancreatic cancer patients and compared this to normal tissue. The findings were astounding, with the discovery of over 2,000 mutated genes that could potentially be involved in pancreatic cancer tissue. The evidence of genetic markers ranged from KRAS, which was present in over 90 percent of the cases, to a variety of other genes present in only 1 to 2 percent of the tumors. The bottom line is that there was no consistency across tissue samples, implying that pancreatic cancer is extremely patient-specific — perhaps more so than any other cancer. This study posed the possibility that pancreatic cancer could actually be a multitude of diseases rather than just one. As a result, it could explain why our population health approach of “one treatment fits all” to attacking pancreatic cancer may not work as effectively as hoped. Perhaps pancreatic cancer can be identified as an ideal target for personalized medicine because of the genetic complexity.

**The Treatment Matrix**

Surgical intervention is conventionally only an option for early-stage disease, which again is identified in less than 15 percent of pancreatic cancer of adenocarcinoma histology (the most common form). Gemcitabine still serves as a standard backbone of chemotherapy treatment, including combinations with such drugs as Tarceva® (erlotinib) or Xeloda® (capecitabine). FOLFIRINOX is another standard regimen, consisting of bolus and infusional 5-fluorouracil, irinotecan and oxaliplatin.

Select hopeful novel treatment candidates in development, such as Amgen’s ganitumab and Clovis’ CO-101, sadly did not meet intended end points of improved survival in clinical trials, and have since been taken back to the drawing board to determine next steps for drug development. Yet other novel agents, such as minnelide, have not even made it to the clinical trial phase. However, clinical trial initiatives aren’t just looking at new agents, but rather combining currently available drug options that have activity against pancreatic cells, such as Abraxane® (docetaxel) with gemcitabine, to gain increments in survival for pancreatic cancer patients.

As we consider the findings from the Australian study, perhaps more studies may focus on personalized medicine, looking at cancer vaccines, targeted therapies or use of biomarkers for determination of appropriate treatment options. Therefore, treatment initiatives will likely continue to evolve in the search for better outcomes for patients with this deadly disease.

**Payor Positioning Challenge**

Clearly, there are few effective drugs in the current clinical armamentarium for treating pancreatic cancer, although as seen with other small-population tumors, such as renal cell cancer, the number of treatment options has been increasing over time — and the same will likely occur for pancreatic cancers. The key will be determining what can be interpreted as significant clinical improvement for these patients.

Stepping back to assess the intent of more broad, sweeping health care reform, we can clearly see the need to provide more consistent standard
health benefits to a greater population. Within that significant intent, however, the management and cost of treating pancreatic cancer as a small-population cancer may create some challenges. The goal — whether driven by health care reform or not — is the need for ensuring good-quality care at an acceptable cost to the system — whether for chronic diseases such as diabetes and asthma, or for pancreatic cancer. The elephant in the room is the current poor prognosis for most patients with pancreatic cancer. Therefore, what type of clinical benefit will be necessary to make a difference and be deemed as a balanced value for both the patient and the health system?

As an example, we can review one recent bold decision regarding coverage of cancer care benefits. CareOregon, a managed Medicaid plan in the state of Oregon, published new guidance on consideration for coverage of cancer treatments, basing the decision on a patient’s prognosis and the survival outcome provided by a given drug regimen (see Figure 2). It isn’t expected that this level of limitation would be something developed by payors across the U.S., yet it still begs discussion in light of health care reform drivers.

Looking at CareOregon’s guidelines, consider this: Given the general prognosis for a pancreatic cancer patient in today’s environment, coupled with the limited survival impact of currently available treatment options, would most of the pancreatic cancer patients therefore be excluded from active treatment?

What challenge does this present for both the physician and the patient? Ideally, because of the unmet needs of pancreatic cancer patients, the option would still be available for treatment should it be warranted as appropriate by a physician; however, that may not be the possibility as we continue to move in the direction of greater focus on the value equation in cancer care.

Turning the thought in a different direction, what if personalized medicine becomes the norm for pancreatic cancer? There has been much discussion around whether personalized medicine will become reality, and if it does, how patients would access and pay for this option.

No doubt, there would be necessity for demonstrated clinical outcomes in order to make any new treatment acceptable. However, coverage parameters may still be challenging. The above-mentioned Australian study identified more than 2,000 expressed genetic markers in pancreatic cancer tissue. It’s not likely that managed care plans would consider it appropriate to screen for 2,000 genes in order to identify a successful treatment plan for pancreatic cancer patients. What then is the necessary clinical information required to support the value of genetic testing? Since KRAS was present in 90 percent of the studied cases in that one study, might that marker become a standard testing point to align with certain potential treatment options?

This article provides no answers, but raises many questions. Perhaps pancreatic cancer warrants a new look. As outlined in the theme of this article, the disease truly may be “more than meets the eye” in terms of its genetic makeup and subsequent evolution in treatment options. In the meantime, it will be important to ensure that patients with this deadly disease are given the fair opportunity of accessing available treatment to hopefully challenge what so commonly presents as a dismal prognosis.

