

A CME-Certified Supplement to

# COMMUNITY ONCOLOGY

— CLINICAL ISSUES IN COMMUNITY PRACTICE —

## Highlights of the 6<sup>th</sup> Annual Community Oncology Conference

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# Highlights of the 6<sup>th</sup> Annual Community Oncology Conference

February 25–26, 2011, Las Vegas, Nevada

## Educational Need

The volume of information emerging from cancer research challenges oncologists' ability to translate evidence into clinical care. Assessments of clinical practice have shown that as many as 45% of patients do not receive evidence-based care and that as much as 25% of the care that patients do receive is unnecessary or potentially harmful. Studies of clinical oncology practices have found that application of evidenced-based care has the potential to improve patient outcomes and reduce mortality. Clinicians have an ongoing need for concise, evidence-based educational activities that can facilitate the integration of new information into clinical oncology practice. Responses to a recent educational needs survey showed that clinical oncology professionals place a high priority on remaining current with emerging data, integrating emerging data into clinical practice, and formulating evidence-based treatment plans that meet individual patient needs.

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## Learning Objectives

After completing this educational activity, participants should be able to:

- Discuss recent developments related to integration of novel agents into the treatment of non-small cell lung cancer
- Describe the scientific rationale for use of PARP inhibitors to treat cancer
- Discuss outcomes of recent clinical trials of PARP inhibitors
- Recognize the role of bone-targeted therapy in clinical oncology practice
- Understand distinctions between bisphosphonates and RANK ligand inhibitors
- Describe recent developments in the treatment of melanoma
- Discuss novel therapies recently approved for treatment of advanced prostate cancer
- Describe recent clinical trial data related to Hodgkin's lymphoma and non-Hodgkin's lymphoma
- Review current and emerging treatment options for colon and other gastrointestinal cancers
- Appreciate differences between traditional and novel HER2-targeted agents

## Target Audience

This activity has been developed for medical oncologists, hematologists, and radiation oncologists.

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**On the cover:** colored scanning electron micrograph of human breast cancer cells. Photo: Steve Gschmeissner/Photo Researchers, Inc.

# Novel HER2-targeted agents for breast cancer therapy

Jame Abraham, MD, FACP | West Virginia University, Morgantown, WV

The development of therapies that target the epidermal growth factor receptor (ErbB) family has helped transform the treatment of breast cancer and cancer in general. The ability to interfere with ErbB2 (human epidermal growth factor receptor 2; HER2) signaling led to an effective treatment for an especially aggressive form of breast cancer. Moreover, research into anti-HER2 therapy provided confirmation of the concept that targeting specific signaling pathways could disrupt cancer progression. Over time, clinical experience showed that some patients with HER2-positive tumors did not benefit from treatment targeting HER2. Until recently, failure of existing anti-HER2 therapy left clinicians and their patients with few HER2-specific options. The outlook has begun to improve with the emergence of several new agents that employ different strategies to inhibit HER2 activity.

Three anti-HER2 drugs have reached phase III clinical evaluation: trastuzumab emtansine (T-DM1), pertuzumab, and neratinib. Although HER2 inhibition is the ultimate effect of all three agents, each employs a different approach to achieve that goal.

## T-DM1

T-DM1 is an antibody-drug conjugate, consisting of trastuzumab linked to a potent cytotoxic drug. The antibody has a binding affinity for HER2, similar to that of trastuzumab. After binding HER2, the antibody allows intracellular delivery of the chemotherapeutic agent DM-1, which is a derivative of maytansine, a plant-derived microtubule polymerization inhibitor.

DM-1 has 20–100 times the potency of another well-known member of the drug class, vincristine.<sup>1</sup> DM-1 underwent testing as a chemotherapeutic agent but proved to be too toxic to use in the conventional manner. In the antibody-drug conjugate, trastuzumab is attached to DM-1 by means of a linker molecule, which prevents release of the cytotoxic drug until the conjugate has been incorporated into a HER2-expressing tumor cell.

