Diagnosis, Prognostic Factors, and Treatment Considerations for Lung Cancer
One goal: discovering and delivering breakthrough medicines to combat cancer.

Millennium: The Takeda Oncology Company is developing an extensive pipeline — among the top in oncology worldwide — with more than 17 compounds in development for a broad range of solid and hematological cancers.

Our pipeline — rich in novel compounds — includes multiple candidates that target seven disease pathways: protein homeostasis, anti-angiogenesis, growth-signaling inhibition, cell-cycle inhibition, apoptosis, immunomodulators and hormone regulation.

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To learn more, visit us at millennium.com.
Improving Value
One Payor’s Approach to Addressing End-of-Life Care and Other Cost and Quality Issues in Lung Cancer
by Bruce Niebylski, MD, Associate Vice President for Medical Affairs, East Region, PriorityHealth
PriorityHealth is considering palliative care and hospice programs as potential resources to offset treatment costs and improve the quality of care for patients in end-of-life scenarios.

Drug Therapy Reviews
Considerations for the Diagnosis, Staging, and Treatment of Lung Cancer in the Managed Care Environment
by David Spigel, MD, Tennessee Oncology
Lung cancer is the leading cause of cancer deaths in the United States, claiming more male and female lives than colon, breast, and prostate cancers combined.

Regulatory & Reimbursement
Lung Cancer: Slaying the Deadly Dragon
by Denise K. Pierce, President, DK Pierce & Associates, Inc.
All stakeholders, payors, providers, patients, and biopharmaceutical companies are looking for ways to bring the best clinical value to the system and to the patient for the treatment of lung cancer.
calendar of events

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

July
7-9 Canadian Orthopaedic Association’s 66th Annual Meeting
Ottawa, Ontario

September
11-13 American College of Clinical Pharmacy’s Annual Meeting
Chicago, Illinois
15 ICORE Healthcare’s Advanced Managed Care Training
New York City, New York
16 ICORE Healthcare’s 8th Annual Oncology Summit/2011 Annual Meeting
New York City, New York
Comparison of Paid Amounts for Top 10 Provider-Administered Drugs, by Site of Service

<table>
<thead>
<tr>
<th>RANKING</th>
<th>J CODE</th>
<th>BRAND NAME</th>
<th>ALLOWED PER 1 M LIVES</th>
<th>UNITS PER 1 M LIVES</th>
<th>CALCULATED UNIT RATE</th>
<th>$/CLAIM</th>
<th>UNITS/CLAIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>J1745</td>
<td>Remicade</td>
<td>$11,319,516</td>
<td>176,801</td>
<td>$64</td>
<td>$4,608</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>J9035</td>
<td>Avastin</td>
<td>$7,439,946</td>
<td>123,003</td>
<td>$60</td>
<td>$5,928</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>J2505</td>
<td>Neulasta</td>
<td>$7,023,023</td>
<td>1,837</td>
<td>$3,823</td>
<td>$4,526</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>J9310</td>
<td>Rituxan</td>
<td>$5,977,651</td>
<td>30,317</td>
<td>$579</td>
<td>$6,816</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>J9355</td>
<td>Herceptin</td>
<td>$3,877,448</td>
<td>58,157</td>
<td>$67</td>
<td>$3,514</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>J9263</td>
<td>Eloxatin</td>
<td>$3,525,041</td>
<td>331,455</td>
<td>$11</td>
<td>$5,249</td>
<td>323</td>
</tr>
<tr>
<td>7</td>
<td>J9170</td>
<td>Taxotere</td>
<td>$3,418,043</td>
<td>8,849</td>
<td>$386</td>
<td>$3,689</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>J0881</td>
<td>Aranesp</td>
<td>$3,405,312</td>
<td>890,540</td>
<td>$4</td>
<td>$1,578</td>
<td>233</td>
</tr>
<tr>
<td>9</td>
<td>J2469</td>
<td>Aloxi</td>
<td>$1,918,375</td>
<td>72,887</td>
<td>$26</td>
<td>$444</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>J3487</td>
<td>Zometa</td>
<td>$1,733,124</td>
<td>7,307</td>
<td>$237</td>
<td>$2,818</td>
<td>27</td>
</tr>
</tbody>
</table>

Comparison of Paid Amounts for Top 10 Provider-Administered Drugs, by Site of Service

The site of service for chemotherapy administration is the new problem payers are facing. Before we think through what this means, let’s review the history of how chemotherapy administration came to be office-administered. Over a decade ago, Medicare realized that administering chemotherapy in a facility might not be the most cost-effective approach to providing its beneficiaries with the drugs they need to battle cancer. So Medicare made a few strategic initiatives to pull chemotherapy administration out of the facility and into basically anywhere else. And it worked. Then providers realized that administering drugs is a pretty good business; in fact, it’s our opinion that the office is where these drugs should be administered. There are four key reasons this is true.

1. Pricing. We have found that office-based providers, based on the mix of drugs that they administer, purchase infused or office-administered drugs (primarily chemotherapy, chemotherapy support, and rheumatology medicines) at a 17% discount to what specialty pharmacies purchase these drugs, thus obfuscating perceived benefits of taking buy-and-bill away. Moreover, significantly better buy-side pricing exists at the office when compared with the facility. From a cost-of-claim perspective, our recently released Trend Report showed cost per claim for commonly administered infused drugs in the facility was about twice that of office-administered claims. This is because many facility contracts call for infused drugs to be reimbursed at “percent of billed charges,” and billed charges are not average wholesale price.

2. Waste. Patients who are intending to receive a drug that was shipped to a physician’s office (rather than taken from the office inventory, administered,
and billed to the payor or government agency) do not receive approximately one-fifth of drugs (based upon cost). This is because patients fail to show up, are not able to receive the next dose due to intolerance or changes in therapies, change benefits, or elect to move into hospice care, just to name a few reasons.

3. Billing inefficiencies. Office-based administration can provide partial vials – Healthcare Common Procedure Coding System codes used for billing these medicines in the office are based on billing units, not vials. Doses that are supplied to an office from a specialty pharmacy bill 11-digit National Drug Code codes and thus generally bill the entire vial.

4. Quality of care. The office oncologist has been following the member for some time; the facility may be seeing him or her for the first time. In addition, member experience is generally better at the local provider than at the facility (just ask the members!), and that whole nosocomial infection issue is another topic in and of itself.

Hopefully we have laid out compelling data to support office administration of cancer infusions. Now for the problem: Lately, there has been a trend to transition administration into the facility. In March of this year, the Community Oncology Alliance published that over the past 3.5 years, 315 of 1,042 oncology practices/clinics were acquired by hospitals and 48 were sending all their patients outside of their practice for chemotherapy. Of note is the 3-million-life Blue Cross plan that sized the impact of its local oncologists sending patients to the facility: It will cost the employers that they serve more than $60 million annually. Oh, and imagine the impact to the members – increased allowed amounts (as outlined above) create increased coinsurances to these members.

If you know me, I don’t like to just describe problems; I like to offer solutions. So here it comes: Pay your providers who administer infused drugs in their office fairly. If you do, they will maintain cost-effective, quality care in their office where it belongs. Give us a call, and we can support you in your efforts in doing this.

Have a terrific summer.

Kjel A. Johnson, PharmD
Publisher
ManagedCare Oncology

References
The American Cancer Society reported that an estimated 225,520 U.S. citizens will have received an initial diagnosis of lung cancer in 2010, making it one of the more ubiquitous cancers we face. It is second only to breast cancer in women and prostate cancer among men. However, lung cancer is a much more deadly diagnosis as reflected in the estimated mortality last year.

Though there has been a statistically significant increase since the mid-1970s, unfortunately, the five-year survival expectation for a lung cancer diagnosis received between 1999 and 2005 is only 16% — reflecting some of the worst current survival odds other than the odds for a diagnosis of hepatic or pancreatic cancer.

### 2010 Estimated New Cases and Deaths

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Male</td>
</tr>
<tr>
<td>Lung</td>
<td>222,520</td>
<td>116,750</td>
</tr>
<tr>
<td>Prostate</td>
<td>217,730</td>
<td>-</td>
</tr>
<tr>
<td>Breast</td>
<td>1,970</td>
<td>207,090</td>
</tr>
</tbody>
</table>

### Trends in Five-Year Survival Rates* (%) by Year of Diagnosis, U.S., 1975 to 2005

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>1975-77</th>
<th>1984-86</th>
<th>1999-2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>54</td>
<td>68*</td>
</tr>
<tr>
<td>Brain</td>
<td>24</td>
<td>29</td>
<td>36*</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>79</td>
<td>90*</td>
</tr>
<tr>
<td>Colon</td>
<td>52</td>
<td>59</td>
<td>66*</td>
</tr>
<tr>
<td>Esophagus</td>
<td>5</td>
<td>10</td>
<td>19*</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>74</td>
<td>79</td>
<td>86*</td>
</tr>
<tr>
<td>Kidney</td>
<td>51</td>
<td>56</td>
<td>69*</td>
</tr>
<tr>
<td>Larynx</td>
<td>67</td>
<td>66</td>
<td>63*</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35</td>
<td>42</td>
<td>54*</td>
</tr>
<tr>
<td>Liver and bile duct</td>
<td>4</td>
<td>6</td>
<td>14*</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13</td>
<td>13</td>
<td>16*</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>82</td>
<td>87</td>
<td>93*</td>
</tr>
<tr>
<td>Myeloma</td>
<td>26</td>
<td>29</td>
<td>37*</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>48</td>
<td>53</td>
<td>69*</td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>53</td>
<td>55</td>
<td>63*</td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>40</td>
<td>46*</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>3</td>
<td>6*</td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>100*</td>
</tr>
<tr>
<td>Rectum</td>
<td>49</td>
<td>57</td>
<td>69*</td>
</tr>
<tr>
<td>Stomach</td>
<td>16</td>
<td>18</td>
<td>27*</td>
</tr>
<tr>
<td>Testis</td>
<td>83</td>
<td>93</td>
<td>96*</td>
</tr>
<tr>
<td>Thyroid</td>
<td>93</td>
<td>94</td>
<td>97*</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>74</td>
<td>78</td>
<td>82*</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>70</td>
<td>68</td>
<td>72*</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>88</td>
<td>84</td>
<td>84*</td>
</tr>
</tbody>
</table>

* Survival rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 9 areas from 1975-77, 1984-86, 1999-2005, and followed through 2006.

† The difference in rates between 1975-77 and 1999-2005 is statistically significant (p <0.05).

Stakeholder Insights

According to the National Lung Cancer Partnership, a not-for-profit advocacy organization, lung cancer is often perceived as a man’s disease. In fact, it is just as common and lethal a cancer in women. Further, roughly 10% to 15% of lung cancer patients have never smoked. That means between 20,000 to 30,000 nonsmokers are diagnosed with lung cancer in the U.S. each year.2

The science is evolving, and this organization has a mission to increase awareness of the disease and advocate for funding from federal research dollars. As the chart below illustrates, lung cancer lags behind other cancers when mortality is factored in.3 However, as noted in the 2010 ICORE Healthcare Medical Injectables & Oncology Trend Report, private industry appears to be supporting the effort with almost 90 drugs in phase 2/phase 3 clinical research for non-small cell lung cancer (NSCLC). With all these new agents in the pipeline, ICORE Healthcare’s proprietary survey research indicates that payors consider a product to have a survival benefit in NSCLC patients if the clinical data show about seven months beyond the standard of care life expectancy.4

U.S. Cancer Deaths vs. Federal Research Funding per Death

*While the Centers for Disease Control and Prevention also funds cancer research, a breakdown of spending between research and public health interventions is not currently available.
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Claims Benchmarks

Even though NSCLC is generally diagnosed at an advanced stage, there are a number of treatment approaches providers can initiate. ICORE Healthcare recently analyzed a dataset of paid claims from 19 million covered lives, including total cost of care parameters, and found that chemotherapy plays a major role in treatment, either alone or in combination with other modalities (62% of patients had chemotherapy claims). Treatment approaches are fragmented, with about three in 10 lung cancer patients having claims for a combination of chemotherapy and radiation therapy. This is followed by about one quarter of the patients having radiation only and 23% of the patients having chemotherapy alone.5 The other patients had claims for treatment that included some form of surgery, most often in combination with other options.

The data presented below from a separate claims analysis show that allowed medical claims for all chemotherapy agents across all cancer diagnoses totaled $41.5 million per 1 million lives. Just 5% of this ($2.16 million) is associated with a lung cancer diagnosis.5

<table>
<thead>
<tr>
<th>TOTAL CHEMOTHERAPY SPEND</th>
<th>OFF-LABEL/ON-LABEL USE IN LUNG CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td><strong>Total Chemo Spend</strong></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>$2,162,943.27</td>
</tr>
<tr>
<td>All cancer diagnoses</td>
<td>$39,372,921.35</td>
</tr>
<tr>
<td>Total</td>
<td>$41,535,864.62</td>
</tr>
</tbody>
</table>

There appears to be a relatively modest cost associated with off-label chemotherapy use in these lung cancer claims at just 13% of the spend. Of the FDA-approved therapies, Avastin and Alimta have the highest unit utilization and allowed $/1 million lives, well beyond other products. Of note,
Claims Benchmarks continued

generic gemcitabine entered the market mix in late 2010.

The majority (78%) of these on-label lung cancer chemotherapy claims were associated with administration in a physician’s office. Claims from hospital settings were about 15% of the total. How does your plan compare?