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

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:

157 Malignant neoplasm of pancreas
157.0 Head of pancreas
157.1 Body of pancreas
157.2 Tail of pancreas
157.3 Pancreatic duct
   - Duct of Santorini
   - Wirsung
157.4 Islets of Langerhans
   - Islets of Langerhans, any part of pancreas
157.8 Other specified sites of pancreas
   - Ectopic pancreatic tissue
   - Malignant neoplasm of contiguous or overlapping sites of pancreas whose point of origin cannot be determined
157.9 Pancreas, part unspecified

FDA-Approved Medications Currently Available to Treat Pancreatic Cancer

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code — Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 1/1/13</th>
<th>Medicare Allowable (ASP + 6%) — Effective 1/1/13-3/31/13</th>
<th>Possible CPT Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>erlotinib (Tarceva)</td>
<td>C9399* — unclassified drugs or biological (hospital outpatient use only)</td>
<td>NDC-level pricing</td>
<td>NDC-level pricing</td>
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<td>erlotinib (Tarceva)</td>
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<td>fluorouracil (Adrucil)</td>
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<td>gemcitabine (Gemzar)</td>
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<td>mitomycin (Mutamycin)</td>
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<td>streptozocin (Zanosar)</td>
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Compendia-Listed Off-Label-Use Medications Currently Available to Treat Pancreatic Cancer

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<th>Current Code Price (AWP-Based Pricing) Effective 1/1/13</th>
<th>Medicare Allowable (ASP + 6%) — Effective 1/1/13-3/31/13</th>
<th>Possible CPT Administration Code(s)</th>
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<td>capecitabine (Xeloda)</td>
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<td>cisplatin (Platinol AQ)</td>
<td>J9060 — injection, cisplatin, powder or solution, per 10 mg</td>
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<td>doxorubicin hydrochloride (Adriamycin)</td>
<td>J9000 — injection, doxorubicin hydrochloride, 10 mg</td>
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<td>epirubicin (Ellence)</td>
<td>J9178 — injection, epirubicin hydrochloride, 2 mg</td>
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<td>flutamide (Eulexin)</td>
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<td>irinotecan (Camptosar)</td>
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<td>paclitaxel (Taxol)</td>
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<td>triptorelin (Trelstar)</td>
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* When billing a nonclassified medication using a CMS 1500 claim form, you must include both the HCPCS code (e.g., J8999 for Nolvadex) in column 24D and the drug name, strength and NDC (National Drug Code) in box 19 in order to ensure appropriate reimbursement.
Ancillary Medications Used in Cancer Treatment

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code — Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 1/1/13</th>
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<tr>
<td>aprepitant (Emend)</td>
<td>J8501 — aprepitant, oral, 5 mg</td>
<td>$8.00</td>
<td>$6.48</td>
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<tr>
<td>granisetron (Kytril)</td>
<td>J1626 — injection, granisetron hydrochloride, 100 mcg</td>
<td>$3.84</td>
<td>$0.63</td>
<td>96374</td>
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<tr>
<td>granisetron (Kytril)</td>
<td>Q0166 — granisetron hydrochloride, 1 mg, oral, FDA-approved prescription antiemetic, for use as a complete therapeutic substitute for an IV antiemetic at time of chemotherapy treatment, not to exceed a 24-hour dosage regimen</td>
<td>$59.01</td>
<td>$1.59</td>
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<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>
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<td>ondansetron (Zofran)</td>
<td>J2405 — injection, ondansetron hydrochloride, per 1 mg</td>
<td>$0.45</td>
<td>$0.17</td>
<td>96372, 96374</td>
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<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>$0.04</td>
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<td>ondansetron (Zofran)</td>
<td>S0119 — ondansetron, oral, 4 mg (for circumstances falling under the Medicare statute, use HCPCS code Q0162)</td>
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<td>palonosetron (Aloxi)</td>
<td>J2469 — injection, palonosetron hydrochloride, 25 mcg</td>
<td>$45.48</td>
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CPT Administration Code Descriptions

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<tr>
<th>CPT Administration Code</th>
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<tr>
<td>96401</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; nonhormonal antineoplastic</td>
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<tr>
<td>96402</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; hormonal antineoplastic</td>
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<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 1 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 96413 in conjunction with 96413.)</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 technique; single or initial substance/drug</td>
</tr>
</tbody>
</table>

References
- FDA-approved indication (product prescribing information).