T-DM1 was evaluated in a single-arm, open-label, phase II clinical trial involving 110 patients with heavily pretreated metastatic HER2-positive breast cancer.<sup>2</sup> The patients in the trial resembled those seen often in clinical practice but rarely in clinical trials. All but one of the patients had disease progression during or after treatment with an anthracycline, a taxane, capecitabine, lapatinib, and trastuzumab. All of the patients had received two prior HER2-directed therapies (trastuzumab and lapatinib), and all had progressive disease with the last regimen received.

Treatment consisted of T-DM1 at a dose of 3.6 mg/kg administered by intravenous infusion every 3 weeks. The primary endpoint was objective response rate (ORR), as determined at 24 weeks by independent review. The secondary endpoints included investigator-assessed ORR, progression-free survival (PFS), duration of response, and clinical benefit rate, as assessed by independent review and the investigators.

The patients had received a median of seven prior therapies for metastatic disease and eight therapies in all clinical settings. Some patients had been treated with as many as 19 prior therapies. The median duration of prior trastuzumab therapy for metastatic disease was 19.4 months, and previous lapatinib therapy had a median duration of 6.9 months.

As single-agent therapy, T-DM1 demonstrated substantial activity in this heavily treated patient population. The independently assessed ORR was 32.7%, and the clinical benefit rate was 44.5% by independent review. The trial provided infor-

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mation about the clinical activity of a new agent in a patient population that had not been studied previously. T-DM1 was well tolerated at the dose and schedule used in the trial, and no dose-limiting cardiotoxicity or new safety signals occurred. Toxicity was considered to be acceptable and manageable in the patient population represented by the trial.

Initial results have been reported from a recently completed phase III randomized clinical trial that compared T-DM1 with trastuzumab-docetaxel\* combination therapy in patients with recurrent locally advanced or metastatic breast cancer.<sup>3</sup> Patients received either T-DM1 at a dose of 3.6 mg/kg every 3 weeks or trastuzumab,\* initiated at 8 mg/kg and followed by 6 mg/kg every 3 weeks, plus docetaxel at a dose of 75 or 100 mg/m<sup>2</sup> every 3 weeks. The primary endpoints were investigator-assessed PFS and safety. Key secondary endpoints included ORR, clinical benefit, overall survival, quality of life, and symptom control.

Enrollment ended in December 2009 with 137 patients, and the data were locked for analysis in April 2010, after a median follow-up of about 6 months in both treatment arms. The results showed an ORR of 32% in the T-DM1 group and 29% in the trastuzumab-docetaxel group. Clinical benefit rates were 37% and 40%, respectively.

Investigators in an ongoing multicenter clinical trial are comparing T-DM1 against the combination of capecitabine and lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab-based therapy. The phase III randomized trial began patient accrual in February and has an accrual target of 580 patients.

Patients have been randomly assigned to receive T-DM1 at a dose of 3.6 mg/kg every 3 weeks or the combination of lapatinib, 1,250 mg/d, and capecitabine,\* 1,000 mg/m<sup>2</sup> twice dai-

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ly. The primary endpoint is PFS, and secondary endpoints include overall survival and quality of life.

### Pertuzumab

Pertuzumab is a monoclonal antibody that targets HER2 to prevent communication, or dimerization, with HER3, a necessary event in the signaling that drives the growth and progression of HER2-positive breast cancer.<sup>4-8</sup> Pertuzumab is the only anti-HER2 agent developed to date that specifically targets the HER2 signaling pathway.

Pertuzumab was evaluated as neoadjuvant therapy for patients with operable or locally advanced/inflammatory HER2-positive breast cancer.<sup>9</sup> The trial protocol required every patient to receive neoadjuvant therapy, followed by surgery and then adjuvant therapy; 417 patients were randomized to receive four regimens of neoadjuvant and adjuvant therapy:

- Docetaxel-trastuzumab, followed by adjuvant FEC (5-fluorouracil, epirubicin, and cyclophosphamide) chemotherapy plus trastuzumab;
- Docetaxel, trastuzumab, and pertuzumab, followed by FEC-trastuzumab;
- Trastuzumab-pertuzumab, followed by docetaxel-trastuzumab; or
- Docetaxel-pertuzumab, followed by FEC-trastuzumab.