<table>
<thead>
<tr>
<th>J-Code</th>
<th>Drug Name</th>
<th>Allowed per 1M Lives</th>
<th>Units per 1M Lives</th>
<th>Claims per 1M Lives</th>
<th>Patients per 1M Lives</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9035</td>
<td>Avastin</td>
<td>$772,192.48</td>
<td>12,334</td>
<td>316</td>
<td>35</td>
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<tr>
<td>J9305</td>
<td>Alimta</td>
<td>$730,602.11</td>
<td>12,715</td>
<td>127</td>
<td>51</td>
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<tr>
<td>J9201</td>
<td>Gemzar</td>
<td>$115,125.40</td>
<td>696</td>
<td>23</td>
<td>20</td>
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<tr>
<td>J9265</td>
<td>Taxol</td>
<td>$75,361.70</td>
<td>1,405</td>
<td>201</td>
<td>52</td>
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<tr>
<td>J9171</td>
<td>Taxotere</td>
<td>$64,785.46</td>
<td>3,208</td>
<td>31</td>
<td>11</td>
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<tr>
<td>J9264</td>
<td>Abraxane</td>
<td>$49,793.59</td>
<td>4,837</td>
<td>18</td>
<td>4</td>
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<tr>
<td>J9170</td>
<td>Taxotere</td>
<td>$46,795.16</td>
<td>100</td>
<td>19</td>
<td>7</td>
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<tr>
<td>J9390</td>
<td>Navelbine</td>
<td>$13,908.83</td>
<td>287</td>
<td>59</td>
<td>12</td>
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<tr>
<td>J9060</td>
<td>Cisplatin</td>
<td>$9,526.56</td>
<td>655</td>
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<td>27</td>
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<td>J9181</td>
<td>Vepesid</td>
<td>$7,981.62</td>
<td>3,833</td>
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<td>J9250</td>
<td>Methotrexate</td>
<td>$2.64</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>J9260</td>
<td>Methotrexate</td>
<td>$1.81</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Grand Total</td>
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<td>40,071</td>
<td>942</td>
<td>250</td>
<td></td>
</tr>
</tbody>
</table>

References

3. © 2010 National Lung Cancer Partnership. All rights reserved. Used with permission.
6. ICORE Healthcare paid claims (commercial and Medicare) 2.6 million lives across three health plans. All statistics are a representation of patients who have at least one diagnosis of lung cancer on the claim.
By Bruce Niebylski, MD, Associate Vice President for Medical Affairs, East Region, PriorityHealth

As a result of the high mortality associated with lung cancer, this disease is the distinct leader among oncologic conditions in terms of indirect costs associated with lost productivity due to death.¹

Managing the Intangibles: One Payor’s Approach to Addressing End-of-Life Care and Other Cost and Quality Issues in Lung Cancer

by Bruce Niebylski, MD, Associate Vice President for Medical Affairs, East Region, PriorityHealth
And while the approximate $36 billion in annual lost productivity assigned to lung cancer is impressive, payors find themselves tasked with controlling the similarly exorbitant direct costs associated with treating the disease. Lung cancer is also a leading cost driver for managed care oncology in this category, ranking third among cancers at all sites with estimated annual treatment expenditures of $10.3 billion.\(^1\)

In addition to contributing to indirect costs resulting from deaths, the remarkable mortality of lung cancer also gives rise to cost-of-care issues surrounding end-of-life scenarios. End-of-life care is becoming a top cost- and quality-related priority for payors with cancer at any site, but these concerns are arguably more significant with lung cancer, where costs in the last year of life nearly mirror those in initial care. While treatment in the early stages of the disease appears to provide the most clinical benefit, the value of end-stage therapy is far more controversial. Still, treatment in the last year of life for members with lung cancer accounts for nearly 42% of all treatment expenditures, compared with a 43% contribution from initial care (see figure). This results in $4.4 billion spent annually on direct costs for initial care and a strikingly similar $4.3 billion spent on end-of-life care for lung cancer, raising red flags among plans as an area requiring further attention.

Beyond drug treatment and end-of-life considerations, numerous other facets of lung cancer management contribute to the overall cost of treating the disease, captured as part of the estimated $10.3 billion spent annually on care. These other components of lung cancer care — including radiation therapy, imaging studies, and hospitalizations — approach and often even surpass pharmacotherapy in their cost implications. For these reasons, an optimal lung cancer management program should not consist of a one-dimensional pharmacy management approach but must rather institute a comprehensive look at all the potential care interventions and their associated costs. In keeping with the premise behind managed healthcare being rooted in preventive medicine, smoking-cessation initiatives should likewise be considered and incorporated in health plans’ overall strategies to minimize the impact of lung cancer in member populations.

### A Comprehensive Approach at PriorityHealth

In keeping with the concepts outlined previously, the oncology management program at PriorityHealth is not merely a pharmacy-based initiative. To achieve a more well-rounded approach, plan stakeholders evaluate the pharmacotherapy

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**Estimates of the Proportion of National Expenditures for Cancer Care in 2006 by Cancer Site and Phase of Care**\(^1\)

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Initial Care</th>
<th>Continuing Care</th>
<th>Last Year of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

logic component of care in addition to the costs associated with imaging, radiation therapy, and time spent outside of the plan’s clinics at other facilities. As part of this comprehensive approach, PriorityHealth is also putting further consideration into palliative care and hospice programs as potential resources to offset treatment costs and improve the quality of care for patients in end-of-life scenarios.

Looking specifically at drug treatment, oncologic agents are managed as part of the larger specialty or biologic drug program. PriorityHealth has a five-tier benefit program that includes all specialty drugs, including cancer therapies, but the plan is trying to segregate cancer as an area deserving of further evaluation and intervention. Within the specialty drug program, approximately 50% of the injectables are subject to prior authorization and typically limited to use only for U.S. Food and Drug Administration (FDA) approved diagnoses, with authorizations granted up to six months. In select cases, authorizations are also granted for use according to the agents’ role in the National Comprehensive Cancer Network’s Clinical Practice Guidelines.

The appeals process in the event of a denial is fairly standard, and physicians for whom authorization is denied are invited to an upcoming Pharmacy and Therapeutics (P&T) committee meeting to discuss the matter if they so choose. However, denial rates at PriorityHealth are less than 1% since the large-group oncology practices within the plan are experienced and have adequate infrastructure to capably navigate the prior authorization process.

For oral oncology agents within the specialty drug program, step therapy may be required if the drug is particularly costly. PriorityHealth’s pharmacy benefits manager automates this undertaking for oral agents, allowing for a high degree of confidence in the utilization of oral agents. While infused agents under the specialty drug program are less tangibly managed, the plan employs manual claims edits to ensure that the correct diagnosis codes are paid according to the authorization.

Regular P&T reviews at PriorityHealth serve to address the issue of emerging chemotherapies and targeted biologics coming to the market, and input is sought from the plan’s oncology community on products for which knowledge is limited among committee members. This outreach to network oncologists is facilitated by an e-mail process, and specialists in cancer at a specific site are often consulted in addition to general oncologists where applicable.

Ever aware of the potential for prejudices among clinicians, the PriorityHealth P&T committee seeks opinions from multiple oncologists whenever possible. Plan stakeholders have discussed the possibility of an oncology subcommittee reporting to the P&T on matters of cancer therapies, but the current oncologist consultation process has performed sufficiently to date.

TAKING A CLOSER LOOK AT LUNG CANCER

Considering the large group of members with a diagnosis of cancer, plan stakeholders at PriorityHealth recognize that an attempt to manage all of them would be overwhelming and less effective than an approach targeting cancer at specific sites. To this end, plan stakeholders cut the claims data based on diagnoses, concentrating initially on the most pressing concerns: lung, breast, colon, and prostate cancer.

Although there is no program designed specifically for lung cancer, each of these four cancer types is subject to standard disease management interventions. The ultimate goal of these interventions is compliance with guidelines, and the plan is continuously working to further develop the initiatives for cancer at each site. As would be expected, lung cancer is a major contributor to the oncology-related costs at PriorityHealth and is justifiably targeted with such management initiatives.

Initial analyses showed that – despite only approximately 600 cases of active lung cancer in a member population of more than 600,000 – the plan spent $7 million on the disease over a period of just nine months.

Of course, drug spend remains a leading cost driver for lung cancer at PriorityHealth, but emerging therapies have altered the treatment landscape and exacerbated financial pressures on all payors. While the taxanes were once singled out as the high-cost therapeutics driving the trend, these agents have been supplanted by even more expensive biologics where inappropriate use can result in a sizable drain on funds. As such, newer targeted therapies, like bevacizumab and pemetrexed, with significant cost and limited indications, represent a potential for savings through evidence-based management. Still, as expenditures are further charac-
Managed Care Oncology
Quarter 2 2011

failing health impact logical discourse at the end of life. In the PriorityHealth network, oncologists are using different approaches to promote early end-of-life discussions, depending on individual practice cultures. One practice, for example, requires documentation of end-of-life conversations with a patient in the chart by his or her second office visit. In addition to initiating end-of-life conversations earlier in the treatment process, PriorityHealth also incorporates the guidance of case managers who get involved with the care of members with late-stage disease. Beyond facilitating the transfer of members into hospice care when appropriate, these case managers assist in managing the multiple comorbidities that frequently occur in terminally ill patients with cancer and coordinate palliative treatment in certain situations. These services improve members’ quality of

cancer discuss future hospice care with their physicians within four to seven months of diagnosis.2

The study, conducted by the Cancer Care Outcomes Research & Surveillance (CanCORS) Consortium, also showed that patients with metastatic disease tended to overestimate how long they had to live: Approximately 30% stated a belief that they would live up to two years, when in reality approximately only 6% actually survive that long.2 By setting expectation levels at the beginning of treatment – the strategy at PriorityHealth – patients are more likely to become aware of the potential for difficult decisions if or when their disease progresses and more likely to plan accordingly. These early conversations also afford providers the opportunity to convey crucial palliative care considerations, presumably before the patients’ emotion and
terized, other components of care, such as radiation therapy and imaging, are also receiving increased attention.

Although treatment variability in oncology is an oft-cited concern among plan stakeholders across the country, the experience at PriorityHealth has been that the Michigan-based provider network is generally a guideline-driven group. Much of this general adherence to treatment protocols among PriorityHealth providers can be attributed to the fact that most oncologists in the state are members of the Michigan Society of Hematology and Oncology (MSHO). MSHO is a very active professional organization that moderates frequent protocol discussions and contracts through a third party to create evidence-based treatment guidelines, thereby encouraging members to stay current and in line with these recommendations. Regardless of the reason, the uniform utilization of potentially costly therapeutics is less of a concern at PriorityHealth than the duration of treatment with these agents and continued use in the face of nonresponse or very limited clinical benefit.

Nowhere are the concerns surrounding length of therapy and continued treatment despite diminished benefits more prevalent than in end-of-life situations. Across the country, chemotherapy and biologic treatment are often overused in patients with late-stage cancer who will reap little or no clinically meaningful benefit and in whom hospice care may actually extend survival. PriorityHealth has broached this sensitive subject by encouraging network oncologists to initiate end-of-life discussions early in the course of care, preferably upon treatment initiation in terminally ill patients. Unfortunately, recent findings from various nationwide locations indicate that only half of patients with stage IV metastatic lung cancer discuss future hospice care with their physicians within four to seven months of diagnosis.2

The study, conducted by the Cancer Care Outcomes Research & Surveillance (CanCORS) Consortium, also showed that patients with metastatic disease tended to overestimate how long they had to live: Approximately 30% stated a belief that they would live up to two years, when in reality approximately only 6% actually survive that long.2 By setting expectation levels at the beginning of treatment – the strategy at PriorityHealth – patients are more likely to become aware of the potential for difficult decisions if or when their disease progresses and more likely to plan accordingly. These early conversations also afford providers the opportunity to convey crucial palliative care considerations, presumably before the patients’ emotion and
life in their final days, in addition to minimizing the unnecessary use of continued chemotherapy in situations where it provides diminishing benefits.

PREVENTIVE MEDICINE AND FUTURE CONSIDERATIONS

On the other end of the lung cancer care continuum, smoking-cessation efforts should play an integral role in plans’ overall strategies for managing the disease. Considering the causative relationship between smoking and lung cancer in approximately 87% of cases, payors would be remiss not to include cessation interventions in implementing an approach founded in preventive medicine. At PriorityHealth, these initiatives take the form of regular messaging about the benefits of quitting smoking in member communications, such as the plan’s quarterly newsletter. The plan likewise works with several employer groups to provide smoking-cessation materials as part of the broader antismoking campaign.

In addition to member education initiatives, PriorityHealth’s coverage of the smoking-cessation agent varenicline has contributed to a reduction in the proportion of plan members who smoke. Although coverage of the drug was at first controversial among plan stakeholders and contributed to an initial $3 million increase in pharmacy spending in the first quarter of its use, smoking among members has dropped from 16% to less than 12%, where it remains today. Enhancing the favorability of this immediate benefit, spending on varenicline eventually tapered off and coverage of the agent did not affect the pharmacy budget in the long run.

Bolstering the impact of pharmacologic smoking-cessation aids, nicotine replacement products are also covered at PriorityHealth with a minimal member copay. The belief among plan stakeholders is that wellness benefits must be as easily attainable as possible to promote preventive care and lifestyle modification, while improving long-term health outcomes and controlling costs. Likewise encouraging health-conscious habits, the plan’s HealthbyChoice Rewards program offers financial incentives for completing an online risk assessment and getting a physical examination. Depending on the member’s employer, incentives may include reduced premiums through a health savings account for healthy behaviors such as quitting smoking.

Looking toward the future, the plan is exploring additional directives to improve disease-related outcomes and manage spending on pharmacotherapy and other elements of care for lung cancer and other oncologic conditions. Considering that treatment variability is already adequately managed at PriorityHealth, plan stakeholders are working on developing imaging protocols to guide the appropriate use of costly computed tomography and magnetic resonance imaging studies in the diagnosis and assessment of the disease. The plan is also beginning to profile specialists and different regions of the coverage area to try to identify best practices in oncology and other disease states. The hope here is that the plan can find top-tier healthcare resources within the contracted area, minimizing the tendency for members to go outside of the network (e.g., to Sloan-Kettering or MD Anderson in the case of cancer) for what they perceive is the best available care.

Despite the potential utility of these proposed interventions, provider initiation and participation in early end-of-life discussions remains the seemingly best means of managing cost and quality of care issues in lung cancer at PriorityHealth. However, an optimal approach for addressing these concerns in the care of members diagnosed with lung cancer should be multifaceted and involve all components of care, including radiation therapy and imaging in addition to drug treatment. Payors must first identify implicit gaps in the quality of care before designing appropriately tailored, cost-saving interventions to adequately manage this deadly and costly disease in a sustainable manner.

References

Lung cancer is the leading cause of cancer deaths in the United States, claiming more male and female lives than colon, breast, and prostate cancers combined.

While the incidence and mortality from the disease have been steadily decreasing for a number of years, the decline has been significantly greater among men than women. This gender-related phenomenon is presumably a function of trends in smoking, in which tobacco use among males has been decreasing for the past several decades while reductions in female smoking habits have been more recent. Still, the epidemiologic burden of cancer at this site remains slightly more prevalent in men, with 116,750 of the 222,520 (approximately 53%) estimated new lung cancer cases diagnosed in the United States in 2010 occurring in males. Also, the American Cancer Society estimates that 157,300 deaths resulted from the disease in 2010, with 86,220 (approximately 55%) of those being in men. Regardless, in addition to being the number one cancer-related killer among both genders, lung cancer represents the second most common cancer in both men (behind prostate cancer) and women (behind breast cancer).