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This information was supplied by RJ Health Systems International, LLC, located in Rocky Hill, Conn. Prices and information supplied herein are effective as of January 1, 2013.
## 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>
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<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._) Malignant neoplasm of thymus, heart and mediastinum — heart (164.1) Myeloid leukemia — acute (205.0.) Hereditary hemolytic anemias — other thalassemia (282.49) Sickle-cell disease (282.6.)</td>
<td>$6.59</td>
<td>$5.53</td>
<td>96401 96409 96413</td>
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<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>
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<td>Compendia-Listed Off-Label Uses</td>
<td>Current Code Price (AWP-Based Pricing)*</td>
<td>Medicare Allowable (ASP + 6%) — Effective 1/1/13-3/31/13</td>
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<tr>
<td>clofarabine (Clolar)</td>
<td>J9027 — injection, clofarabine, 1 mg</td>
<td>Lymphoid leukemia — acute (204.0)</td>
<td>Myeloid leukemia — acute (205.0) Low-grade myelodysplastic syndrome lesions (238.72) High-grade myelodysplastic syndrome lesions (238.73) Myelodysplastic syndrome with 5q deletion (238.74) Myelodysplastic syndrome, unspecified (238.75)</td>
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<td>dactinomycin (Cosmegen)</td>
<td>J9120 — injection, dactinomycin, 0.5 mg</td>
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<td>Malignant melanoma of skin (172.) Kaposi’s sarcoma (176.) Malignant neoplasm of ovary and other uterine adnexa (183.) Malignant neoplasm of other and unspecified female genital organs (184.) Malignant neoplasm of penis and other male genital organs (187.) Malignant neoplasm of eye (190.) Complications of transplanted organ — kidney (996.81) Complications of transplanted organ — heart (996.83)</td>
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<tr>
<td>decitabine (Dacogen)</td>
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<td>Lymphoid leukemia — acute (204.0) Myeloid leukemia — acute (205.0) Myeloid leukemia — chronic (205.1)</td>
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<td>degarelix (Firmagon)</td>
<td>J9155 — injection, degarelix, 1 mg</td>
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<td>flouxuridine (FUDR)</td>
<td>J9200 — injection, flouxuridine, 500 mg</td>
<td>Malignant neoplasm of stomach (151.) Malignant neoplasm of small intestine including duodenum (152.) Secondary malignant neoplasm of liver (197.7)</td>
<td>Malignant neoplasm of colon (153.) Malignant neoplasm of rectum, rectosigmoid junction and anus (154.) Malignant neoplasm of liver and intrahepatic bile ducts (155.) Malignant neoplasm of kidney, except pelvis (189.0)</td>
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<td>$65.32</td>
<td>96422 96423 96425</td>
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<td>panitumumab (Vectibix)</td>
<td>J9303 — injection, panitumumab, 10 mg</td>
<td>Malignant neoplasm of colon (153.) Malignant neoplasm of rectum, rectosigmoid junction and anus (154.)</td>
<td>Malignant neoplasm of trachea, bronchus and lung (162.)</td>
<td>$103.89</td>
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<td>generic (Brand) Name</td>
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<td>Medicare Allowable (ASP + 6%) — Effective 1/1/13-3/31/13</td>
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<tr>
<td>vinblastine (Velban)</td>
<td>J9360 — injection, vinblastine sulfate, 1 mg</td>
<td>Malignant neoplasm of female breast (174...) Malignant neoplasm of male breast (175...) Kaposi’s sarcoma (176...) Malignant neoplasm of placenta (181) Malignant neoplasm of testis (186...) Lymphosarcoma, reticulosarcoma and other specified malignant tumors of lymphatic tissue (200...) Hodgkin’s disease (201...) Other malignant neoplasms of lymphoid and histiocytic tissue (202...)</td>
<td>Malignant neoplasm of esophagus (150...) Malignant neoplasm of trachea, bronchus and lung (162...) Malignant melanoma of skin (172...) Malignant neoplasm of cervix and uteri (180...) Malignant neoplasm of ovary and other uerine adnexe (183...) Malignant neoplasm of other and unspecified female genital organs (184...) Malignant neoplasm of prostate (185) Malignant neoplasm of penis and other male genital organs (187...) Malignant neoplasm of bladder (188...) Malignant neoplasm of kidney and other and unspecified urinary organs (189...) Malignant neoplasm of eye (190...) Malignant neoplasm of brain (191...) Neoplasm of uncertain behavior of connective and other soft tissue (238.1) Autoimmune hemolytic anemia (283.0) Immune thrombocytopenic purpura (287.31)</td>
<td>$3.18</td>
<td>$1.17</td>
<td>96409</td>
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</tbody>
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*The code price is based on the HCPCS code description. HCPCS (Healthcare Common Procedure Coding System) codes are a component of CMS (Centers for Medicare & Medicaid Services). The code price is an AWP-based pricing methodology developed by RJ Health Systems International, LLC, Rocky Hill, Conn.

**Oncology-Related J-Code References**
- Full prescribing information for each drug listed.

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Title: A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer.

Authors: Kindler HL, Richards DA, Garbo LE, et al.


Purpose: Pancreatic cancer is the fourth leading cause of cancer death in the United States. First-line therapy for metastatic disease consists of single-agent gemcitabine (Gemzar) or gemcitabine combinations. Slight improvement in overall survival (OS) has been noted with the addition of erlotinib (Tarceva) to gemcitabine with longer improvements in OS noted in patients with good performance status treated with the multidrug combination FOLFIRINOX (Adrucil, leucovorin, Camptosar, Eloxatin). Still, more effective therapy with novel agents is needed. The insulin-like growth factor-1 receptor (IGF1R) and its ligands, IGF-1 and IGF-2, are overexpressed in both normal and malignant pancreatic cells. Pharmacological blockade of IGF1R inhibits the growth and viability of pancreatic cancer cells, and tumor cells with KRAS mutations remain sensitive to IGF1R inhibition. Ganitumab is a fully humanized monoclonal antibody inhibitor of IGF1R that prevents the binding of IGF-1 and IGF-2 to IGF1R. In human pancreatic xenografts, ganitumab exhibited single-agent activity that was enhanced with the addition of gemcitabine. In a phase 1B study, the combination was associated with disease control (complete response + partial response + stable disease) in 80 percent of patients with advanced solid tumors. Pancreatic tumors also express higher levels of apoptosis ligand 2/tumor necrosis factor receptor–related apoptosis-inducing ligand (TRAIL), death receptor (DR) 4 and DR5 than does normal pancreatic tissue. Conatumumab is an investigational, fully humanized monoclonal antibody agonist of DR5 that induces apoptosis. Like ganitumab, it showed single-agent activity versus a pancreatic cancer xenograft model that was enhanced by the addition of gemcitabine.

Methods: Patients ≥ 18 years of age with a histologically or cytologically documented metastatic adenocarcinoma of the pancreas who had no previous therapy (chemo or radiation) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were eligible to participate. Other eligibility criteria included adequate end-organ function and if the patient was diabetic, the condition had to be adequately controlled. Patients were randomized 1:1:1 to receive gemcitabine in combination with ganitumab, conatumumab or placebo. Gemcitabine was administered at a dose of 1,000 mg/m² intravenously on days one, eight and 15 of a 28-day cycle. Ganitumab, 12 mg/kg intravenously; conatumumab, 10 mg/kg intravenously; or placebo was administered by one-hour infusions that, if tolerated, could be
subsequently reduced to 30 minutes. Both monoclonal antibodies were administered on an every-two-weeks basis, days one and 15. The primary end point of the study was six-month survival rate. Secondary end points included objective response rate (ORR) and safety.