The primary endpoint was pathologic complete response (pCR). Secondary endpoints were clinical response, disease-free survival, breast conservation rate, and biomarker evaluation.

The neoadjuvant combination of docetaxel, trastuzumab, and pertuzumab resulted in the highest pCR rate (45.8%), which was significantly better than the response rate associated with docetaxel-trastuzumab (29.0%;  $P = 0.0141$ ) and docetaxel-pertuzumab (24.0%;  $P = 0.003$ ). The conventional docetaxel-trastuzumab regimen was superior to trastuzumab-pertuzumab, which had the lowest pCR (16.8%;  $P = 0.0198$ ).

An analysis of pCR by hormone-receptor status showed that all of the neoadjuvant regimens performed better in tumors that were negative for both estrogen and progesterone receptor status. However, the docetaxel-trastuzumab-pertuzumab combination achieved a much higher pCR in hormone receptor-negative tumors (63% vs 27%–37% for the other three regimens).

To summarize the findings of this trial, the combination of trastuzumab, pertuzumab, and docetaxel consistently resulted in the highest pCR rate. The biologic doublet of trastuzumab and pertuzumab demonstrated considerable antitumor activity without chemotherapy. Consistent with expectations, all of the neoadjuvant regimens showed greater activity in hormone receptor-negative tumors. The addition of pertuzumab was associated with good tolerability and absence of any meaningful increase in cardiac risk over the course of four cycles of neoadjuvant therapy.

Clinical evaluation of pertuzumab includes an ongoing international phase III randomized trial in patients with HER2-positive metastatic breast cancer. Known by the acronym CLEOPATRA, the trial has an accrual target of 800 patients at 250 sites worldwide. Patients are being randomized to receive docetaxel plus trastuzumab and placebo or to the combination of docetaxel, trastuzumab, and pertuzumab. The key endpoints are PFS, overall survival, and biomarker analysis.

### Neratinib

Neratinib is an orally administered irreversible pan-ErbB receptor tyrosine kinase inhibitor that targets ErbB (HER) 1, 2, and 4. Lapatinib, which also targets multiple receptor tyrosine kinases of the HER family, is a reversible inhibitor. Compared with lapatinib, neratinib has greater potency and a lower molecular weight.

Lapatinib and neratinib have been

evaluated in phase II clinical trials involving patients with HER2-positive, trastuzumab-refractory breast cancer and patients with no prior exposure to trastuzumab. In trastuzumab-refractory tumors, ORR was about 5% with lapatinib and 26% with neratinib. Among patients with HER2-positive tumors and no prior trastuzumab treatment, ORR was 35% with lapatinib and 56% with neratinib. The principal toxicity of neratinib is diarrhea, which affects about 25% of patients and can be severe.

Neratinib was evaluated in an open-label, multicenter, phase II breast cancer trial involving 66 patients with a history of treatment with trastuzumab and 70 patients with no prior exposure to the agent.<sup>10</sup> The patients received 240 mg of neratinib daily, and the primary endpoint was 16-week PFS, as determined by independent review. Analysis of the primary endpoint showed a 16-week PFS of 78% among patients with no prior exposure to trastuzumab and 59% for patients previously treated with the monoclonal antibody. The overall response rates were 24% and 56%, respectively, in patients with and without prior trastuzumab treatment.

Neratinib was evaluated in another trial involving patients with HER2-expressing metastatic breast cancer.<sup>11</sup> Some patients received neratinib as first-line therapy, whereas others had been treated with as many as three prior regimens. Patients received a 240-mg daily dose of the HER2 inhibitor along with 80 mg/m<sup>2</sup> of paclitaxel. Treatment was associated with objective responses in 61 of 97 evaluable patients, resulting in an overall response rate of 67%. Subgroup analysis showed that 43 of 60 patients (72%) with prior exposure to a taxane drug had an objective response, as did 55 of 97 patients (57%) with prior trastuzumab exposure and 9 of 13 patients (69%) previously treated with lapatinib.