Approximately 87% of lung cancer cases are directly attributable to smoking, marking the disease as one of the most preventable cancers identified by the medical community. The high incidence and significant mortality associated with lung cancer make this fact even more remarkable considering that a single lifestyle modification can drastically decrease a patient’s likelihood of being diagnosed with and dying from the disease. In fact, those...
who stop smoking before age 50 cut their risk of dying within the following 15 years in half compared with those who continue to smoke.³

Although the overwhelming majority of lung cancer occurs in smokers, other causative agents have been identified as playing a role in the remaining 13% of cases. Secondhand exposure to smoke or other substances such as radon, asbestos, and arsenic have been linked to an increased risk of developing lung cancer; however, these environmental or occupational risk factors pale in comparison to the role that smoking has on the incidence and mortality of the disease. Diagnoses of lung cancer among nonsmokers tend to be more common in women — suggesting a potential link between the disease and estrogen — but this theory requires further study.

Regardless of etiology, lung cancer is primarily diagnosed in older individuals, with an average age at diagnosis of 71 years. Approximately two out of three individuals diagnosed with the disease are older than age 65, and less than 3% of cases occur in those younger than age 45.² Non-small cell lung cancer (NSCLC) accounts for approximately 80% of cases, with adenocarcinomas being the most common variant.⁴ Considering the high frequency of NSCLC, the subsequent review of diagnosis and treatment considerations in managed care will focus mainly on this specific type of lung cancer.

**DIAGNOSIS AND STAGING**

As is the case with many cancers of the internal organs, lung cancer is difficult to detect early in the pathophysiologic process since many signs and symptoms do not appear until the disease has already progressed to an advanced stage. Patients presenting with classic localized symptoms such as chest pain, persistent coughing, shortness of breath, and/or new-onset wheezing are subject to a physical exam and medical history by their physicians. If the presence of risk factors or the nature of these symptoms indicates a potential diagnosis of lung cancer, the patient is typically referred for some form of imaging study, such as a chest X-ray, computed tomography (CT) scan, magnetic resonance imaging scan, or positron emission tomography scan. However, these latter two are generally reserved for determining if the cancer has spread beyond the lungs and assessing prognosis rather than for the principal diagnosis.

In addition to imaging studies, various methods for sampling lung tissue to evaluate histology/cytology are required to confirm a diagnosis of lung cancer. These procedures may include traditional methods — such as a sputum cytology test, bronchoscopy, or fine-needle aspiration biopsy — or more recently introduced techniques like CT-guided needle biopsy. Beyond these relatively noninvasive methods for obtaining tissue samples, various surgical procedures may be employed as well, although these are, again, more often used to assess the spread of cancer beyond the lungs and for staging the disease.

Lung cancer is typically staged according to the conventional American Joint Committee on Cancer’s TNM (tumor, node, metastases) staging system, with designations ranging from 0 (carcinoma in situ) to IV (advanced metastatic disease).⁵ Similar to cancers at other sites, the stage of a particular patient’s NSCLC is indicative of prognosis, which can generally be
characterized by declining five-year survival rates with advancing stages (see table above). The aggressive course of NSCLC and considerable mortality associated with the disease is evidenced by the dramatic decrease in survival accompanying each subsequent stage. As outlined previously, advanced imaging studies and specific types of exploratory surgery often play an integral role in the staging process, which is critical in determining the appropriate course of treatment. Parallel to the staging criteria, treatment is selected on the basis of the size and location of the primary tumor, number and location of metastases, and the presence and extent of lymph node involvement.

For most patients with early-stage NSCLC (i.e., stage 0 or I), surgery is the primary treatment approach, with complete tumor resection and the possibility of a curative result as the goal. Despite the overwhelming mortality associated with lung cancer, there are approximately 400,000 Americans alive today who have been diagnosed with lung cancer, indicating that the probability of a cure is realistic in some cases. As the disease progresses to subsequent stages where a cure is less likely, the role of radiation therapy and chemotherapy intensifies while surgery becomes less practical in advanced disease. To eliminate any remaining traces of the tumor and prevent recurrence, radiation and chemotherapy are often used as adjuvant treatment following surgery in stages II through IIIA. In advanced metastatic disease (i.e., stage IV), chemotherapy and/or treatment with targeted biologics comprise the initial management strategy, as a cure is unlikely, but referral of patients to hospice care is also an option for improving patient quality of life. These varied and complex roles of chemotherapy and targeted biologics in the treatment continuum of NSCLC require further elucidation.

CONSIDERATIONS FOR PHARMACOLOGIC TREATMENT

As discussed previously, staging is the initial factor taken into consideration when determining the appropriate course of treatment in NSCLC, both in those patients who are candidates for surgery and those who are not. In looking at pharmacotherapy specifically, staging guides clinicians in their choice of drug regimen, as does individual patient characteristics such as comorbidities. Beyond staging, performance status is also used to determine if a patient is an ideal candidate for certain types of chemotherapy or treatment with next-generation therapies. Higher performance status indicates better physical functioning and increased capacity to tolerate highly cytotoxic regimens. Of course, the patient’s wishes also come into play when selecting a treatment regimen – some will favor the different modes of administration or adverse event profiles associated with certain therapies over others.

The most common regimen used in treating NSCLC is usually a combination of two agents: a platinum-agent (e.g., carboplatin or cisplatin) and a next-generation drug (e.g., paclitaxel, pemetrexed, gemcitabine, bevacizumab). Specifically, either carboplatin or cisplatin in combination with paclitaxel is often selected as first-line therapy. Another next-generation drug, erlotinib, is delivered orally but is used as monotherapy in the treatment of NSCLC. While the biologic cetuximab (Erbitux) is not U.S. Food and Drug Administration (FDA) approved for the treatment of lung cancer, this next-generation drug has demonstrated efficacy in combination with the older chemotherapy regimen of cisplatin plus vinorelbine.

As the treatment armamentarium grows via emerging therapies from the pipeline, common regimens have also changed recently, especially with the growing use of pemetrexed as first-line therapy. Although combination therapy has been the norm for several years, there has likewise been more confidence among clinicians to use the aforementioned oral agent erlotinib as monotherapy in patients with endothelial growth-factor receptor mutations.

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<th>Stage</th>
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<td>IA</td>
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Five-Year Survival Rate by Stage for Patients with NSCLC5

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<th>Stage</th>
<th>Five-year Survival Rate</th>
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| IA    | 49% 
| IB    | 45% 
| IIA   | 30% 
| IIB   | 31% 
| IIIA  | 14% 
| IIIB  | 5% 
| IV    | 1% |

Three-Year Survival Rate by Stage for Patients with NSCLC5

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<th>Stage</th>
<th>Three-year Survival Rate</th>
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| IA    | 49% 
| IB    | 45% 
| IIA   | 30% 
| IIB   | 31% 
| IIIA  | 14% 
| IIIB  | 5% 
| IV    | 1% |
For whom it is predicted to work well.

While the goal of chemotherapy in earlier-stage NSCLC is to shrink tumors before surgery or eradicate remaining traces of the cancer after surgery in hopes of a complete cure, chemotherapy in late-stage disease is used primarily to extend survival prior to death. The potential for cure in NSCLC exists in the early stages through stage III, but a cure in stage IV is very rare unless the patient has limited or oligometastatic disease. Unfortunately, no one regimen appears better than any of the others for increasing the likelihood of a treatment response in patients with metastatic lung cancer; however, data have shown that certain subsets of patients broken out by cancer cell type may respond better to certain regimens. For example, patients with nonsquamous NSCLC tend to respond better to cisplatin plus pemetrexed than cisplatin plus gemcitabine. Furthermore, in general, the addition of a targeted biologic therapy to a traditional chemotherapy regimen (e.g., bevacizumab plus combination carboplatin/paclitaxel) appears to elicit improved outcomes over the traditional chemotherapy regimen alone (e.g., carboplatin and paclitaxel).

In the event of a recurrence, there are still some options with surgery and radiation, but most patients are offered systemic chemotherapy if they are candidates for continued treatment with combination platinum/next-generation drugs or erlotinib monotherapy. It is often advisable that an alternate regimen be selected for treating a recurrence than the original regimen that was used to treat the primary presentation of NSCLC. For those who decline further treatment, or are incapable of adequately tolerating additional chemotherapy, referral to a hospice program and the administration of palliative care are the appropriate next steps, despite these interventions being underused in managed care. In many cases, continued treatment does not necessarily equate to increased survival over palliative care in the hospice setting; however, certain regimens have demonstrated the capacity to extend overall survival time by a matter of months over other therapies or supportive care. For example, while combination cisplatin/pemetrexed has elicited extended survival time in patients with advanced-stage disease, cisplatin/gemcitabine has not. Biologic therapies such as bevacizumab in combination with carboplatin have likewise shown potential for extending survival time, as has erlotinib monotherapy vs. supportive care. As such, this decision is one that must be weighed carefully with the patient to determine if the extended survival offered by further treatment is sufficient enough to offset the declining quality of life associated with chemotherapy in patients with deteriorating performance status.

**FUTURE PERSPECTIVES IN MANAGED CARE**

Considering the widespread prevalence and striking mortality associated with lung cancer, payor-led management initiatives targeting the disease are certainly deserving of further attention from plan stakeholders. A logical place to initiate this discussion of potential interventions for lung cancer is with prevention/screening. Similar to lung cancer, cervical cancer was once considered to be a leading cause of cancer-related deaths in the United States, characterized by disease diagnosed at advanced and virtually untreatable stages. Since the introduction of routine Pap tests as a screening intervention for cervical cancer, however, the death rate associated with the disease has declined by nearly 70%. Until recently, no screening test for lung
cancer had demonstrated an analogous capacity to significantly reduce patients’ risk of dying from this disease as Pap tests had for cervical cancer. However, preliminary results from the National Lung Cancer Screening Trial (NLST) may soon change the way payors view screening for cancer at this site.

The NLST compared mortality among individuals at high risk for lung cancer receiving either spiral CT scans or chest X-rays to screen for the disease. The study randomized more than 50,000 people ages 55 to 74 who were current or former smokers to receive either three spiral CT scans or three chest X-rays, each one year apart. Initial results from the study demonstrated that participants who received spiral CT scans had a 20% lower risk of dying from lung cancer than those who received chest X-rays. Those in the spiral CT screening intervention group were also 7% less likely to die from any cause than those who were screened via chest X-ray, although the exact reasons for this are not yet clear.

Of course, screening for lung cancer in a managed care plan population is a novel concept; therefore, this preventative intervention is likely to be met with resistance by payors because of the high cost of advanced imaging studies. Despite the fact that only members at high risk for lung cancer (e.g., smokers) would be indicated for a spiral CT screening, additional data on the effectiveness of this method for decreasing lung cancer mortality and an endorsement from a regulatory body or professional organization (e.g., Centers for Medicare & Medicaid Services or the National Comprehensive Cancer Network, respectively) would likely be necessary for payors to follow suit.

At the opposite end of the lung cancer management spectrum, appropriate care in end-of-life scenarios is another area that payors are exploring further in order to improve quality of services provided to members with the disease. Due to the high mortality and low survival rates in patients with advanced NSCLC, the decision between continuing to treat stage IV patients or referring them to hospice is one that has come under constant scrutiny. Regardless of what payors perceive as being appropriate care in end-of-life situations, it should be thoroughly defined and communicated to network providers as well as included in decisions shaping medical policy at managed care organizations.

Separate from screening and end-of-life considerations, emerging therapies and advances in molecular diagnostics will continue to impact ever-evolving lung cancer treatment strategies well into the future. Beyond the benefits of novel targeted therapies, accompanying assays for specific biomarkers should serve to personalize treatment, optimizing clinical efficacy for patients as well as cost-effectiveness for payors. The clinician component of this equation cannot be overlooked, though: A multidisciplinary care team of network oncologists and providers from different specialties – pulmonology, thoracic surgery, pathology, and radiology in the case of lung cancer – will prove vital for ensuring that these advanced pharmacologic tools are applied in a clinically appropriate and judicious manner. Payors stand to benefit from this collaboration when they allow providers some latitude in designing an individualized treatment plan, so long as evidence-based standards remain paramount.

References
Gone are the days of the Marlboro Man, riding his trusty steed across the television screen to a scenic backdrop of snow-capped mountains – all advertising the “romance” and “manliness” of cigarette smoking. However, in this age of social media and electronics communication, one can easily join “member communities” such as those at https://camel.tobaccopleasure.com to see that cigarette marketing is still very much alive.

Despite changes in some of the direct societal media exposure to cigarettes, lung cancer still remains the number one cancer killer – and cigarette smoking a primary, though not the only, causative factor for its incidence. In 2010, with 222,500 estimated new cases of lung cancer, there were more than 150,000 deaths attributable to the disease. One of the most interesting trends of the disease is that, while the incidence and mortality for men has decreased, lung cancer rates are going up in women, including those who don’t smoke.

According to data provided by the National Cancer Institute, the median age at diagnosis of lung cancer in the United States is 70 years and the average age at death is 72.¹ Although this is primarily a disease of the Medicare beneficiary, we likely can identify one or more family members or friends/colleagues who have been
touched by a patient diagnosed with lung cancer at a much earlier age, bringing this disease more into the realm of commercial payors.

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for 85% of all cases, and resulting in the highest mortality in cancer. Therefore, much of this article focuses on NSCLC as it relates to treatment options and reimbursement considerations.

THE ARSENAL OF TREATMENTS FOR LUNG CANCER

Combination cytotoxic “backbone” chemotherapy is the standard first-line therapy in NSCLC, with other treatment options providing varied responses in second- and third-line settings. The Lung Cancer Clinical Practice Guidelines from the National Comprehensive Cancer Network denotes that cisplatin or carboplatin has proven effective for first-line NSCLC therapy when used in combination with such drugs as paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, and pemetrexed.

Although platinum-containing regimens are still a standard treatment for lung cancer, we see examples of targeted agents such as erlotinib, bevacizumab, and cetuximab added to the standard regimens in second- and third-line therapy. This concept is emphasized by a lineup of newer agents being studied for lung cancer. In NSCLC, several drugs and biologics are in studies – most as an addition to current backbone chemotherapy regimens. Examples of these investigational agents include celecoxib, necitumumab, afatinib, cediranib, talactoferrin, and gefitinib. The intent of current clinical trials is to lean on the time-tested clinical outcomes of the chemotherapy regimen (an estimated 35% response rate) but provide targeted outcomes that excel beyond the standard benefit.

PATIENT SELECTION AND DRUG APPLICATION

The addition of biologics, rather than single-agent use, raises concerns for the payor environment, no matter who the payor. In addition, there are provider concerns about the patient’s financial cost-share responsibility when increasing overall cost of care. Prior to addressing these issues directly, let’s first look at the evolution of care and costs.