**Results:** A total of 125 patients were randomized to receive ganitumab (n = 42), conatumumab (n = 41) and placebo (n = 42), and 40, 41 and 40 patients received the investigational products, respectively. The median number of cycles in the ganitumab group was four, the conatumumab group was four and the placebo group was two. The six-month survival rate was 57 percent (95 percent confidence interval [CI], 41-70 percent) in the ganitumab arm and 50 percent (95 percent CI, 33-64 percent) in the placebo arm. The 12-month survival rates were 39 percent (95 percent CI, 25-54 percent) and 23 percent (95 percent CI, 12-38 percent), respectively. The ORRs in the ganitumab, conatumumab and placebo arms were 10 percent, 3 percent and 3 percent, with all responses being partial responses. The most common grade ≥ 3 adverse events in the ganitumab, conatumumab and placebo arms, respectively, included neutropenia (18/22/13 percent), thrombocytopenia (15/17/8 percent), fatigue (13/12/5 percent), increased alanine aminotransferase (15/5/8 percent) and hyperglycemia (18/2/3 percent).

**Conclusion:** Ganitumab combined with gemcitabine had tolerable toxicity and showed a trend toward an improved six-month survival and overall survival. Additional investigation of this combination is warranted. Conatumumab and gemcitabine showed some evidence of activity as assessed by the six-month survival rate.

**Managed Care Implications:** New drug combinations are needed to treat patients with metastatic pancreatic cancer. Monoclonal antibodies such as ganitumab may offer patients a survival advantage when combined with gemcitabine.

**Title:** A multicentre randomized phase II trial of gemcitabine alone vs. gemcitabine and S-1 combination therapy in advanced pancreatic cancer: GEMSAP study.

**Authors:** Nakai Y, Isayama H, Sasaki T, et al.


**Purpose:** Prognosis for patients with advanced pancreatic cancer remains poor. Single-agent gemcitabine (Gemzar) is superior to bolus 5-fluorouracil (5-FU; Adrucil) with response rates of 5 percent and a median overall survival (OS) of 5.7 months. This has led to combination therapy with only erlotinib (Tarceva) in combination with gemcitabine showing a statistically significant but clinically small improvement in OS. S-1 is an oral fluoropyrimidine consisting of tegafur, a prodrug of 5-FU, and two biochemical modulators that has been shown to have activity as a single agent in patients with advanced pancreatic cancer comparable to that of gemcitabine. The combination of gemcitabine and S-1 is reportedly well tolerated and active in this patient population. This phase 2 study will compare gemcitabine alone vs. gemcitabine and S-1 in patients with advanced pancreatic cancer.

**Methods:** Eligibility for this multicenter, open-label, randomized trial included patients with unresectable locally advanced or metastatic pancreatic adenocarcinoma who had received no prior treatment (including surgery and/or radiation), had an ECOG performance status of 0-2, were at least 20 years of age, had a life expectancy of > 12 weeks and had adequate end-organ function. Patients were randomized 1:1 to receive either gemcitabine, 1,000 mg/m² intravenously on days one, eight and 15 of a four-week cycle or gemcitabine, 1,000 mg/m²
intravenously on days one and 15 and S-1 orally twice daily for two weeks followed by a two-week rest between each four-week cycle. Three doses of S-1 were established according to body surface area (BSA): BSA ≤ 1.25, 80 mg per day; BSA > 1.25 but ≤ 1.5, 100 mg per day; BSA ≥ 1.5, 120 mg per day. All therapy was administered until disease progression, unacceptable toxicity or withdrawal of consent. The primary end point of the study was progression-free survival (PFS) with secondary end points including OS, overall response rate (ORR) and safety.

Results: A total of 106 patients were randomized, 53 to each treatment arm. The baseline characteristics, age, performance status, extent of disease and CA 19.9 levels were well balanced. The ORR was 18.8 percent (95 percent CI, 10.6-31.4 percent) in the gemcitabine and S-1 arm compared to 9.4 percent (95 percent CI, 4.9-20.3 percent) in the gemcitabine arm (p = 0.265) with only one patient in the combination arm achieving a complete response. The median duration of response was 10.0 months in the gemcitabine plus S-1 group and 10.6 months in the gemcitabine arm. The disease control rate was 79.2 percent in the combination arm vs. 56.6 percent in those patients treated with gemcitabine alone (p = 0.021). The median PFS for the combined therapy was 5.4 months (95 percent CI, 3.7-9.4 months) vs. 3.6 months (95 percent CI, 2.0-5.1 months) in the monotherapy arm. PFS was significantly improved in the gemcitabine plus S-1 group with a hazard ratio of 0.64 (95 percent CI, 0.42-0.97 months; p = 0.036). The median OS was 13.5 months (95 percent CI, 7.8-16.3 months) in the combination arm vs. 8.8 months (95 percent CI, 7.0-10.6 months) in the monotherapy arm. The improvement in OS did not meet statistical significance with a p value of 0.104. The one-year survival rate was 52.8 percent in the gemcitabine and S-1 arm vs. 30.2 percent in the gemcitabine arm (p = 0.031). The incidence of grade 3 and 4 neutropenia was similar in both treatment arms, while nonhematologic adverse events, such as stomatitis, diarrhea and rash, were more commonly seen in those patients treated with gemcitabine and S-1.

Conclusion: Gemcitabine and S-1 combination therapy demonstrated a longer PFS in patients with advanced pancreatic cancer. An improved OS duration of 4.7 months was also noted with the combination but was not statistically significant.