Investigators in several ongoing clinical trials are evaluating neratinib in several settings of HER2-positive breast cancer. In a randomized phase II trial sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP), patients with locally advanced breast cancer will receive neoadjuvant therapy with weekly paclitaxel plus neratinib or trastuzumab, followed by doxorubicin and cyclophosphamide, surgery, and adjuvant trastuzumab.

Investigators in another trial are evaluating neratinib as extended adjuvant therapy in patients with early breast cancer (stages II–IIIC) already treated with trastuzumab. Patients are being randomized to receive treatment with neratinib or placebo and are being followed for 1 year.

### Novel evaluation of trastuzumab

The emergence of other HER2-targeted therapies does not mean that trastuzumab will disappear from clinical use anytime in the near future. In fact, the NSABP has launched a randomized phase III clinical trial to evaluate a novel use of trastuzumab. The trial will involve patients who have early breast cancer with low-level HER2 expression, defined as 1+ or 2+ staining by immunohistochemistry and negative by fluorescence in situ hybridization.

Patients in both arms will receive the same standard postoperative chemotherapy: docetaxel-cyclophosphamide or doxorubicin-cyclophosphamide followed by paclitaxel. One group will also receive trastuzumab for a year after completing chemotherapy. If trastuzumab results in a significant benefit compared with chemotherapy alone, the potential patient population with indications for this anti-HER2 antibody could expand substantially.

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# Recent developments in therapy for gastrointestinal cancers

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**G**astrointestinal (GI) oncology comprises a diverse group of diseases affecting an extensive area of the body. The discussion that follows will focus on four topics: adjuvant therapy for colon cancer, palliative care for metastatic colorectal cancer, gastroesophageal cancer, and pancreatic cancer.

## Adjuvant therapy for colon cancer

Risk assessment related to adjuvant therapy is complicated by the fact that some patients with stage II colon cancer—such as T4bN0—have a worse prognosis than patients with certain types of stage III colon cancer.<sup>1</sup> As a result, some patients with stage II disease might require adjuvant therapy, and some with stage III colon cancer might not. Making that distinction is no simple matter.

For years, 5-fluorouracil (5-FU) represented the standard of care for adjuvant therapy in colon cancer. Efforts to move beyond 5-FU have met with mixed results. Evaluations of oxaliplatin- and capecitabine-based regimens as substitutes for 5-FU have yielded positive results. On the other hand, evaluations of irinotecan, bevacizumab, and cetuximab have had negative outcomes.

Although oxaliplatin-based therapy has improved colon cancer outcomes compared with 5-FU, not all patients, particularly older patients, have benefited. In a pooled analysis of data from two large clinical trials, patients were stratified by age (< 70 years vs ≥ 70 years).<sup>2</sup> As shown in Table 1, younger patients derived significant benefit from oxaliplatin-based therapy, with respect to disease-free survival (DFS), overall survival (OS), and time to recurrence (TTR). In contrast, the hazard ratios (HRs) for DFS and OS trended in favor of the 5-FU arm among older patients, and TTR was similar between arms. Moreover, the 6-month mortality among older patients was almost twice as high in the oxaliplatin group, although the difference from the control arm did not achieve statistical significance.

### *Bevacizumab*

The role of targeted agents in GI cancers has been the subject of multiple clinical studies. Investi-

gators in two large, multicenter randomized clinical trials evaluated adjuvant bevacizumab in patients with stages II–III colon cancer.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 trial involved 2,710 patients, all of whom received oxaliplatin-based chemotherapy and were then randomized to receive treatment with placebo or bevacizumab.<sup>3</sup> Treatment with bevacizumab began concurrently with chemotherapy and continued for 12 months, 6 months after chemotherapy ended. Patients randomized to receive bevacizumab had a 3-year DFS of 77.4%, compared with 75.5% for chemotherapy alone, a difference that translated into a nonsignificant 11% reduction in HR ( $P = 0.15$ ).<sup>3</sup>

Similar results emerged from the AVANT (AVAstin adjuvaNT) trial, which involved 3,451 patients with stage III or high-risk stage II colon cancer.<sup>4</sup> The randomized trial had three treatment arms: oxaliplatin-based chemotherapy alone; the same chemotherapy plus bevacizumab, 5 mg/kg during chemotherapy followed by 7.5 mg/kg for 6 months; and capecitabine-oxaliplatin chemotherapy plus bevacizumab, 7.5 mg/kg during chemotherapy and for 6 months afterward. The primary endpoint was DFS among patients with stage III disease. When the trial ended, both bevacizumab arms had HRs trending toward worse DFS compared with chemotherapy alone.