An analysis published in 2006 looked at the evolution of Medicare drug reimbursement and its implications for patient access to care. This analysis provides a snapshot of the deep contrast between treatment options in the late 1990s compared with those of the current day. This study assessed metastatic cancer patients receiving care between 1995 and 1998, and a significant portion of these patients had advanced lung cancer.

Overall, during the time frame of the analysis, few metastatic lung cancer patients were receiving chemotherapy, as treatment options were just gaining ground in that patient population. For those patients who did receive chemotherapy, the study demonstrated that the monthly drug costs for a metastatic lung cancer patient were on average $3,600, as compared with costs for patients with metastatic breast cancer ($1,000) and colorectal cancer ($1,400). This time period demonstrated the early market entry of higher-cost agents to treat NSCLC, which previously had very few treatment options in advanced disease.

Metastatic disease is only one stage of disease to focus on for costs in NSCLC, but it is one area that continues to provide some controversy on the “value” of treatment vs. cost of care. When you look at overall lung cancer healthcare expenditures in 2006, an estimated $10.3 billion in costs were incurred, making it the third most costly cancer, behind breast and colorectal cancers. For lung cancer, a majority of these expenditures occur in the initial care stage and last year of life, with continuing care a very narrow band of costs. As far as a breakdown of specific costs, again only for 2006, the figure below outlines...
that chemotherapy costs for lung cancer account for 20.4% of overall costs, which compares with 14.8% and 9.2% for breast and colon cancer, respectively, for that same year.6

As mentioned previously, one of the trends of treatment for lung cancer includes adding targeted therapies to current standard chemotherapy regimens. Another consideration is the phenomenon of maintenance therapy, whether it’s “continuation maintenance” (use of at least one agent given in first-line, beyond four to six cycles, in the absence of disease progression) or “switch maintenance” (initiation of a different agent, not included as part of a first-line regimen, in the absence of disease progression).

For both of these trends, questions raised by payors include:

- Is the addition of another biologic to the standard regimen a greater benefit to overall survival and the patient’s quality of outcome?
- How do we know when maintenance therapy is truly a benefit to the patient’s survival vs. just an incremental cost to the patient and the health system?

As a means to better understand and manage potential escalating healthcare costs of NSCLC, many providers and payors have targeted lung cancer as a primary tumor for clinical pathway development. The pathways integrate an evidence-based approach to utilization of regimens, based on clinical data that has answered key questions about safety and efficacy. When the questions cannot be answered clearly, the pathways tend to focus on primary use of the basic backbone chemotherapy outlined previously.

A significant complement to the pathways is the use of biomarkers for selection of appropriate patients for certain targeted therapies. As an example, epidermal growth factor receptor (EGFR), which is often overexpressed in NSCLC, is linked to cancer proliferation. Using predictive clinical and molecular biomarkers to determine EGFR mutations in patients can then serve to “partner” that patient with the EGFR tyrosine kinase inhibitors to which they would most likely respond. These agents could include erlotinib or gefitinib. Other work is being conducted in the biomarker arena to consider additional options, such as vascular endothelial growth factor, combining EGFR mutational status with fluorescence in situ hybridization testing, and many others.

WORK IN PROGRESS
All stakeholders, payors, providers, patients, and biopharmaceutical companies are looking for ways to bring the best clinical value to the system and to the patient for the treatment of lung cancer. Applying evidence-based pathways decisions is but one way; molecular and clinical biomarkers is yet another.

The bottom line remains that lung cancer is still the leading cause of cancer deaths in the U.S. Novel treatments that bring value to the system, creative ways to determine who would respond best to treatment, and mechanisms to minimize significant impact on a patient’s financial viability will all continue to play an important role in the battle to treat this challenging disease.

References
Investigational Agents for Lung Cancer

by Howard "Skip" Burris, MD, Director of Drug Development, Sarah Cannon Research Institute

The treatment of lung cancer is rapidly changing with the discovery of new targets and mutations, coupled with the development of agents effective against these pathways.

It seems like only yesterday that we divided lung cancer into non-small cell and small-cell classes. The current doublets of a taxane, paclitaxel or docetaxel, pemetrexed, gemcitabine, or vinorelbine given with a platinum, either cisplatin or carboplatin, have improved overall survival for patients. The addition of bevacizumab (Avastin, Genentech) to paclitaxel and carboplatin, and continued in a maintenance fashion, has improved survival by several months. Side effects seen in the squamous subtype of patients, specifically pulmonary hemorrhage, have limited the use of bevacizumab to the adenocarcinoma population.

For less obvious reasons, the benefits of pemetrexed added to a platinum seem greatest in the adenocarcinoma patients as well. Fortunately, a role has developed for maintenance pemetrexed in these patients as a result of well-conducted clinical trials. An ongoing study is evaluating these two most commonly utilized regimens for nonsquamous-cell patients in a randomized design. A combination of paclitaxel, carboplatin, and bevacizumab, for four cycles, followed by maintenance bevacizumab, is
being compared with pemetrexed and carboplatin, for four cycles, with pemetrexed continued until progression.

Meanwhile, the lung cancer subsets have grown to include squamous, epidermal growth factor receptor (EGFR) mutated, and anaplastic lymphoma kinase (ALK) mutated, with further evaluation of PI3K, RAS, RAF, and HER2 classifications of tumors being studied.

The impact of tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib in these EGFR-mutated patients is substantial. These patients are often nonsmokers, Asian, or female, and often have a bronchoalveolar pattern to their lung cancer. Recent results from the IPASS study demonstrated an improved response rate of 43% to gefitinib vs. 32% with paclitaxel and carboplatin. Crossover was allowed, and overall survival (OS) was similar, but obvious differences in the toxicity profile and convenience were noted. It remains interesting and controversial that gefitinib is no longer marketed in the U.S. based on earlier, less focused studies involving unselected patient populations. Erlotinib is the TKI commonly used in the U.S. for these patients, and it actually has a broad label for many scenarios.

The ALK pathway is the latest in lung cancer targets to show the benefit of selected patient populations. Crizotinib (Pfizer), an oral twice-daily therapy, was presented by Dr. Bang at the American Society of Clinical Oncology 2010 plenary session. The activity of this agent in patients selected by the ALK mutation was demonstrated with waterfall plots showing 40 of 53 patients on therapy for more than three months and some tumor shrinkage in all but four patients. The toxicity profile was also modest, with only low-grade gastrointestinal and skin side effects. Somewhat disappointingly, the traditional chemotherapy vs. crizotinib randomized studies involving hundreds of patients are under way despite strong evidence that a selected group will derive the benefit.

MetMAb (Genetech), a fully humanized monoclonal antibody, targets the MET pathway through inhibition of hepatocyte growth factor. In a randomized, placebo-controlled study of 128 second/third-line non-small cell lung cancer (NSCLC) patients, surprising but encouraging data emerged. Dr. Spigel, Sarah Cannon Research Institute, presented the findings, which showed no difference in the overall population (hazard ratio [HR] 1.09), at the 2010 European Society of Medical Oncology meeting. Fortunately, tissue was required on all patients prior to randomization. Those patients with MET overexpression (2+ or 3+ by immunohistochemistry) obtained marked benefit with the antibody for both progression-free survival (PFS) (HR 0.56) and OS (HR 0.55). In contrast, the MET-low patients not only did not benefit from the antibody but also actually fared worse than the placebo group for both PFS (HR 2.01) and OS (HR 3.02). Additional preclinical and clinical work will be conducted to evaluate this data, and confirmatory studies will move forward in the MET-high patients.

The squamous NSCLC population has not seen the advantages from many of the new agents. Novel insulin-like growth factor receptor inhibitors, telomerase inhibitors, and angiogenesis inhibitors are being evaluated in this disease setting with trials ongoing and data still to come. Iniparib, BSI 201, with its parp-inhibitory and platinum-enhancing profile, is being studied by the Sarah Cannon Research Institute in an 800-patient randomized phase 3 study. Patients with squamous-cell-predominant NSCLC receive gemcitabine and carboplatin +/- iniparib with an overall primary endpoint of survival.

After making an impact in many tumor types including breast cancer and lymphoma, the targeted biologics are helping us to make strides against subsets of NSCLC, an all-too-prevalent and very lethal cancer. Rapid accrual to important ongoing clinical trials is essential for furthering their development.

References
ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer.

**Limitations of Use:** ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.

**Myelosuppression is usually the dose-limiting toxicity with ALIMTA therapy.**

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**Contraindication:** ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any other ingredient used in the formulation.

**Warnings and Precautions:** Patients must be instructed to take folic acid and vitamin B₁₂ with ALIMTA as a prophylaxis to reduce treatment-related hematologic and GI toxicities.

Pretreatment with dexamethasone or its equivalent has been reported to reduce the incidence and severity of skin rash.

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia). Reduce doses for subsequent cycles based on hematologic and nonhematologic toxicities.

ALIMTA should not be administered to patients with a creatinine clearance <45 mL/min. One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B₁₂ died of drug-related toxicity following administration of ALIMTA alone.

Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA.

In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicities.

Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm³, the platelet count is ≥100,000 cells/mm³, and creatinine clearance is ≥45 mL/min.

Pregnancy Category D—ALIMTA may cause fetal harm when administered to a pregnant woman. Women should be apprised of the potential hazard to the fetus and should be advised to use effective contraceptive measures to prevent pregnancy during treatment with ALIMTA.

The effect of third space fluid, such as pleural effusion and ascites, on ALIMTA is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to ALIMTA administration.
ALIMTA (pemetrexed for injection)

**Drug Interactions:** Concomitant administration of nephrotoxic drugs or substances that are tubularly secreted could result in delayed clearance of ALIMTA.

See Warnings and Precautions for specific information regarding ibuprofen administration.

**Use in Specific Patient Populations:** It is recommended that nursing be discontinued if the mother is being treated with ALIMTA or discontinue the drug, taking into account the importance of the drug for the mother.

The safety and effectiveness of ALIMTA in pediatric patients have not been established.

Dose adjustments may be necessary in patients with hepatic insufficiency.

**Dosage and Administration Guidelines:** Complete blood cell counts, including platelet counts and periodic chemistry tests, should be performed on all patients receiving ALIMTA.

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Modify or suspend therapy according to the Dosage Reduction Guidelines in the full Prescribing Information.

**Abbreviated Adverse Reactions (% incidence):** The most severe adverse reactions (grades 3/4) with ALIMTA in combination with cisplatin versus gemcitabine in combination with cisplatin, respectively, for the 1st-line treatment of patients with advanced non-small cell lung cancer (NSCLC) were neutropenia (15 vs 27); leukopenia (5 vs 8); thrombocytopenia (4 vs 13); anemia (6 vs 10); fatigue (7 vs 5); nausea (7 vs 4); vomiting (6 vs 6); anorexia (2 vs 1); and creatinine elevation (1 vs 1).

Common adverse reactions (all grades) with ALIMTA in combination with cisplatin versus gemcitabine in combination with cisplatin, respectively, were nausea (56 vs 53); fatigue (43 vs 45); vomiting (40 vs 36); anemia (33 vs 46); neutropenia (29 vs 38); anorexia (27 vs 24); constipation (21 vs 20); leukopenia (18 vs 21); stomatitis/pharyngitis (14 vs 12); alopecia (12 vs 21); diarrhea (12 vs 13); thrombocytopenia (10 vs 27); neuropathy/sensory (9 vs 12); taste disturbance (8 vs 9); rash/desquamation (7 vs 8); and dyspepsia/heartburn (5 vs 6).

For additional safety and dosing guidelines, please see brief summary of Prescribing Information on adjacent page.
**ALIMTA® (pemetrexed for injection)**

**BRIEF SUMMARY.** For complete safety, please consult the full Prescribing Information.

1 **INDICATIONS AND USAGE**

1.1 Nonsquamous Non-Small Cell Lung Cancer — Combination with cisplatin

ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer.

1.5 Limitations of Use

ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer [see Clinical Studies (14.1, 14.2, 14.3) in the full Prescribing Information].

2 **DOSEAGE AND ADMINISTRATION**

2.1 Combination Use with cisplatin

Nonsquamous Non-Small Cell Lung Cancer

The recommended dose of ALIMTA is 500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m² infused over 2 hours beginning approximately 30 minutes after the end of ALIMTA administration. Patients should receive appropriate hydration prior to and/or after receiving cisplatin. See cisplatin package insert for more information.

2.2 Premedication Regimen

Vitamin Supplementation

To reduce toxicity, patients treated with ALIMTA must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of ALIMTA; and dosing should continue during the full course of therapy and for 21 days after the last dose of ALIMTA. Patients must also receive one (1) intramuscular injection of vitamin B₁₂ during the week preceding the first dose of ALIMTA and every 3 cycles thereafter. Pretreatment with folic acid injections may be given the same day as ALIMTA. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 mcg, and the dose of vitamin B₁₂ was 1000 mcg. The most commonly used dose of oral folic acid in clinical trials was 400 mcg [see Warnings and Precautions (5.1)].

Corticosteroid

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after ALIMTA administration [see Warnings and Precautions (5.1)].

2.4 Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations

Monitoring

Complete blood cell counts, including platelet counts, should be performed on all patients receiving ALIMTA. Patients should be monitored for nadir and recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm², the platelet count is ≥100,000 cells/mm², and creatinine clearance is ≥45 mL/min.

Periodic hematology tests should be performed to evaluate renal and hepatic function [see Warnings and Precautions (5.4)].

Dose Reduction Recommendations

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in Tables 1-3, which are suitable for using ALIMTA as a single-agent or in combination with cisplatin.

<table>
<thead>
<tr>
<th>Table 1: Dose Reduction for ALIMTA and Cisplatin — Hematologic Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nadir ANC</strong> &lt;500/mm³ and nadir platelets &lt;50,000/mm³</td>
</tr>
<tr>
<td>Nadir platelets &lt;50,000/mm³ without bleeding regardless of nadir ANC</td>
</tr>
<tr>
<td>Nadir platelets &lt;50,000/mm³ with bleeding regardless of nadir ANC</td>
</tr>
</tbody>
</table>

* These criteria meet the CTC version 2.0 (NCI 1998) definition of Grade 2 bleeding. If patients develop nonhematologic toxicities (excluding neurotoxicity) >Grade 3, treatment should be withheld until resolution to less than or equal to the patient’s pre-therapy value. Treatment should be resumed according to guidelines in Table 2.