Managed Care Implications: Combination therapy is superior to single-agent therapy in patients with advanced pancreatic cancer. Identification of the most active combination(s) is still ongoing, but oral S-1 may play a role in future studies.

Title: Clinical and immunologic evaluation of dendritic cell-based immunotherapy in combination with gemcitabine and/or S-1 in patients with advanced pancreatic cancer.

Authors: Kimura Y, Tsukada J, Tomoda T, et al.


Purpose: Pancreatic cancer is the fifth leading cause of cancer deaths worldwide, with a five-year survival rate of only 5 percent. Since early-detection methods are under development and the disease is usually diagnosed in its advanced stage, surgical resection can only be performed on a small number of patients. Gemcitabine (Gemzar) has been established as the most active single chemotherapy agent, with moderate increases in survival seen in comparison to 5-fluorouracil (5-FU; Adrucil). Recent studies report
that 5-FU, an oral form of 5-FU, can improve the prognosis of patients with gemcitabine refractory disease as well as chemo-naive patients with pancreatic cancer. Since most patients treated with gemcitabine do not survive longer than six months and effective treatment options are limited, new treatment modalities are needed. Immunotherapy is potentially another option for patients with advanced pancreatic cancer. Dendritic cells (DCs) are antigen-presenting cells with the capacity to elicit a primary immune response. DCs can be pulsed with peptides derived from the known tumor-associated antigens, such as MUC1, to induce antigen-specific cytotoxic T lymphocytes that can kill tumors. Recent reports suggest that gemcitabine may enhance responses to specific vaccines or immunotherapy by inducing T-cell activation, resulting in proliferation of γ interferon production and proliferation of CD14+ monocytes. DCs were enhanced in patients treated with gemcitabine. Previous reports also suggest that 5-FU induces cytokines and natural killer cell activity in vivo and in vitro. Thus, the most effective treatment strategy may require a combined approach of immunotherapy and chemotherapy.

**Methods:** This retrospective study included 49 patients with advanced pancreatic cancer refractory to standard therapy who were treated with DC-based immunotherapy in combination with standard chemotherapeutic agents gemcitabine and/or S-1. Patients were treated with gemcitabine 800-1,000 mg/m² intravenously on days one, eight and 15, followed by a one-week rest period (three on, one off). S-1, 60-80 mg/m² orally, was administered for four weeks followed by a two-week rest period (four on, two off). Autologous DCs (1 x 10⁷) were administered intradermally every 14 days. Tolerable doses of 1 to 5 KE of OK-432, a streptococcal immunological adjuvant, were administered together with the DC vaccine. Lymphokine-activated killer (LAK) cells were simultaneously injected intravenously in 34 patients at 14-day intervals. Clinical responses were stratified according to RECIST criteria.

**Results:** Of the 49 patients receiving DC-based immunotherapy in combination with chemotherapy, there was a complete response rate (CR) of 4.1 percent, a partial response rate (PR) of 10.2 percent and a stable disease rate (SD) of 12.2 percent. Overall survival ranged from 57 to 975 days with a median survival of 360 days. Of the 34 patients who received LAK cells in addition to DCs, their CR rate was 5.9 percent, PR rate was 26.5 percent and SD rate was 14.7 percent. In the 15 patients not receiving LAK cells, their CR was 0 percent, PR was 13.3 percent and SD was 6.7 percent. The median survival time (MST) for patients receiving LAK cells was 396 days in comparison to 229 days in those patients not receiving LAK cells (p = 0.075). These data suggest that LAK cell therapy increases the anticancer effect of DC vaccination. Patients treated with DCs and gemcitabine alone experienced a MST of 360 days in comparison to 168 days in those patients treated with DCs and S-1. In the DCs, gemcitabine and S-1 treated patients, the MST was 508 days, which was not statistically significant when compared to the other two treatment groups. No patient experienced a grade 3 or 4 adverse event during the treatment period. The most common toxicities reported were leukocytopenia, anemia and nausea.

**Conclusion:** Dendritic cell vaccination–based immunotherapy combined with chemotherapy was shown to be safe and possibly effective in patients with advanced pancreatic cancer refractory to standard therapy.

**Managed Care Implications:** Vaccine therapy may play an important role in combination with chemotherapy in patients with advanced pancreatic cancer by enhancing the immune response. Additional studies in both chemo-refractory and chemo-naive patients with metastatic disease are ongoing.

**Title:** Gemcitabine plus erlotinib followed by capecitabine versus
capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomized phase 3 trial of the "Arbeitsgemeinschaft Interistische Onkologie" (AIO-PK0104).


Purpose: As of 2008, 165,100 new cases of pancreatic cancer were diagnosed worldwide with nearly the same number of deaths, 161,800, reported. Gemcitabine (Gemzar) has been regarded as the standard of care for over a decade, providing clinical benefit and a moderate improvement in survival for patients with advanced disease. Several randomized phase 3 trials have failed to show survival benefit for gemcitabine-based combination therapy; however, meta-analyses suggest a possible survival benefit for use of platinum analogues or fluoropyrimidines in combination with gemcitabine in selected patients with metastatic disease and good performance status. Based upon results from a randomized trial, the combination of gemcitabine and erlotinib (Tarceva), a novel anti-EGFR (epidermal growth factor receptor) tyrosine kinase inhibitor, received U.S. regulatory approval for treatment of advanced pancreatic cancer. The observed survival advantage in this unselected patient population was statistically significant but clinically rather modest, 5.9 vs. 6.2 months (p = 0.038). Early clinical data support the investigation of erlotinib in combination with the oral fluoropyrimidine capcitabine (Xeloda). Another phase 2 study in gemcitabine-pretreated patients with advanced pancreatic cancer found the combination of capcitabine and erlotinib to be safe and feasible. However, no internationally accepted standard approach for salvage chemotherapy after failure of first-line gemcitabine has been established.