To gain more insight into the AVANT results, investigators analyzed the primary outcome (DFS) as a function of time, specifically, the time from randomization (Figure 1). During the first year, bevacizumab-treated patients had a substantially better DFS than did the control arm, reflected in HRs of 0.63 and 0.61. By 18 months,

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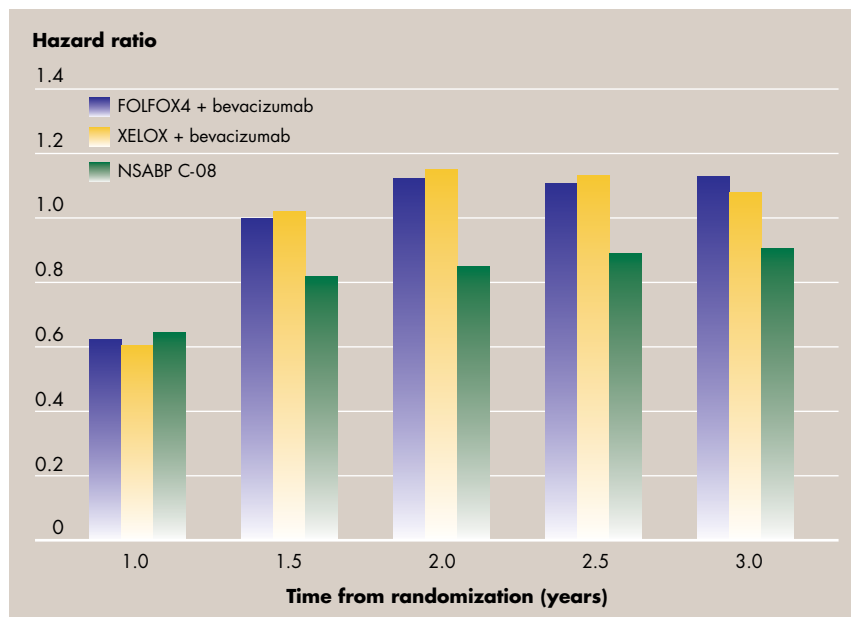
TABLE 1

## Efficacy of FOLFOX by age

Age	Number	Hazard ratio (95% CI), expl vs ctrl <sup>a</sup>			Deaths within 6 mo, expl vs ctrl, %
		DFS	OS	TTR	
< 70 yr	3,977	0.77 (0.68, 0.86)	0.81 (0.71, 0.93)	0.76 (0.67, 0.86)	0.81 vs 0.81 ( <i>P</i> = 1.0)
≥ 70 yr	703	1.04 (0.80, 1.35)	1.19 (0.90, 1.57)	0.92 (0.69, 1.23)	2.57 vs 1.37 ( <i>P</i> = 0.25)

FOLFOX = folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin; CI = confidence interval; expl = experimental arm; ctrl = control arm; DFS = disease-free survival; OS = overall survival; TTR = time to recurrence  
<sup>a</sup>Endpoint; values < 1 favor the experimental arm over the control arm (IV 5-FU)

Adapted, with permission, from Jackson McCleary et al<sup>2</sup>



**FIGURE 1** Disease-free survival as a function of time from randomization. FOLFOX4 = folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin; XELOX = capecitabine and oxaliplatin; NSABP = National Surgical Adjuvant Breast and Bowel Project. From De Gramont et al<sup>4</sup> and Alberts et al.<sup>5</sup>

the HR for both bevacizumab arms had surpassed 1.0 and remained there to the end of follow-up. Thus, patients derived a substantial benefit during the bevacizumab treatment period, but the benefit disappeared after bevacizumab treatment ended. The NSABP C-08 trial showed a similar trend (Figure 1), although the HR remained < 1.0 after the use of bevacizumab was discontinued.