<table>
<thead>
<tr>
<th>Table 2: Dose Reduction for ALIMTA and Cisplatin — Nonhematologic Toxicities **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade 3 or 4 Toxicities except mucositis</strong></td>
</tr>
<tr>
<td><strong>Any diarrhea requiring hospitalization (irrespective of Grade)</strong> or Grade 3 or 4 diarrhea</td>
</tr>
<tr>
<td><strong>Grade 3 or 4 mucositis</strong></td>
</tr>
</tbody>
</table>

**s** NCI Common Toxicity Criteria (CTC).

<table>
<thead>
<tr>
<th><strong>Table 3: Dose Reduction for ALIMTA</strong> (single-agent or in combination) and Cisplatin — Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTC Grade</strong></td>
</tr>
<tr>
<td>0-1</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>

Discontinuation Recommendation

ALIMTA therapy should be discontinued if a patient experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Renal Impaired Patients

In clinical studies, patients with creatinine clearance ≤45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients [see Clinical Pharmacology (12.3) in the full Prescribing Information]. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is <45 mL/min [see Laboratory Monitoring and Dose Reduction/Discontinuation Recommendations (2.4) in the full Prescribing Information].

Caution should be exercised when administering ALIMTA concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min [see Drug Interactions (7.1)].

3 **DOSE FORMS AND STRENGTHS**

ALIMTA, pemetrexed for injection, is a white to either light-yellow or green-yellow lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg pemetrexed.

4 **CONTRAINDICATIONS**

ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any other ingredient used in the formulation.

5 **WARNINGS AND PRECAUTIONS**

5.1 Premedication Regimen

Need for Folate and Vitamin B₁₂ Supplementation

Patients treated with ALIMTA must be instructed to take folic acid and vitamin B₁₂ as a prophylactic measure to reduce treatment-related hematologic and GI toxicity [see Dosage and Administration (2.3)]. In clinical studies, less overall toxicity and reductions in Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B₁₂ was administered.

Corticosteroid Supplementation

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid in clinical trials. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction [see Dosage and Administration (2.3)].

5.2 Bone Marrow Suppression

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia) [see Adverse Reactions (6.1)]. Myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle [see Dosage and Administration (2.4)].

5.3 Decreased Renal Function

ALIMTA is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance ≤45 mL/min. Insufficient numbers of patients have been studied with creatinine clearance <45 mL/min to give a dose recommendation. Therefore, ALIMTA should not be administered to patients whose creatinine clearance is <45 mL/min [see Dosage and Administration (2.4)].

One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B₁₂ died of drug-related toxicity following administration of ALIMTA alone.

5.4 Use with Non-Steroidal Anti-Inflammatory Drugs with Mild to Moderate Renal Insufficiency

Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Other NSAIDs should also be used with caution [see Drug Interactions (7.1)].

5.5 Required Laboratory Monitoring

Patients should not begin a new cycle of treatment unless the ANC≥1500 cells/mm³, the platelet count is ≥100,000 cells/mm³, and creatinine clearance is ≥45 mL/min [see Dosage and Administration (2.4)].

5.6 Pregnancy Category D

Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. Pemetrexed administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic and teratogenic in mice at greater than 1/33rd the recommended human dose. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised not to become pregnant while taking ALIMTA (pemetrexed for injection).
of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with ALIMTA [see Use in Specific Populations (8.1)].

5.7 Third Space Fluid

The effect of third space fluid, such as pleural effusion and ascites, on ALIMTA is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to ALIMTA administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

In clinical trials, the most common adverse reactions (incidence ≥20%) were fatigue, nausea, and anorexia. Additional common adverse reactions (incidence ≥20%) included vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation.

Non-Small Cell Lung Cancer (NSCLC) — Combination with Cisplatin

Table 4 provides the frequency and severity of adverse reactions that have been reported in >5% of 839 patients with NSCLC who were randomized to study and received ALIMTA plus cisplatin and 830 patients with NSCLC who were randomized to study and received gemcitabine plus cisplatin. All patients received study therapy as initial treatment for locally advanced or metastatic NSCLC and patients in both treatment groups were fully supplemented with folic acid and vitamin B12.

Table 4: Adverse Reactions in Fully Supplemented Patients Receiving ALIMTA plus Cisplatin in NSCLC

<table>
<thead>
<tr>
<th>Reactiona</th>
<th>ALIMTA/cisplatin (N=839)</th>
<th>Gemcitabine/cisplatin (N=830)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades Toxicity (%)</td>
<td>Grade 3-4 Toxicity (%)</td>
</tr>
<tr>
<td>All Adverse Reactions</td>
<td>90</td>
<td>37</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine elevation</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Clinical Constitutional Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Anorexia</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis/Pharyngitis</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia/Heartburn</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Dermatology/Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Rash/Deshuqation</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

a For the purpose of this table a cut off of 5% was used for inclusion of all events where the reporter considered a possible relationship to ALIMTA.

b Refer to NCI CTC Criteria version 2.0 for each Grade of Toxicity.

c According to NCI CTC Criteria version 2.0, this adverse event term should only be reported as Grade 1 or 2.

No clinically relevant differences in adverse reactions were seen in patients based on histology.

In addition to the lower incidence of hematologic toxicity on the ALIMTA and cisplatin arm, use of transfusions (RBC and platelet) and hematopoietic growth factors was lower in the ALIMTA and cisplatin arm compared to the gemcitabine and cisplatin arm.

The following additional adverse reactions were observed in patients with non-small cell lung cancer randomly assigned to receive ALIMTA plus cisplatin.

Incidence 1% to 5%

Body as a Whole — tremor, neutropenia, infection, pyrexia, generalized discomfort — anorexia

Metabolism and Nutrition — increased AST, increased ALI

Renal — creatinine clearance decrease, renal failure

Special senses — conjunctivitis

Incidence Less than 1%

Cardiovascular — arrhythmia

General Disorders — chest pain

Metabolism and Nutrition — increased GGT

Neurology — motor neuropathy

6.2 Additional Clinical Trials Experience

Across clinical trials, sepsis, which in some cases was fatal, occurred in approximately 1% of patients.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of ALIMTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal — colitis

General Disorders and Administration Site Conditions — edema, injury, poisoning, and prorectal complications — Radiation recall has been reported in patients who have previously received radiotherapy.

Respiratory — interstitial pneumonitis

Skin — Bullous conditions have been reported, including Stevens-Johnson syndrome and toxic epidermal necrolysis, which in some cases were fatal.

7 DRUG INTERACTIONS

7.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Ibuprofen

Although ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed, it can be administered with ALIMTA in patients with normal renal function (creatinine clearance >80 mL/min). Caution should be taken when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min) [see Clinical Pharmacology (12.3) in the full Prescribing Information].

Other NSAIDs

Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA.

In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing with short elimination half-lives for a period of 2 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

7.2 Nephrotoxic Drugs

ALIMTA is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of ALIMTA. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of ALIMTA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects — Pregnancy Category D [see Warnings and Precautions (5.6)].

Based on its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies of ALIMTA in pregnant women. Pemetrexed was embryotoxic, fetotoxic, and teratogenic in mice. In mice, repeated intraperitoneal doses of pemetrexed when given during organogenesis caused fetal malformations (incomplete ossification of talus and skull bone; about 1/833rd the recommended intravenous human dose on a mg/m² basis), and cleft palate (1/33rd the recommended intravenous human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced litter sizes. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use effective contraceptive measures to prevent pregnancy during the treatment with ALIMTA.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of ALIMTA in pediatric patients have not been established.
8.5 Geriatric Use
ALIMTA is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Renal function monitoring is recommended with administration of ALIMTA. No dose reductions other than those recommended for all patients are necessary for patients 65 years of age or older [see Dosage and Administration (2.4)].

In the initial treatment non-small cell lung cancer clinical trial, 37.7% of patients treated with ALIMTA plus cisplatin were ≥65 years and Grade 3/4 neutropenia was greater as compared to patients <65 years (19.9% versus 12.2%). For patients <65 years, the HR for overall survival was 0.96 (95% CI: 0.83, 1.10) and for patients ≥65 years the HR was 0.89 (95% CI: 0.74, 1.06) in the intent-to-treat population.

8.6 Patients with Hepatic Impairment
There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed [see Clinical Pharmacology (12.3) in the full Prescribing Information].

Dose adjustments based on hepatic impairment experienced during treatment with ALIMTA are provided in Table 2 [see Dosage and Administration (2.4)].

8.7 Patients with Renal Impairment
ALIMTA is known to be primarily excreted by the kidneys. Decreased renal function will result in reduced clearance and greater exposure (AUC) to ALIMTA compared with patients with normal renal function [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in the full Prescribing Information]. Cisplatin coadministration with ALIMTA has not been studied in patients with moderate renal impairment.

8.8 Gender
In the initial treatment non-small cell lung cancer trial, 70% of patients were males and 30% females. For males the HR for overall survival was 0.97 (95% CI: 0.85, 1.10) and for females the HR was 0.86 (95% CI: 0.70, 1.06) in the intent-to-treat population.

8.9 Race
In the initial treatment non-small cell lung cancer trial, 78% of patients were Caucasians, 13% East/Southeast Asians, and 9% others. For Caucasians, the HR for overall survival was 0.92 (95% CI: 0.82, 1.04), for East/Southeast Asians the HR was 0.86 (95% CI: 0.61, 1.21), and for others the HR was 1.24 (95% CI: 0.84, 1.84) in the intent-to-treat population.

10 OVERDOSAGE
There have been few cases of ALIMTA overdose. Reported toxicities included neutropenia, anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anemia. In addition, infection with or without fever, diarrhea, and mucositis may be seen. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician.

In clinical trials, leucovorin was permitted for CTC Grade 4 leukopenia lasting ≥ 3 days, CTC Grade 4 neutropenia lasting ≥ 3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100 mg/m<sup>2</sup>, intravenously once, followed by leucovorin, 50 mg/m<sup>2</sup>, intravenously every 6 hours for 8 days.

The ability of ALIMTA to be dialyzed is unknown.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in the in vivo micronucleus assay in mouse bone marrow but was not mutagenic in multiple in vitro tests (Ames assay, CHO cell assay). Pemetrexed administered at i.v. doses of 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m<sup>2</sup> basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling.

Patients should be instructed to read the patient package insert carefully.

17.1 Need for Folic Acid and Vitamin B<sub>12</sub>
Patients treated with ALIMTA must be instructed to take folic acid and vitamin B<sub>12</sub> as a prophylactic measure to reduce treatment-related hematologic and gastrointestinal toxicity [see Dosage and Administration (2.3)].

17.2 Low Blood Cell Counts
Patients should be adequately informed of the risk of low blood cell counts and instructed to immediately contact their physician should any sign of infection develop including fever. Patients should also contact their physician if bleeding or symptoms of anemia occur.

ALIMTA® (pemetrexed for injection)
TREATMENT OF
Lung Cancer

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

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

### Associated ICD-9-CM Codes:

162 Malignant neoplasm of trachea, bronchus, and lung

162.0 Trachea
- Cartilage of trachea
- Mucosa of trachea

162.2 Main bronchus
- Carina
- Hilus of lung

162.3 Upper lobe, bronchus or lung

162.4 Middle lobe, bronchus or lung

162.5 Lower lobe, bronchus or lung

162.8 Other parts of bronchus or lung
- Malignant neoplasm of contiguous or overlapping sites of bronchus or lung whose point of origin cannot be determined

162.9 Bronchus and lung, unspecified
## FDA-Approved Medications Currently Available to Treat Lung Cancer

<table>
<thead>
<tr>
<th>Generic (Brand) Name</th>
<th>HCPSC Code – Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 5/1/11</th>
<th>Medicare Allowable (ASP + 6%) – Effective 4/1/11-6/30/11</th>
<th>CPT® Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bevacizumab (Avastin)</td>
<td>J9035 – injection, bevacizumab, 10 mg</td>
<td>$70.04</td>
<td>$59.84</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>docetaxel (Taxotere)</td>
<td>J9171 – injection, docetaxel, 1 mg</td>
<td>$22.24</td>
<td>$21.24</td>
<td>96413</td>
</tr>
<tr>
<td>doxorubicin HCl (Adriamycin)</td>
<td>J9000 – injection, doxorubicin hydrochloride, 10 mg</td>
<td>$13.20</td>
<td>$3.50</td>
<td>96409</td>
</tr>
<tr>
<td>erlotinib (Tarceva)</td>
<td>J8999* – prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>etoposide (Vepesid)</td>
<td>J8560 – etoposide, oral, 50 mg</td>
<td>$57.33</td>
<td>$35.00</td>
<td>N/A</td>
</tr>
<tr>
<td>etoposide (Toposar)</td>
<td>J9181 – injection, etoposide, 10 mg</td>
<td>$0.53</td>
<td>$0.63</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>gefitinib (Iressa)</td>
<td>J8565 – gefitinib, oral, 250 mg</td>
<td>$68.08</td>
<td>none reported</td>
<td>N/A</td>
</tr>
<tr>
<td>gemcitabine (Gemzar)</td>
<td>J9201 – injection, gemcitabine hydrochloride, 200 mg</td>
<td>$144.41</td>
<td>$113.55</td>
<td>96413</td>
</tr>
<tr>
<td>mechlorethamine HCl (Mustargen)</td>
<td>J9230 – injection, mechlorethamine hydrochloride (nitrogen mustard), 10 mg</td>
<td>$178.71</td>
<td>$157.86</td>
<td>96409</td>
</tr>
<tr>
<td>methotrexate</td>
<td>J8610 – methotrexate, oral, 2.5 mg</td>
<td>$3.61</td>
<td>$0.11</td>
<td>N/A</td>
</tr>
<tr>
<td>methotrexate</td>
<td>J9250 – methotrexate sodium, 5 mg</td>
<td>$0.30</td>
<td>$0.19</td>
<td>96372, 96401, 96409, 96450</td>
</tr>
<tr>
<td>methotrexate</td>
<td>J9260 – methotrexate sodium, 50 mg</td>
<td>$2.95</td>
<td>$1.91</td>
<td>96372, 96401, 96409, 96450</td>
</tr>
<tr>
<td>paclitaxel (Taxol)</td>
<td>J9265 – injection, paclitaxel, 30 mg</td>
<td>$15.54</td>
<td>$6.00</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>pemetrexed (Alimta)</td>
<td>J9305 – injection, pemetrexed, 10 mg</td>
<td>$62.70</td>
<td>$52.35</td>
<td>96409</td>
</tr>
<tr>
<td>porfimer sodium (Photofrin)</td>
<td>J9600 – injection, porfimer sodium, 75 mg</td>
<td>$22,324.74</td>
<td>$3,075.86</td>
<td>96409</td>
</tr>
<tr>
<td>topotecan (Hycamtin)</td>
<td>J8705 – topotecan, oral, 0.25 mg</td>
<td>$92.42</td>
<td>$77.13</td>
<td>N/A</td>
</tr>
<tr>
<td>topotecan (Hycamtin)</td>
<td>J9351 – injection, topotecan, 0.1 mg</td>
<td>$20.41</td>
<td>$19.67</td>
<td>96413</td>
</tr>
<tr>
<td>vinorelbine tartrate (Navelbine)</td>
<td>J9390 – injection, vinorelbine tartrate, 10 mg</td>
<td>$36.48</td>
<td>$13.09</td>
<td>96409</td>
</tr>
</tbody>
</table>