Methods: Adults between the ages of 18 and 75 with a histologically or cytologically confirmed diagnosis of treatment-naive (stage III or IV) pancreatic cancer with adequate end-organ function were eligible. Patients were also required to have a Karnofsky performance status of at least 60 percent. Patients were randomized 1:1 to receive gemcitabine, 1,000 mg/m² intravenously over 30 minutes weekly for seven weeks followed by a one-week rest, then every three of four weeks in combination with erlotinib 150 mg orally daily. In case of treatment failure, second-line therapy consisted of single-agent capcitabine 1,000 mg/m² orally twice a day for 14 days followed by a seven-day rest period. This was considered the reference arm. The experimental arm consisted of capcitabine and erlotinib followed by gemcitabine in those patients who progressed. The dosing was identical to the reference arm for all three drugs. Treatment in either arm continued until disease progression, unacceptable toxicity or withdrawal of patient consent. The primary end point of the study was time to treatment failure (TTF2) after second-line therapy. Secondary end points included overall survival and safety.

Results: A total of 281 patients were randomized with 274 eligible for the trial (Gem + E/Cap n = 143 and Cap + E/Gem n = 131). The groups were well balanced with regard to age, stage of disease and performance status. The median number of cycles administered was five in each group (range 0-26). Median TTF2 was estimated at 4.2...
months in each arm (HR 1.00; 95 percent CI, 0.78-1.28 months; p = 1.0). The objective response rate (ORR) during first-line therapy was 16 percent for gemcitabine and erlotinib versus 5 percent for capecitabine and erlotinib with a corresponding disease control rate (complete response + partial response + stable disease) of 51 percent and 38 percent, respectively. The use of second-line chemotherapy showed a further objective disease control rate of 22 percent in those patients treated with capecitabine and 36 percent for those treated with gemcitabine. Time to treatment failure after first-line therapy (TTF1) was significantly prolonged in the gemcitabine/erlotinib arm (3.2 vs. 2.2 months), but this advantage did not translate into a difference in TTF2. The one-year overall survival rate was 22 percent in the gemcitabine/erlotinib arm followed by capecitabine and 23 percent in the capecitabine/erlotinib arm followed by gemcitabine. The median overall survival was 6.2 months with gemcitabine/erlotinib followed by gemcitabine and 6.9 months with capecitabine/erlotinib followed by gemcitabine (HR 1.02; p = 0.90). Hematologic toxicity was more common in the gemcitabine-containing arm whereas stomatitis and hand-foot syndrome occurred more often in the capecitabine/erlotinib arm. Skin rash was associated with both TTF2 (grade 0/1/2-4: 2.9/4.3/6.7 months, p < 0.0001) and survival (3.4/7.0/9.6 months, p < 0.0001). A KRAS wild type status (52/173 patients or 30 percent) was associated with an improved overall survival (HR 1.68; p = 0.005).

**Conclusion:** Both treatment strategies are feasible and demonstrate comparable efficacy. KRAS may serve as a biomarker in patients with advanced pancreatic cancer treated with erlotinib.

**Managed Care Implications:** New drug combinations show promise in patients with advanced pancreatic cancer. KRAS testing is important in determining appropriate therapy.

**Title:** Prospective randomized evaluation of traditional Chinese medicine combined with chemotherapy: a randomized phase II study of wild toad extract plus gemcitabine in patients with advanced pancreatic adenocarcinoma.

**Authors:** Meng Z, Garrett CR, Shen Y, et al.


**Purpose:** Traditional Chinese medicine is currently practiced worldwide and is frequently used to treat cancer, either alone or in combination with Western medicines. Huachansu is sterilized hot water extract of dried toad skin and is used for the treatment of liver, lung, pancreatic and colorectal cancers in China. Its two active chemical components are indole alkaloids and steroidal cardiac glycosides. Three of the major cardiac glycosides (bufalin, resibufogenin and cinobufagin) are responsible for the anticancer activity of huachansu. These effects include vasoconstriction, anti-inflammation, increased vascular resistance and inhibition of cancer proliferation. In vitro studies have shown inhibition of human heptocellular, gastric and colon cancer cell line proliferation. Additionally, huachansu has been shown to inhibit proliferation and induce apoptosis in gastric carcinoma cell lines. This activity was mediated through S-phase arrest and inhibition of bcl-2 expression as well as marked inhibition of the biosynthesis of DNA and RNA. Previous phase 1 dose-escalation trials have shown antitumor activity based on radiographic response. Tolerance was excellent and toxicity was not observed in the study. Due
to its wide use in China, its clearly defined mechanism of action, and preclinical and early clinical studies indicating efficacy and no previous study combining huachansu with conventional chemotherapy, this present study was undertaken.

**Methods:** Patients 18 years of age or older with a histological or cytological diagnosis of unresectable (locally advanced and/or metastatic) pancreatic carcinoma with measurable disease, a Karnofsky performance status of > 60 percent and a life expectancy of at least three months were eligible for enrollment. This randomized, phase 2, single-institution, single-blind study compared gemcitabine 1,000 mg/m² intravenously over 30 minutes on days one, eight and 15, with either huachansu 20 ml/m² intravenously over two hours daily for five days a week for three weeks followed by one week off or the same dose of gemcitabine and an intravenous saline (placebo) infusion with the same schedule as the huachansu. Cycles were repeated every 28 days. Assessment of response via roentgenogram, computed tomography or magnetic resonance imaging was performed approximately every eight weeks. Blood counts were assessed on a weekly basis. The primary objective was to compare the four-month progression-free survival (PFS) rates of the two treatment arms. Secondary end points included time to progression (TTP), overall response rate (ORR) and toxicity.