Analysis of OS in AVANT also showed no benefit from treatment with bevacizumab and possibly some harm. The HR in both bevacizumab groups was about 30% higher than in the chemotherapy-alone group.<sup>4</sup>

The rapid decline in benefit after discontinuation of bevacizumab has led to discussions about a possible rebound effect that makes tumors more aggressive.

One potential explanation for the AVANT findings relates to use of additional therapy after disease recurrence. DFS factors in all deaths, including those that occur after recurrence. An examination of the palliative therapies that patients received after recurrence showed that patients were more likely to receive bevacizumab if it had not been part of their adjuvant therapy before.<sup>4</sup> This imbalance in post-recurrence treatment se-

lection might well have influenced both DFS and OS.

### Cetuximab

Considerable enthusiasm surrounded the launch of an adjuvant trial involving the targeted agent cetuximab. Available science suggested that adding cetuximab to chemotherapy would improve outcomes in patients with stage III colon cancer and the wild-type *KRAS* gene. Instead, treatment with chemotherapy alone was associated with better DFS in patients with both wild-type and mutated *KRAS* genes.<sup>5</sup>

The negative outcome of the cetuximab trial led to discussion and speculation about potential explanations. Adjuvant therapy targets micrometastases. Studies involving experimental models suggest that cancer cells may evade systemic therapy by means of epithelial mesenchymal transition.<sup>6</sup> The cells transform their gene-expression profile and appearance and, in the process, might terminate epidermal growth factor receptor (EGFR) expression, which normally is ubiquitous among epithelial cancers. In effect, the cells shed the target of therapy.

### Tumors with dMMR

High-risk stage II colon cancer also has posed a challenge to chemotherapy, so much so that oncologists often consider the subset equivalent to stage III in terms of risk. Markers of high-risk stage II colon cancer include T4N0 disease and the number of lymph nodes examined. On the other hand, a deficiency in mismatch repair enzyme expression portends a favorable prognosis.<sup>7</sup> When there is uncertainty about the need to treat stage II disease, testing for mismatch repair deficiency (dMMR) can provide valuable guidance. Tumors with dMMR affect about 15% of all patients with colon cancer and have about a 70% reduction in the risk

of recurrence.<sup>8</sup> These patients have a 5-year recurrence risk of 5% and do not require systemic therapy.

### Treatment for metastatic colon cancer

Treatment paradigms for metastatic colorectal cancer have continued to evolve as new therapeutic candidates and options have been developed and evaluated. The evolution has brought about the recognition that some patients with stage IV disease can be cured by an interdisciplinary approach to treatment. In the palliative setting, commonly used chemotherapy combinations (FOLFOX, XELOX, FOLFIRI) achieve similar results. The XELIRI regimen (capecitabine plus irinotecan) has overlapping toxicities that can be problematic. Most patients with stage IV colorectal cancer can tolerate a two-drug combination but do not necessarily need combination therapy. The addition of biologic agents, notably bevacizumab, to chemotherapy has improved outcomes but not to the extent that had been hoped.

The current status of treatment paradigms (Table 2) is one of refinement, not breakthroughs. However, the use of molecular predictive markers has brought the field to the brink of individualized therapy, which could revolutionize treatment of metastatic colorectal cancer.

Experience with conventional chemotherapy has given rise to the concept that patients derive maximal benefit from exposure to all three drugs with proven activity in the metastatic setting: 5-FU, oxaliplatin, and irinotecan.<sup>9</sup> In most cases, the benefit reaches a plateau after about 2 years. The addition of biologic agents to chemotherapy has moved the therapeutic potential beyond that plateau.