*When billing a nonclassified medication using a CMS 1500 claim form, you must include both the HCPCS code (i.e., J8999 for CeeNU) in column 24D and the drug name, strength, and NDC (National Drug Code) in box 19 to ensure appropriate reimbursement.
# Compendia-Listed Off-Label-Use Medications Currently Available to Treat Lung Cancer

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code – Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 5/1/11</th>
<th>Medicare Allowable (ASP + 6%) – Effective 4/1/11-6/30/11</th>
<th>CPT® Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amifostine (Ethyol)</td>
<td>J0207 – injection, amifostine, 500 mg</td>
<td>$564.95</td>
<td>$320.09</td>
<td>96374</td>
</tr>
<tr>
<td>bleomycin (Blenoxane)</td>
<td>J9040 – injection, bleomycin sulfate, 15 units</td>
<td>$45.30</td>
<td>$27.18</td>
<td>96401, 96409</td>
</tr>
<tr>
<td>carboplatin (Paraplatin)</td>
<td>J9045 – injection, bleomycin sulfate, 15 units</td>
<td>$48.55</td>
<td>$4.11</td>
<td>96409, 96413, 96415</td>
</tr>
<tr>
<td>cetuximab (Erbitux)</td>
<td>J9055 – injection, cetuximab, 10 mg</td>
<td>$58.46</td>
<td>$50.47</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>cisplatin (Platinol AQ)</td>
<td>J9060 – injection, cisplatin, powder or solution, per 10 mg</td>
<td>$4.33</td>
<td>$2.07</td>
<td>96409, 96413, 96415</td>
</tr>
<tr>
<td>cyclophosphamide (Cytoxan)</td>
<td>J8530 – cyclophosphamide, oral, 25 mg</td>
<td>$2.09</td>
<td>$0.84</td>
<td>N/A</td>
</tr>
<tr>
<td>cyclophosphamide (Cytoxan)</td>
<td>J9070 – cyclophosphamide, 100 mg</td>
<td>$16.66</td>
<td>$7.56</td>
<td>96409, 96413, 96415</td>
</tr>
<tr>
<td>doxorubicin (Doxil)</td>
<td>J9001 – injection, doxorubicin hydrochloride, all lipid formulations, 10 mg</td>
<td>$646.74</td>
<td>$513.97</td>
<td>96413</td>
</tr>
<tr>
<td>epirubicin (Ellence)</td>
<td>J9178 – injection, epirubicin HCl, 2 mg</td>
<td>$5.38</td>
<td>$1.91</td>
<td>96409, 96413</td>
</tr>
<tr>
<td>fluorouracil (Adrucil)</td>
<td>J9190 – injection, fluorouracil, 500 mg</td>
<td>$3.44</td>
<td>$1.54</td>
<td>96409</td>
</tr>
<tr>
<td>hydroxyurea (Hydra)</td>
<td>J8999* – prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>hydroxyurea (Hydra)</td>
<td>S0176 – hydroxyurea, oral, 500 mg</td>
<td>$1.28</td>
<td>S0176 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>ifosfamide (Ifex)</td>
<td>J9208 – injection, ifosfamide, 1 g</td>
<td>$42.00</td>
<td>$31.81</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>irinotecan (Camptosar)</td>
<td>J9206 – injection, irinotecan, 20 mg</td>
<td>$31.48</td>
<td>$5.00</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>lomustine (CeeNu)</td>
<td>J8999* – prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>lomustine (CeeNu)</td>
<td>S0178 – lomustine, oral, 10 mg</td>
<td>$10.59</td>
<td>S0178 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>mitomycin (Mutamycin)</td>
<td>J9280 – injection, ifosfamide, 1 g</td>
<td>$67.20</td>
<td>$20.76</td>
<td>96409</td>
</tr>
<tr>
<td>oxaliplatin (Eloxatin)</td>
<td>J9263 – injection, paclitaxel, 30 mg</td>
<td>$11.89</td>
<td>$8.52</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>paclitaxel protein-bound particles (Abraxane)</td>
<td>J9264 – injection, paclitaxel protein-bound particles, 1 mg</td>
<td>$11.20</td>
<td>$9.39</td>
<td>96413</td>
</tr>
<tr>
<td>panitumumab (Vectibix)</td>
<td>J9303 – injection, panitumumab, 10 mg</td>
<td>$101.85</td>
<td>$87.26</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>procarbazine (Matulane)</td>
<td>J8999* – prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>procarbazine (Matulane)</td>
<td>S0182 – procarbazine HCl, oral, 50 mg</td>
<td>$55.68</td>
<td>S0182 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>tamoxifen (Novadex)</td>
<td>J8999* – prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
</tr>
<tr>
<td>tamoxifen (Novadex)</td>
<td>S0187 – tamoxifen citrate, oral, 10 mg</td>
<td>$1.89</td>
<td>S0187 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>temozolomide (Temodar)</td>
<td>J8700 – temozolomide, oral, 5 mg</td>
<td>$11.08</td>
<td>$9.49</td>
<td>N/A</td>
</tr>
<tr>
<td>teniposide (Vumon)</td>
<td>Q2017 – injection, teniposide, 50 mg</td>
<td>$376.55</td>
<td>$322.60</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>trastuzumab (Herceptin)</td>
<td>J9355 – injection, trastuzumab, 10 mg</td>
<td>$83.03</td>
<td>$70.38</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>vinblastine (Velban)</td>
<td>J9360 – injection, vinblastine sulfate, 1 mg</td>
<td>$3.18</td>
<td>$1.03</td>
<td>96409</td>
</tr>
<tr>
<td>vincristine (Vincasar)</td>
<td>J9370 – vincristine sulfate, 1 mg</td>
<td>$5.68</td>
<td>$4.00</td>
<td>96409</td>
</tr>
</tbody>
</table>

*When billing a nonclassified medication using a CMS 1500 claim form, you must include both the HCPCS code (i.e., J8999 for CeeNu) in column 24D and the drug name, strength, and NDC (National Drug Code) in box 19 to ensure appropriate reimbursement.
## Ancillary Medications Used in Cancer Treatment

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code – Code Description</th>
<th>Current Code Price (AWP-Based Pricing)</th>
<th>Medicare Allowable (ASP + 6%) – Effective 4/1/11-6/30/11</th>
<th>CPT® Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aprepitant (Emend)</td>
<td>J8501 – aprepitant, oral, 5 mg</td>
<td>$7.39</td>
<td>$6.02</td>
<td>N/A</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>J1626 – injection, granisetron hydrochloride, 100 mcg</td>
<td>$3.89</td>
<td>$1.79</td>
<td>96374</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>Q0166 – granisetron hydrochloride, 1 mg oral, FDA-approved prescription antiemetic, for use as a complete therapeutic substitute for an IV antiemetic at time of chemotherapy treatment, not to exceed a 24-hour dosage regimen</td>
<td>$59.01</td>
<td>$0.34</td>
<td>N/A</td>
</tr>
<tr>
<td>granisetron (Kytril)</td>
<td>S0091 – granisetron hydrochloride, 1 mg (For circumstances falling under the Medicare statute, use Q0166.)</td>
<td>$59.01</td>
<td>S0091 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>J2405 – injection, ondansetron hydrochloride, per 1 mg</td>
<td>$0.60</td>
<td>$0.15</td>
<td>96372, 96374</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>Q0179 – ondansetron hydrochloride, 8 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 48-hour dosage regimen (Code price is per 8 mg.)</td>
<td>$39.36</td>
<td>$1.04</td>
<td>N/A</td>
</tr>
<tr>
<td>ondansetron (Zofran)</td>
<td>S0181 – ondansetron hydrochloride, oral, 4 mg (For circumstances falling under the Medicare statute, use Q0179.)</td>
<td>$23.98</td>
<td>S0181 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>palonosetron (Aloxi)</td>
<td>J2469 – injection, palonosetron hydrochloride, 25 mcg</td>
<td>$44.52</td>
<td>$18.87</td>
<td>96374</td>
</tr>
</tbody>
</table>
## CPT® Administration Code Descriptions

<table>
<thead>
<tr>
<th>CPT® Administration Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96401</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; nonhormonal antineoplastic</td>
</tr>
<tr>
<td>96402</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; hormonal antineoplastic</td>
</tr>
<tr>
<td>96409</td>
<td>Chemotherapy administration, intravenous push technique; single or initial substance/drug</td>
</tr>
<tr>
<td>96413</td>
<td>Chemotherapy administration, intravenous infusion technique; up to one hour, single or initial substance/drug</td>
</tr>
<tr>
<td>96415</td>
<td>Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure.) (Use 96415 in conjunction with 96413.)</td>
</tr>
<tr>
<td>96450</td>
<td>Chemotherapy administration, into CNS (e.g., intrathecal), requiring and including spinal puncture</td>
</tr>
<tr>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
<tr>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push; single or initial substance/drug</td>
</tr>
</tbody>
</table>

### References
- FDA-approved indication (product-prescribing information).
- Compendia references available upon request.

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This information was supplied by RJ Health Systems International LLC, located in Wethersfield, Conn. Prices and information supplied herein are effective as of May 1, 2011.
**Oncology-Related HCPCS Codes**

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

<table>
<thead>
<tr>
<th>generic (Brand) Name</th>
<th>HCPCS Code – Code Description</th>
<th>FDA-Approved Uses</th>
<th>Compendia-Listed Off-Label Uses</th>
<th>Current Code Price (AWP-Based Pricing)*</th>
<th>Medicare Allowable (ASP + 6%) **</th>
<th>CPT® Admin Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>azacitidine (Vidaza)</td>
<td>J9025 – injection, azacitidine, 1 mg</td>
<td>Myeloid leukemia – chronic (205.1_) Low-grade myelodysplastic syndrome lesions (238.72) High-grade myelodysplastic syndrome lesions (238.73) Myelodysplastic syndrome with 5q deletion (238.74) Myelodysplastic syndrome, unspecified (238.75)</td>
<td>Malignant neoplasms of retroperitoneum and peritoneum – specified parts of peritoneum (158.8) Malignant neoplasms of retroperitoneum and peritoneum – peritoneum, unspecified (158.9) Malignant neoplasms of pleura (163.1) Malignant neoplasms 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>$6.03</td>
<td>$5.26</td>
<td>96401 96409 96413</td>
</tr>
<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>
<td>$141.75</td>
<td>$116.57</td>
<td>96413 96415</td>
</tr>
<tr>
<td>daunorubicin (Cerubidine)</td>
<td>J9150 – injection, daunorubicin, 10 mg</td>
<td>Lymphoid leukemia – acute (204.0) Myeloid leukemia – acute (205.0) Monocytic leukemia – acute (206.0) Acute erythremia and erythroleukemia (207.0) Megakaryocytic leukemia (207.2) Leukemia of unspecified cell type – acute (208.0)</td>
<td>Malignant neoplasms of bone and articular cartilage (170) Malignant neoplasms of kidney and other and unspecified urinary organs – kidney, except pelvis (189.0) Reticulosarcoma (200.0) Lymphosarcoma (200.1) Burkitt’s tumor or lymphoma (200.2) Marginal zone lymphoma (200.3) Mantle cell lymphoma (200.4) Primary central nervous system lymphoma (200.5) Anaplastic large-cell lymphoma (200.6) Large-cell lymphoma (200.7) Other named variants (200.8) Nodular lymphoma (202.0) Mycosis fungoides (202.1) Sézary’s disease (202.2) Malignant histiocytosis (202.3) Leukemic reticuloendotheliosis (202.4) Letterer-Siwe disease (202.5) Malignant mast cell tumors (202.6) Peripheral T-cell lymphoma (202.7) Other lymphomas (202.8) Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue (202.9) Myeloid leukemia – chronic (205.1)</td>
<td>$25.20</td>
<td>$13.42</td>
<td>96409 96413</td>
</tr>
<tr>
<td>generic (Brand Name)</td>
<td>HCPCS Code – Code Description</td>
<td>FDA-Approved Uses</td>
<td>Compendia-Listed Off-Label Uses</td>
<td>Current Code Price (AWP-Based Pricing)*</td>
<td>Medicare Allowable (ASP + 6%) **</td>
<td>CPT® Admin Code(s)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------</td>
<td>------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>---------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>decitabine (Dacogen)</td>
<td>J0894 – injection, decitabine, 1 mg</td>
<td>Low-grade myelodysplastic syndrome lesions (238.72) High-grade myelodysplastic syndrome lesions (238.73) Myelodysplastic syndrome with 5q deletion (238.74) Myelodysplastic syndrome, unspecified (238.75)</td>
<td>Lymphoid leukemia – acute (204.0_) Myeloid leukemia – acute (205.0_) Myeloid leukemia – chronic (205.1_)</td>
<td>$36.91</td>
<td>$31.30</td>
<td>96413 96415</td>
</tr>
<tr>
<td>degarelix (Firmagon)</td>
<td>J9155 – injection, degarelix, 1 mg</td>
<td>Malignant neoplasm of prostate (185)</td>
<td>N/A</td>
<td>$5.52</td>
<td>$2.82</td>
<td>96402</td>
</tr>
<tr>
<td>fludarabine (Fludara)</td>
<td>J9185 – injection, fludarabine phosphate, 50 mg</td>
<td>Lymphoid leukemia – chronic (204.1_)</td>
<td>Reticulosarcoma (200.0_) Lymphosarcoma (200.1_) Burkitt’s tumor or lymphoma (200.2_) Marginal zone lymphoma (200.3_) Mantle cell lymphoma (200.4_) Primary central nervous system lymphoma (200.5_) Anaplastic large-cell lymphoma (200.6_) Large-cell lymphoma (200.7_) Other named variants (200.8_) Nodular lymphoma (202.0_) Mycosis fungoides (202.1_) Sézary’s disease (202.2_) Malignant histiocytosis (202.3_) Leukemic reticuloendotheliosis (202.4_) Letterer-Siwe disease (202.5_) Malignant mast cell tumors (202.6_) Peripheral T-cell lymphoma (202.7_) Other lymphomas (202.8_) Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue (202.9_) Lymphoid leukemia – acute (204.0_) Myeloid leukemia – acute (205.0_) Low-grade myelodysplastic syndrome lesions (238.72) High-grade myelodysplastic syndrome lesions (238.73) Myelodysplastic syndrome with 5q deletion (238.74) Myelodysplastic syndrome, unspecified (238.75) Monoclonal paraproteinemia (273.1) Macroglobulinemia (273.3) Chronic glomerulonephritis – with lesion of membranes glomerulonephritis (582.1) Nephritis and nephropathy, not specified as acute or chronic – with lesion of membranes glomerulonephritis (583.1) Systemic lupus erythematosus (710.0) Enlargement of lymph nodes (785.6)</td>
<td>$205.14</td>
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<td>nelarabine (Arranon)</td>
<td>J9261 – injection, nelarabine, 50 mg</td>
<td>Anaplastic large-cell lymphoma (200.6)</td>
<td>Lymphoid leukemia – chronic (204.1)</td>
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<td>$112.31</td>
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Lymphosarcoma (200 1.)  
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Mantle cell lymphoma (200.4_)  
Primary central nervous system lymphoma (200.5_)  
Anaplastic large-cell lymphoma (200.6_)  
Large-cell lymphoma (200.7_)  
Other named variants (200.8_)  
Nodular lymphoma (202.0_)  
Mycosis fungoides (202.1_)  
Sézary’s disease (202.2_)  
Malignant histiocytosis (202.3_)  
Leukemic reticuloendotheliosis (202.4_)  
Letterer-Siwe disease (202.5_)  
Malignant mast cell tumors (202.6_)  
Peripheral T-cell lymphoma (202.7_)  
Other lymphomas (202.8_)  
Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue (202.9_)  
Myeloid leukemia – chronic (205.1_) | $3,280.00 | $2,726.85 | 96401  
96413  
96415 |

* Current code prices are effective as of 5/1/11. The code price is based on the Healthcare Common Procedure Coding System (HCPCS) code description. HCPCS 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, Wethersfield, Conn.
** Effective 4/1/11–6/30/11

Oncology-Related J-Code References

- Full prescribing information for each drug listed.