**Results:** A total of 80 patients were enrolled in the study, of which 76 received at least one cycle of therapy and were evaluable. Thirty-nine patients received combination therapy (Arm A) and 37 patients received gemcitabine and placebo (Arm B). A median of two cycles of therapy was administered in both arms of the study. The four-month PFS was 99 days in those patients receiving gemcitabine and huachansu and 98 days in those patients receiving gemcitabine and placebo (p = 0.679). Median overall survival was 160 days for Arm A and 156 days for Arm B (p = 0.339). The ORR was 9 percent and 3 percent in arms A and B (p = 0.332), respectively. There was also no statistically significant difference in TTP, 98 days for Arm A versus 115 days for Arm B (p = 0.825). The incidence of grade 3 and 4 toxicity in both groups was low and consisted of neutropenia, thrombocytopenia, nausea and vomiting.

**Conclusion:** Huachansu when combined with gemcitabine did not improve the outcome of patients with locally advanced and/or metastatic pancreatic cancer.

**Managed Care Implications:** The addition of traditional Chinese medicine to Western medicine will continue, particularly in the area of oncology. While this study was negative, other combinations may prove to be effective.
chemotherapy regimens. Fluorouracil (5-FU; Adrucil)-based regimens have been the standard treatment for the disease with an objective response rate (ORR) of 0 to 7 percent. Gemcitabine (Gemzar) therapy has been reported to be superior to 5-FU and became the first-line treatment for the disease in 1997. Combination therapy with 5-FU and gemcitabine has been found to be tolerable, but no randomized studies have demonstrated the combination to be of greater benefit than gemcitabine monotherapy. Capecitabine (Xeloda) has shown activity for patients with metastatic pancreatic cancer in phase 2 clinical trials. Its oral administration and lack of overlapping toxicity make it an ideal agent to pair with gemcitabine. A recent phase 3 trial of gemcitabine/capecitabine vs. gemcitabine alone showed the combination to significantly improve the ORR (19.1 percent vs. 12.4 percent; p = 0.034), progression-free survival (HR [hazard ratio] 0.78; 95 percent CI, 0.66-0.93; p = 0.004) and a trend toward improved overall survival (HR 0.86; 95 percent CI, 0.72-1.02 months; p = 0.08). The objective of this study was to evaluate the efficacy and safety of standard dose capecitabine and gemcitabine as first-line therapy for treatment of patients with advanced pancreatic cancer.

Methods: Patients with histologically confirmed unresectable locally advanced or metastatic adenocarcinoma of the pancreas who had not received prior chemotherapy or radiation were eligible. Additional eligibility criteria included ages 18-80, ECOG performance status 0-2, a life expectancy of > 3 months, a measurable lesion and adequate end-organ function. Patients received gemcitabine 1,000 mg/m² intravenously over 30 minutes on days one, eight and 15, and 1,660 mg/m² of capecitabine orally on days 1-21 every four weeks. Treatment continued until disease progression, development of severe toxicity or withdrawal of patient consent. Dose reductions due to toxicity were established. The primary end point of the study was response rate with the secondary end point being the toxicity associated with the regimen.

Results: A total of 50 patients were evaluable for response on an intention-to-treat basis. The median age was 53 years (range 39-76). Twenty-nine patients had metastatic lesions with the other 21 having unresectable locally advanced disease. The response rate was 48 percent (95 percent CI, 22.5-57.1 percent) with all responders having a partial response. An additional 20 patients (40 percent) had stable disease. The median time to progression was 6.5 months (95 percent CI, 2.3-8.7 months) and the one-year survival rate was 45 percent. The median overall survival was 11.5 months (95 percent CI, 8.68-14.0 months) for patients with stage III disease and 9.4 months (95 percent CI, 3.56-14.2 months) for those patients with stage IV disease. Grade 3-4 toxicities associated with the combination therapy included neutropenia (22 percent), thrombocytopenia (6 percent) and hand-foot syndrome (10 percent).

Conclusion: The combination of gemcitabine and capecitabine was well-tolerated and demonstrated promising efficacy in the treatment of advanced pancreatic cancer.

Managed Care Implications: While intravenous 5-FU has shown limited activity in the treatment of advanced pancreatic cancer, the administration of oral capecitabine daily for 21 days may lead to an increase in response
rate, particularly when combined with other active chemotherapeutic agents such as gemcitabine.

>Title: A multi-institutional phase 2 study of imatinib mesylate and gemcitabine for first-line treatment of advanced pancreatic cancer.

Authors: Moss RA, Moore D, Mulcahy ME, et al.


Purpose: Pancreatic cancer carries a dismal prognosis and remains a significant cause of cancer morbidity and mortality. Gemcitabine (Gemzar) has replaced fluorouracil (5-FU; Adrucil) as the standard treatment for patients with the disease, showing a modest but statistically significant improvement in overall survival when the two drugs were compared. In multiple trials, single-agent gemcitabine has achieved a median overall survival of six months in patients with advanced-stage disease. New treatment strategies are needed. One strategy is for more effective therapy to improve the access of chemotherapy to the interior of the tumor. Inhibition of platelet-derived growth factor receptors (PDGFRs) may decrease tumor interstitial fluid pressure (IFP) and allow better penetration of gemcitabine. Imatinib mesylate (Gleevec) is an oral small molecule that inhibits PDGF, as well as the tyrosine kinases associated with BCR-ABL and c-kit. The rationale for using imatinib in anticancer therapy focuses on PDGFRs. PDGFRs are expressed on several tumor types, including pancreatic, are found in both tumor pericytes and tumor vasculature and are thought to play a role in the control of IFP. Several preclinical studies have demonstrated improved activity of cytotoxic chemotherapeutic agents, including gemcitabine, when combined with imatinib. Phase 1 trials using gemcitabine and imatinib in solid tumors have been reported. Due to significant toxicity with standard dosing, a schedule of imatinib 400 mg orally daily on days one to five and eight to 12 and gemcitabine at a fixed dose of 1,500 mg/m² was used. Partial responses were noted as was a striking degree of stabilization of disease (31 percent of patients at 12 weeks). Based on these promising results, this phase 2 study was undertaken.