#### Bevacizumab

Adding the angiogenesis inhibitor bevacizumab to chemotherapy raised the standard for therapeutic

**TABLE 2**

### Treatment paradigms for metastatic colorectal cancer

- Some patients with stage IV disease can be cured by an interdisciplinary approach
- In the palliative setting: FOLFOX = XELOX = FOLFIRI (XELIRI has problems with toxicity)
- Most patients tolerate a chemotherapy doublet, *but not all need it*
- The addition of biologics to chemotherapy has improved outcomes, *but not as much as we hoped*
- We are on the verge of individualized therapy based on molecular predictive factors

efficacy in metastatic colorectal cancer. A landmark phase III clinical trial showed a dramatic effect on OS, progression-free survival (PFS), objective response rate, and duration of response rate compared with chemotherapy alone.<sup>10</sup>

As more potent chemotherapy regimens have emerged, adding bevacizumab has led to a more modest improvement in key clinical outcomes.<sup>11</sup> Moreover, clinical experience with bevacizumab and chemotherapy has revealed potential problems with toxicity, particularly in oxaliplatin-containing regimens. Because of cumulative toxicity, fewer patients remain on therapy over time. Patients who remain on therapy continue to benefit from the addition of bevacizumab, so duration of therapy has become a key consideration in the treatment of metastatic colorectal cancer.<sup>12</sup>

#### EGFR inhibitors

As compared with bevacizumab, drugs that inhibit EGFR have a more direct or targeted effect on cancer. EGFR inhibitors target specific signaling pathways involved in tumor progression. Clinical experience with drugs in this class has shown that patients whose tumors bear *KRAS* mutations (about 40% of all patients with colorectal cancer) do not benefit from EGFR inhibition. In contrast,

patients whose tumors have wild-type *KRAS* have significant improvement in survival when treated with an EGFR inhibitor.<sup>13</sup>

The impact of *KRAS* status was demonstrated clearly in a clinical trial that evaluated conventional chemotherapy alone or in combination with the EGFR inhibitor cetuximab.<sup>14</sup> In the intention-to-treat analysis, patients treated with cetuximab had a modest, though statistically significant, improvement in response rate and PFS, and the benefit appeared late. A prespecified subgroup analysis by *KRAS* status showed a substantially greater effect of cetuximab in patients with wild-type *KRAS* tumors, including almost a 60% improvement in 1-year PFS.<sup>14</sup> Similar results emerged from a large randomized clinical trial comparing chemotherapy alone or in combination with panitumumab.<sup>15</sup> Other clinical trials, however, have yielded confounding results with the addition of an EGFR inhibitor to chemotherapy. In one study, patients with colorectal cancer bearing wild-type *KRAS* derived no significant benefit from the combination of chemotherapy and cetuximab.<sup>16</sup>

Taken together, the phase III trials of add-on therapy with an EGFR inhibitor would appear to yield a null result. In fact, the magnitude of the benefit from EGFR inhibition, if any, appears to depend on the patient population. Use of an EGFR inhibitor in a more selected group of patients, ie, later in the treatment paradigm, appears to offer the most benefit.

The major clinical trials of EGFR inhibitors in metastatic colorectal cancer have demonstrated that testing for *KRAS* status before starting therapy is essential. The data from trials of first- and second-line therapies have consistently shown that wild-type *KRAS* tumors are more susceptible to EGFR inhibition and that *KRAS*-mutant tumors are relatively insensitive.

Most patients with metastatic

colorectal cancer are in a palliative setting. The principal concerns are prolonging survival and preserving quality of life. Given those realities, bevacizumab represents a better option than EGFR inhibition for most patients. Bevacizumab offers more consistent efficacy and has a more favorable toxicity profile.

### Esophageal and gastric cancers

Both of these cancers remain relatively uncommon in the United States, but their epidemiology is going in opposite directions. The incidence of esophageal cancer, cancer of the gastroesophageal junction (GEJ), and cancer of the cardia has increased 300% over the past 10 years.<sup>17</sup> The rise has coincided with increased prevalence of obesity, gastroesophageal reflux disease, and Barrett's esophagus, in addition to the conventional risk factors of tobacco and alcohol use. In contrast, the incidence of gastric cancer has decreased, especially the proportion of squamous cell cancers. Mortality remains high for both types of cancer: 88% for esophageal cancer and 50% for gastric cancer.