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Prognosis for advanced non-small cell lung cancer (NSCLC) remains less than optimal. Oral agents, such as vandetanib and S-1, may offer some benefit, but new drugs and/or drug combinations are needed to have a significant improvement in overall survival.

**Title:** Anaplastic lymphoma kinase inhibition in non-small cell lung cancer.

**Authors:** Kwak EL, Bang Y-J, Camidge DR, et al.


**Purpose:** Genetic mutations that drive cell proliferation may allow for treatment with specific inhibitors that target the mutated pathway. Translocations of the anaplastic lymphoma kinase (ALK) gene have been identified in several types of cancers, including non-small cell lung cancer (NSCLC). In this disease, EML4-ALK is an abnormal fusion gene that encodes a cytoplasmic chimeric protein with kinase activity. EML4-ALK is uncommon, occurring in 2% to 7% of all NSCLC patients. The majority of these patients have never smoked or have a history of only light tobacco intake. The primary histology in these patients is adenocarcinoma. In the preclinical analyses of various malignant cell lines, selective ALK inhibitors were shown to reduce the proliferation rate of cells carrying genetic alterations of the gene. Crizotinib, an oral adenosine 5’-triphosphate-competitive selective inhibitor of ALK and MET tyrosine kinases with activity at nanomolar concentrations, was chosen to investigate. This study evaluates a two-part phase 1 study of crizotinib in regard to its adverse event profile and efficacy in patients with NSCLC carrying the ALK rearrangement.

**Methods:** Following the screening of more than 1,500 patients with NSCLC for the presence of ALK rearrangement, 82 patients were identified as eligible for the clinical trial. All patients underwent a baseline tumor assessment and at least one postbaseline assessment. Eligibility criteria included measurable disease, adequate end-organ function, resolution of all previous treatment-related toxic effects to grade 1 or less, and an Eastern Cooperative Oncology Group (ECOG) performance status of between 0 (fully active) and 2 (up and about more than 50% of waking hours). Oral crizotinib was administered on a continuous 28-day schedule. Doses of crizotinib were escalated from 50 mg orally once a day to 300 mg orally twice a day using standard dose-escalation design. The patients in this study were enrolled in an expanded cohort study with an established dose of crizotinib of 250 mg orally twice a day. Patients were assessed for adverse events once every two weeks for the first two cycles and every four weeks thereafter, and for response to therapy via radiologic assessment at baseline and following every two cycles. The primary objective of the study was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS) as calculated from the date of the first crizotinib dose until the date of objective tumor progression or death from any cause and any adverse events attributed to the oral ALK inhibitor.

**Results:** Patients tended to be of younger age than the average patient.
with NSCLC (mean: 51 years; range: 25 to 78 years) with a history of never having smoked or of former light smoking (≤10 pack years). Ninety-four percent (76 of 81) had received at least one prior chemotherapy regimen, and 6% (five of 81) were treated with crizotinib as first-line therapy. The ORR was 57% (47 of 82) with 46 partial responses and one complete response at a median treatment duration of 6.4 months. Twenty-seven additional patients (33%) had stable disease. The disease control rate at eight weeks was 87%. The estimated probability of six-month PFS was 72% with no median for the study reached. The major adverse events were gastrointestinal and consisted primarily of grade 1 nausea and diarrhea. Mild visual disturbances were reported by 34 patients (41%).

Conclusion: The inhibition of ALK in lung tumors with ALK rearrangement resulted in tumor shrinkage or stable disease in most patients treated.

Managed Care Implications: Identification of specific activating mutations or translocations may lead to a target therapy approach. Those patients with ALK translocations may benefit from therapy with crizotinib. Further studies will identify whether this will be as a single agent or as part of a multidrug/modality treatment.

Title: First-cycle rash and survival in patients with advanced non-small cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study.


Purpose: Platinum-based doublets are the backbone for the treatment of patients with advanced NSCLC. The phase 3 First-Line Erbitux in Lung Cancer Study (FLEX) showed that the addition of epidermal growth factor receptor (EGFR) inhibitor cetuximab (Erbitux) to cisplatin (Platinol) and vinorelbine (Navelbine) improved overall survival compared with chemotherapy alone. Rash and other skin adverse events have been associated with the EGFR-targeting drugs such as the monoclonal antibodies. Studies have suggested that rash might be associated with the efficacy of some EGFR-targeted therapy, including cetuximab, in this patient population. The rash associated with cetuximab generally is seen two to three weeks after starting therapy and is confined to certain areas of the body, such as the face, neck, scalp, and shoulders, which are rich in sebaceous glands, although it can develop in other areas of the body as well. The exact pathogenesis of the rash is unclear, although many proposed mechanisms have been put forth. In studies in patients with advanced colon cancer and treated with cetuximab, it was noted that the occurrence and severity of an acnelike rash was shown to be associated with an improved clinical outcome. In patients with squamous cell carcinoma of the head and neck treated with cisplatin or carboplatin (Paraplatin) in combination with cetuximab, an improved clinical outcome was noted with the occurrence of skin rash that developed within the first 21 days of therapy. This study accessed first-cycle rash and efficacy in patients who were randomly assigned to receive cisplatin, vinorelbine, and cetuximab as first-line therapy for advanced NSCLC.

Methods: The FLEX study was a multinational, multicenter, open-label, phase 3 trial for chemotherapy-naive patients ages 18 and older with advanced EGFR-expressing histologically or cytologically proven stage IIIB or IV NSCLC. Patients were randomly assigned in a 1:1 ratio to receive chemotherapy +/- cetuximab. Chemotherapy consisted of
cisplatin 80 mg/m² intravenously on day one and vinorelbine 25 mg/m² intravenously on days one and eight of a 21-day cycle for up to six cycles. For those patients assigned to receive cetuximab, the loading dose was 400 mg/m² intravenously over two hours on day one, followed by weekly doses of 250 mg/m². Cetuximab therapy continued after the end of chemotherapy until there was documentation of disease progression. The primary endpoint of the FLEX study was overall survival (OS). Cetuximab could be held secondary to the severity of skin rash for up to two consecutive cycles with a permanent dose reduction following the second and third reaction. First-cycle skin rash was defined as an acnelike rash of any grade that arose between days one and 21. This subgroup analysis assessed whether patients who developed an acnelike rash in the first 21 days of therapy had a significantly improved clinical outcome.

**Results:** Five hundred and eighteen patients were in the chemotherapy + cetuximab group, 290 (60%) of whom had a first-cycle rash. Patients treated with chemotherapy and cetuximab with a first-cycle rash had a significantly prolonged OS compared with patients in the same treatment group who did not develop a rash. Median OS was 15.0 months (confidence interval [CI] 12.8 to 16.4) vs. 8.8 months (CI 7.6 to 11.1) between the two groups. The hazard ratio (HR) was 0.631 (0.515 to 0.774) with a p value of < 0.0001.

**Conclusion:** First-cycle rash was associated with a better outcome in patients with advanced NSCLC who received a combination of chemotherapy (cisplatin + vinorelbine) + cetuximab as first-line therapy. Rash might be a surrogate clinical marker that could be used to tailor cetuximab treatment to those patients with NSCLC who would most likely derive a significant benefit.

**Managed Care Implications:** The identification of patients who would benefit from the use of cetuximab within the first 21 days of therapy could become an important clinical tool. Additional studies are needed to assess whether cetuximab could be stopped earlier in patients who do not develop a rash within this time period or whether an increase in dose is warranted.

**Title:** Vandetanib + docetaxel vs. docetaxel as second-line treatment for patients with advanced non-small cell lung cancer (ZODIAC): a double-blind, randomized phase 3 trial.

**Authors:** Herbst RS, Sun Y, Eberhardt WEE, et al.


**Purpose:** A majority of patients with NSCLC are diagnosed with advanced disease and respond to initial therapy, but ultimately relapse. For those patients able to receive second-line therapy, a number of drugs – docetaxel (Taxotere), pemetrexed (Alimta), erlotinib (Tarceva), and gefitinib (Iressa) – have been approved. No drug has been proven to be superior to another as second-line therapy, and responses for the most part are short-lived with the vast majority of patients succumbing to their disease. One strategy to improve efficacy in the second-line setting is to combine chemotherapeutic agents with drugs that are selective for targeting signaling pathways associated with disease progression. Vandetanib is an oral agent that targets the vascular endothelial growth receptor (VEGFR) and EGFR signaling. It is also a potent inhibitor of rearranged during transfection (RET) tyrosine kinase, an important growth driver in some tumors. A phase 2 study in patients
with relapsed NSCLC has shown an improvement in PFS and ORR when vandetanib was combined with docetaxel vs. docetaxel alone. This provided the rationale for this phase 3 study.

**Methods:** This multinational, randomized, double-blind, phase 3 trial accepted patients age 18 or older with a histological or cytological confirmation of locally advanced or metastatic stage IIIB-IV NSCLC following progression on first-line therapy containing a platinum compound. Additional eligibility criteria included World Health Organization performance status of 0 to 1, measurable disease, no prior docetaxel therapy, and adequate cardiac, hematopoietic, hepatic, and renal function. Patients were randomly assigned to receive docetaxel (75 mg/m²) intravenously every three weeks to a maximum of six cycles in combination with vandetanib (100 mg/m²/d) orally or placebo until disease progression, unacceptable toxicity, or withdrawal of consent. The primary objective of the trial was to assess whether the two-drug combination (docetaxel + vandetanib) prolonged PFS compared with docetaxel alone. Secondary outcomes included OS, ORR (complete + partial), disease control rate (complete + partial + stable disease for ≥ six weeks), and safety.

**Results:** A total of 1,391 patients were evaluated. Six hundred and ninety-four were treated with docetaxel + vandetanib, and 697 were treated with docetaxel + placebo. A significant improvement in PFS was noted in the patients treated with docetaxel + vandetanib. Median PFS was 4.0 months with the combination therapy and 3.2 months in the placebo group (HR 0.79, CI 0.70 to 0.90; p < 0.001). A significant improvement in ORR was also noted in the docetaxel + vandetanib-treated patients (17% vs. 10%, p = 0.0001). Only partial responses were noted in the vandetanib-treated group, while six complete responses and 65 partial responses were noted in the placebo-treated arm. The disease control rate was similar in both groups, 60% with vandetanib + docetaxel and 55% with placebo + docetaxel (p = 0.06). Adverse events grade 3 or higher were more prevalent in the docetaxel + vandetanib-treated patients. These included rash (9% vs. 1%), neutropenia (29% vs. 24%), and febrile neutropenia (9% vs. 7%).

**Conclusion:** The addition of vandetanib to docetaxel provides a significant improvement in PFS in patients with advanced NSCLC after progression following first-line therapy.

**Managed Care Implications:** Oral targeted therapy in combination with standard chemotherapy is becoming more common in patients with NSCLC. Additional trials will prove which agent(s) have the most activity with an acceptable safety profile.

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**Title:** Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small cell lung cancer: results from a randomized phase 3 trial (AVAil).

**Authors:** Reck M, von Pawel J, Zatloukal P, et al.


**Purpose:** Advanced NSCLC is the leading cause of cancer-related deaths. While there is no universally accepted standard regimen for first-
line therapy in this disease, cisplatin (Platinol) and gemcitabine (Gemzar) are widely used in Europe secondary to their efficacy and tolerability. Bevacizumab (Avastin) is an anti-vascular endothelial growth factor monoclonal antibody with activity in colorectal, metastatic breast, and renal cancers. It has also shown efficacy and established safety in the first-line treatment of nonsquamous cell NSCLC in two randomized phase 3 trials. This trial, AVAiL, evaluates bevacizumab in combination with cisplatin and gemcitabine.

**Methods:** Patients with a histologically or cytologically confirmed advanced (stage IIIIB or IV) or recurrent nonsquamous cell NSCLC were eligible. Other inclusion criteria included age 18 and older, ECOG performance status of 0 to 1, and adequate end-organ function. Patients with ≥ grade 2 hemoptysis, central nervous system metastases, and/or a history of thrombotic disorders were excluded. Patients were randomized to receive bevacizumab (7.5 mg/kg or 15 mg/kg) intravenously or placebo on day one in combination with cisplatin (80 mg/m²) intravenously on day one and gemcitabine (1,250 mg/m²) intravenously on days one and eight. Chemotherapy was administered every three weeks for up to six cycles based upon disease progression or unacceptable toxicity. Bevacizumab or placebo was administered every three weeks until disease progression. The primary endpoint was PFS. The secondary endpoint was OS.