Methods: Patients were required to have an ECOG performance status of 0 to 2, be at least 18 years of age and have measurable disease. Patients had to be deemed ineligible for curative resection and could not have had prior chemotherapy for metastatic disease, with the exception of patients with prior surgical resection and a history of adjuvant fluorouracil if at least six months had passed between the last dose of chemotherapy and the recurrence of the pancreatic cancer. Patients also needed to have adequate end-organ function. Therapy consisted of gemcitabine 1,200 mg/m²/120 minutes as an intravenous infusion on days three and 10. Imatinib, 400 mg orally, was given once a day with meals on days one to five and eight to 12. Cycles were repeated every 21 days. The primary end point of the study was progression-free survival (PFS). Secondary end points included overall response rate (ORR), toxicity, overall survival (OS) and one-year survival rate.

Results: A total of 42 patients were evaluable for response. The median number of cycles completed was three (range 0-17). One patient had a partial response, 16 had stable disease, 18 had progressive disease and seven were not assessed. The median PFS was 3.9 months (95 percent CI, 2.1-5.1 months). The median OS was 6.3 months (95 percent CI, 5.2-8.5 months) and the one-year survival rate was 26.5 percent (95 percent CI, 13.8-39.1 percent). Hematologic toxicity was significant, with 50 percent of patients having a grade 3 or higher neutropenia and 17 percent having a grade 3 or higher thrombocytopenia. This resulted in numerous dose reductions. Grade 3 or higher nonhematologic toxicity included dehydration (9 percent of patients), skin rash (9 percent) and fatigue (5 percent).

Conclusion: Imatinib in combination with gemcitabine is tolerated in locally advanced, metastatic or recurrent pancreatic cancer. However, the combination does not show a statistically significant improvement in PFS or OS when compared to single-agent gemcitabine.

Managed Care Implications: Drugs with unique mechanisms of action will be studied for the treatment of advanced pancreatic cancer. While this study was negative, imatinib may be used in other drug combinations in this particular patient population.
This resource guide features links and websites on pancreatic 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 website provides a comprehensive guide to pancreatic cancer, including information about risk factors, diagnosis, staging and treatment.

www.cancer.org/cancer/pancreaticcancer

American Society of Clinical Oncology (ASCO). This nonprofit organization was founded in 1964 and its members include oncology practitioners from all disciplines and subspecialties. ASCO is committed to conquering cancer through research, education, prevention and delivery of high-quality patient care. The gastrointestinal cancer Web portal of ASCO’s official journal, the Journal of Clinical Oncology, features the latest research findings presented through scientific abstracts, videos, Web links and other materials.

http://gi.jco.org

Lustgarten Foundation. The mission of this nonprofit foundation is to advance scientific and medical research in the prevention, diagnosis, treatment and cure of pancreatic cancer. The foundation’s work includes increasing public awareness of pancreatic cancer, providing support for patients and their families and friends, increasing funding and support of scientific research, and encouraging dialogue within the medical and scientific communities about research efforts. The foundation’s website includes information on research initiatives, funding and awards, scientific conferences, news and resources for patients.

www.lustgarten.org

CancerNet. This is the American Society of Clinical Oncology’s patient website, featuring peer-reviewed information on pancreatic cancer. Statistics, staging and treatment information, medical illustrations and research findings are available.

www.cancer.net/cancer-types/pancreatic-cancer

Mayo Clinic. Mayo Clinic’s award-winning consumer website offers health information and self-improvement tools. Mayo Clinic’s medical experts and editorial professionals bring you access to the knowledge and experience of Mayo Clinic for all your consumer health information needs. This website section is devoted to issues regarding pancreatic cancer.

www.mayoclinic.com/health/pancreatic-cancer/DS00357

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 pancreatic cancer, clinical trial information, glossaries, statistics and much more.


National Cancer Institute (NCI). The NCI, part of the U.S. National Institutes of Health, conducts and supports cancer-related research, training and health information dissemination. This website provides information on treatment, screening, testing and clinical trials, research and literature related to pancreatic cancer.

www.cancer.gov/cancertopics/types/pancreatic

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 pancreatic adenocarcinoma. Users must register to access guidelines.


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 provides information on treatment options, clinical trials and other resources for pancreatic cancer.

www.oncolink.org/types/article.cfm?c=4&ss=7&ss=49&id=1739&CFID=57821805&CFTOKEN=94323401

Pancreatic Cancer Action Network. Founded in 1999, this nonprofit organization works to support patients and advance research in pancreatic cancer. The organization offers the Patient and Liaison Services (PALS) program to help link physicians and patients to clinical trials. PALS features a searchable database of clinical trials in the U.S. and Canada and no-cost, peer-reviewed educational materials. The organization’s website also includes information on research, grants and advocacy.

www.pancan.org

*Note: ICORE Healthcare does not endorse or verify the information presented.
The first day of the Summit will provide a forum for nationally recognized payors, oncologists and industry thought leaders to explore and discuss the key issues and challenges we face in an evolving specialty pharmacy market. Please join us for this exciting two-day event that will include discussions on other therapies as well, including autoimmune and neurological conditions.
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