**Results:** A total of 1,043 patients were enrolled in the trial. Three hundred and forty-five were treated with chemotherapy + bevacizumab 7.5 mg/kg, 351 received chemotherapy + bevacizumab 15 mg/kg, and the final 347 received chemotherapy + placebo. Significant prolongation of PFS was noted in the groups treated with bevacizumab vs. the group treated with placebo at 32 months. For the patients treated with 7.5 mg/kg of bevacizumab, the HR was 0.75 (95% CI 0.64 to 0.87) with a p value of 0.0003. For the 15 mg/kg dose, the HR was 0.85 (95% CI 0.78 to 1.00) with a p value of 0.0456. The median OS was greater than 13 months in all treatment groups and was not increased by the addition of bevacizumab. Almost two-thirds of the patients received multiple lines of poststudy therapy. Safety data was consistent with what had been previously reported.

**Conclusion:** Final analysis of the AVAiL trial confirms the efficacy of bevacizumab when combined with gemcitabine and cisplatin as first-line therapy for advanced NSCLC (non-squamous type). The PFS benefit did not translate into a significant improvement in OS secondary to high use of efficacious second-line therapy.

**Managed Care Implications:** The combination of gemcitabine/cisplatin/bevacizumab compares favorably with that of carboplatin/paclitaxel/bevacizumab in patients with advanced nonsquamous NSCLC. This allows for the consideration of alternative therapy in those patients unable to receive carboplatin or paclitaxel.

**Title:** Phase 3 trial comparing oral S-1 + carboplatin with paclitaxel + carboplatin in chemotherapy-naive patients with advanced non-small cell lung cancer: results of a West Japan Oncology Study Group.

**Authors:** Okamoto I, Yoshioka H, Morita S, et al.


**Purpose:** Lung cancer is the leading cause of cancer deaths worldwide, with NSCLC accounting for 85% of all lung cancers. For most patients with NSCLC, first-line therapy consists of a platinum-based chemotherapy with moderate improvement in survival and quality of life when compared with best supportive care. Thus, new therapies are needed to ameliorate symptoms and prolong
survival in this patient population. S-1 is an oral fluoropyrimidine agent that consists of tegafur, 2,4-dihydroxypyridine, and potassium oxonate in a molar ratio of 1:0.4:1. Phase 2 trials with oral S-1 in patients with previously untreated advanced NSCLC yielded a response rate of 22% and a median survival of 10.2 months in a small group of patients. A phase 1/2 study of carboplatin (Paraplatin)/S-1 therapy at a dose of S-1 (40 mg twice a day; days one to 14) and carboplatin area under the concentration (AUC) = 5 on day one of a 21-day cycle have results similar to those reported by other platinum-containing doublets with a more favorable toxicity profile. This study compares that combination with the standard of paclitaxel (Taxol) + carboplatin.

Methods: Eligibility included a diagnosis of NSCLC confirmed either histologically or cytologically, clinical stage IIIIB not amenable to curative treatment or stage IV, a measurable lesion, no prior chemotherapy, an ECOG performance status of 0 or 1, and adequate end-organ (bone marrow, hepatic, and renal) function. Patients were randomized to receive either carboplatin (AUC = 6) + paclitaxel (200 mg/m²), both intravenously on day one or carboplatin (AUC = 5) intravenously on day one with S-1 (40 mg/m² orally twice a day – days one through 14). All chemotherapy was repeated every 21 days to a maximum of six cycles, unless there was earlier evidence of disease progression or intolerance to study treatment. The primary endpoint of the study was to establish the noninferiority of S-1 + carboplatin when compared with carboplatin + paclitaxel as first-line therapy in advanced NSCLC in terms of OS. Secondary endpoints included tumor response, treatment safety, and PFS.

Results: Five hundred and sixty-four patients from 30 institutions were enrolled in this open-label, multicenter, randomized phase 3 trial in a 1:1 ratio. The intent-to-treat (ITT) population numbered 563 patients, following one dropout, with 281 patients assigned to receive carboplatin + paclitaxel and 282 assigned to carboplatin + S-1. The number of treatment courses administered was 1,037 in the carboplatin/paclitaxel arm (median 4; range 1 to 6) vs. 987 courses in the carboplatin/S-1 group (median 4; range 1 to 6). Dose reductions were more prevalent in the carboplatin/paclitaxel group (8.7% vs. 5.0%), primarily due to neuropathy. The median OS was 15.2 months for the carboplatin/S-1-treated patients and 13.3 months for those patients treated with carboplatin/paclitaxel. One-year survival was 57.3% and 55.5%, respectively. The median PFS was 4.1 months in the carboplatin/S-1 arm and 4.8 months in the carboplatin/paclitaxel arm in the ITT population. Response to treatment (complete response [CR] + partial response [PR]) was superior in the carboplatin/paclitaxel arm (29.0% vs. 20.4%; p = 0.019) whereas overall disease control (CR + PR + stable disease rate) was similar in both groups, 73.5% vs. 71.7%, respectively (p = 0.635). As expected, rates of leucopenia or neutropenia of grade 3/4, febrile neutropenia, alopecia, and neuropathy were more frequent in the carboplatin/paclitaxel-treated patients, whereas thrombocytopenia, nausea, vomit-
ing, and diarrhea were more common in the carboplatin/S-1-treated patients.

**Conclusion:** Oral S-1 with carboplatin was noninferior in terms of OS compared with carboplatin + paclitaxel when used in the first-line setting for patients with advanced NSCLC. Carboplatin + S-1 is a viable treatment option.

**Managed Care Implications:** New therapies in the first-line setting for advanced NSCLC continue to evolve. Oral agents may play a larger role when combined with platinum-based doublets.

**Title:** Weekly paclitaxel combined with monthly carboplatin vs. single-agent therapy in patients ages 70 to 89: IFCT-0501 randomized phase 3 study in advanced NSCLC.

**Authors:** Quoix EA, Oster J, Westeel V, et al.

**Reference:** J Clin Oncol. 2010;28:18s(suppl; abstr 2).

**Purpose:** There has been a significant increase in the number of lung cancers reported in the elderly as a result of both increase in life expectancy and the increase in incidence of cancer with age. More than one-third of patients diagnosed with lung cancer are older than age 70. Trials including this patient population are few, and therefore present treatment may not be adequate. Current recommendations establish monotherapy with either gemcitabine (Gemzar) or vinorelbine (Navelbine) as treatment of choice. This study compares single agent with doublet therapy in this elderly population.

**Methods:** Patients ages 70 to 89 with a diagnosis of advanced NSCLC who were not able to be irradiated were eligible. Other eligibility criteria included a performance status of 0, 1, or 2. Patients were randomized to receive either gemcitabine 1,150 mg/m² intravenously or vinorelbine 30 mg/m² intravenously on days one and eight of a 21-day cycle (Arm A) or combination therapy with carboplatin (Paraplatin) AUC = 6 intravenously every four weeks with paclitaxel (Taxol) 90 mg/m² intravenously on days one, eight, and 15 (Arm B). Up to five cycles of monotherapy and four cycles of doublet therapy could be administered. Second-line therapy for both groups, whether secondary to disease progression or toxicity, was erlotinib (Tarceva) 150 mg orally per day. The primary endpoint of the study was OS.

**Results:** Four hundred and fifty-one of a planned 522 patients were enrolled. At the second planned analysis, after two-thirds of the expected deaths had occurred, the difference in OS between the two arms was significant, and thus the study was closed. The median age of the patients was 77.2 years (range 70 to 89), and 73.6% were males. The two arms were well balanced for all patient characteristics. OS was significantly longer in the doublet arm (Arm B) – 10.3 months (95% CI 8.3 to 13.3) vs. 6.2 months (95% CI 5.3 to 7.4; p = 0.00004). PFS also favored the doublet (6.1 months vs. 3.0 months; p = 0.0001). The improvement in PFS is reflected in the OS with a one-year survival of
45.1% in Arm B and 26.9% in Arm A. Median OS time and one-year survival time in the single-agent arm were nearly those produced by previous studies in the elderly, whereas the survival time and one-year survival time in the doublet arm are what would be expected in the general population of any age with advanced NSCLC and a performance status of 0 to 2. Grade 3 and 4 hematologic toxicities were significantly more frequent for patients in the doublet arm (113 vs. 30), although there was no statistically significant difference in early death (Arm A, 23.7% vs. Arm B, 16.6%).

**Results:*** The paclitaxel and carboplatin doublet provides a significantly longer survival to elderly patients ages 70 to 89 with advanced NSCLC than the current standard singlet therapy. Its acceptable toxicity makes it the new treatment paradigm for performance status 0 to 2 patients in this age range.

**Managed Care Implications:*** Older patients of good performance status can and should be treated with doublet therapy as first-line therapy for advanced NSCLC. Additional supportive care measures (e.g., white cell growth factors) may be needed to decrease the incidence of hematologic toxicity.

**Title:** Results of a randomized phase 3 trial of nab-paclitaxel (nab-P) and carboplatin as first-line therapy in advanced non-small cell lung cancer.

**Authors:** Socinski MA, Bondarenko IN, Karaseva NA, et al.

**Reference:** J Clin Oncol. 28(suppl; abstr LBA7511):S18.

**Purpose:** Platinum-based doublet therapy remains the primary first-line treatment for advanced NSCLC. Combinations such as carboplatin (Paraplatin) and paclitaxel (Taxol) produce ORRs of between 15% and 25%. Albumin-bound paclitaxel (Abraxane) leverages the albumin receptor (gp60)/caveolin-1 SPARC transcytosis pathway, which results in higher intratumor drug concentrations that may contribute to the higher response rates noted in early clinical trials. This phase 3 trial studied the efficacy of nab-PC vs. PC in advanced NSCLC of all histologic types.

**Methods:** The study population included chemotherapy-naive patients with stage IIIB or IV NSCLC. All patients had an ECOG performance status of 0 or 1. Patients were randomized to receive either nab-paclitaxel at 100 mg/m² intravenously on days one, eight, and 15 in combination with carboplatin at an AUC of 6 on day one (n = 525) or paclitaxel 200 mg/m² intravenously and carboplatin (AUC = 6) on day one only (n = 525). Chemotherapy was repeated every three weeks. The nab-paclitaxel group received no premedications, and the drug was delivered over 30 minutes. Those patients receiving paclitaxel were premedicated with dexamethasone and an antihistamine with the drug administered over three hours. The primary endpoint of the study was ORR by independent radiologic review (IRR). Secondary endpoints included adverse events.

**Results:** The baseline characteristics of the two groups, including histology, were similar. Dose intensity with nab-PC (82 mg/m²/wk) was higher than with PC (65 mg/m²/wk). The ORR by IRR was superior for the nab-PC-treated patients (33% vs. 25%; p = 0.005), which is indicative of a 31% improvement. The ORR by histology also differed. Response rates for squamous cell carcinoma were 41% for nab-PC and 24% for PC. For the nonsquamous cell patients, response rates were similar at 26% (nab-PC) and 25% (PC). Patients treated with nab-P reported fewer adverse reactions commonly associated with cremophor-based-P, including peripheral neuropathy and serious hypersensitivity reactions. Patients receiving nab-P did have a higher incidence of grade 4 neutropenia and grade 3/4 thrombocytopenia and anemia.

**Conclusion:** Nab-PC significantly improved ORR vs. PC as first-line therapy for advanced NSCLC. It was particularly more active in patients with squamous cell histology, which may be in part attributed to caveolin-1 (CAV1) overexpression and the high intratumor accumulation of nab-P via the gp60/CAV1 pathway.

**Managed Care Implications:** Nab-paclitaxel may be more effective in the first-line treatment of patients with advanced NSCLC than paclitaxel. It offers a drug with less toxicity, which is easier to administer in the outpatient setting. Maturity of the data from this study to include progression-free response rates and OS will be important in identifying the exact role of nab-paclitaxel in this patient population.
This resource guide features links and websites specific to lung cancer that may be of use to the reader in daily practice.*

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

**American Lung Association.** The American Lung Association is the oldest voluntary health organization in the United States. Its website offers information on smoking cessation and a free interactive decision support tool to assist patients and providers in making treatment decisions.
www.lungusa.org

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

**eMedicine Health.** Owned and operated by WebMD, this consumer health information website contains health and medical articles written by physicians, including information regarding lung cancer.
www.emedicinehealth.com/lung_cancer/article_em.htm

**Lung Cancer Alliance.** The Lung Cancer Alliance is the only national nonprofit organization dedicated solely to patient support and advocacy for people living with lung cancer and those at risk for the disease.
www.lungcanceralliance.org

**Lung Cancer Online Foundation.** This website is a comprehensive annotated directory of Internet resources on lung cancer for patients and families.
http://lungcanceronline.org

**Lungcancer.org.** Lungcancer.org is a program of CancerCare, a national nonprofit organization that provides free professional support services to anyone affected by lung cancer. Services include counseling, education, and financial assistance.
www.lungcancer.org

**Lung Cancer Research Foundation.** This foundation is dedicated to supporting national research studies and activities focused on developing innovative strategies for better treatments, screening, and prevention of lung cancer.
www.lungcancerresearchfoundation.org

**Mayo Clinic.** The largest integrated not-for-profit group practice in the world, the Mayo Clinic uses its vast physician expertise to provide information and resources to help consumers manage their health. This website section is devoted to issues about lung cancer.
www.mayoclinic.com/health/lung-cancer/DS00038

**MedlinePlus.** A service of the U.S. National Library of Medicine and the U.S. National Institutes of Health, this website offers links to peer-reviewed articles and abstracts on lung cancer, clinical trial information, glossaries, statistics, and more.
www.nlm.nih.gov/medlineplus/lungcancer.html

**National Cancer Institute (NCI).** The NCI conducts and supports cancer-related research, training, and health information dissemination. This online guide provides patient information plus links to published literature and research on lung cancer.
www.cancer.gov/cancertopics/types/lung

**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 lung cancer. Users must register to access guidelines.
www.nccn.org/professionals/physician_gls/f_guidelines.asp

**National Lung Cancer Partnership.** Originally founded by physicians and scientists, this organization is dedicated to raising public awareness of the disease and generating funding for lung cancer research.
www.nationallungcancerpartnership.org

**U.S. Food and Drug Administration (FDA).** The FDA is conducting a project to evaluate potential endpoints for cancer drug approval for lung and other common cancers. Guidance documents regarding current conclusions of these endpoints will be published.
www.fda.gov/drugsdevelopmentapprovalprocess/developmentresources/cancerdrugs

*Note: ICORE Healthcare does not endorse or verify the information presented.*
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• The impact of healthcare reform on Medicare and cancer treatment
• The role of genetic testing in managing oncology care
• Discussion around state Medicaid

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