Results of two recent clinical trials have established a role for biologic therapy for gastric cancer. Between 20% and 30% of gastric cancers overexpress the human epidermal growth factor receptor 2 (HER2). The Trastuzumab in Gastric Cancer (ToGA) trial expanded the concept of targeting HER2 expression from breast cancer to gastric cancer.<sup>18</sup> Patients were screened for HER2 expression, and those with HER2-positive tumors were randomized to receive treatment with chemotherapy (5-FU or capecitabine plus cisplatin) with or without trastuzumab. The primary endpoint was OS.

The data were stratified by tumor histology (intestinal, diffuse, or mixed) and by localization (GEJ or gastric). A higher proportion of intestinal-type tumors and cancers of the

GEJ exhibit HER2 overexpression. The results showed that the addition of trastuzumab to chemotherapy significantly increased median OS from 11.1 months to 13.8 months, representing a 26% reduction in HR ( $P = 0.0046$ ).<sup>18</sup> Patients in the trastuzumab arm also experienced improvement in PFS, a secondary endpoint (6.7 months vs 5.5 months;  $P = 0.0002$ ).

Analysis of survival data by HER2 expression solidified the rationale for targeting HER2. The largest difference in OS was observed among patients who had 3+ overexpression by immunohistochemistry (IHC 3+) and who were also positive by fluorescence in situ hybridization (FISH): 17.9 months versus 12.3 months, a 42% reduction in HR. In contrast, patients with IHC 3+/FISH- tumors had an almost identical median OS regardless of whether they received trastuzumab.<sup>18</sup>

An exploratory analysis aimed at identifying the optimal patient population for trastuzumab showed that patients with IHC 2+/FISH+ or IHC 3+ tumors had a median OS of 16.0 months with trastuzumab versus 11.8 months with chemotherapy alone, which translated into a 35% reduction in HR. Moreover, survival curves separated early, reflecting the added benefit of trastuzumab.<sup>18</sup>

Another key trial examined the addition of bevacizumab to capecitabine-cisplatin chemotherapy for patients with locally advanced or metastatic gastric cancer.<sup>19</sup> The primary endpoint was OS, and the results failed to demonstrate a benefit of adding bevacizumab to chemotherapy. The median OS was 12.1 months with bevacizumab and 10.1 months with placebo ( $P = 0.1002$ ). PFS was significantly different in favor of the bevacizumab arm (6.7 months vs 5.3 months;  $P = 0.0037$ ), suggesting some level of activity. Moreover, overall response rate showed a significant advantage for bevacizumab therapy (46% vs 37%;  $P = 0.0315$ ).

Analysis of the data by geographic region further complicated interpretation of the results. Patients from Asia, who constituted half of the study population, derived no benefit from bevacizumab. European patients had a modest improvement in survival with bevacizumab, and patients from Latin American had significant improvement when bevacizumab was added to chemotherapy. Whether these observations warrant another large randomized clinical trial remains under consideration.

### Pancreatic cancer

Pancreatic cancer continues to have a dismal prognosis, despite multiple efforts to develop more effective therapy and to identify biomarkers that would lead to diagnosis of more patients with early-stage disease. However, French investigators reported truly practice-changing results at the 2010 American Society of Clinical Oncology meeting.<sup>20</sup> The trial involved 342 patients with metastatic pancreatic cancer, randomized to receive standard therapy with gemcitabine\* or combination chemotherapy with 5-FU,\* leucovorin,\* oxaliplatin,\* and irinotecan\* (FOLFIRINOX).

Not surprisingly, FOLFIRINOX was associated with significantly more hematologic toxicity, including neutropenia (79.9% vs 54.8%;  $P = 0.0001$ ); febrile neutropenia (7.2% vs 2.4%;  $P = 0.009$ ); and thrombocytopenia (75.2% vs 54.8%;  $P = 0.008$ ). More than 40% of patients in the experimental arm needed growth factor support, compared with 5.3% in the gemcitabine arm. However, only one toxic death occurred in each treatment group.

The FOLFIRINOX regimen was associated with an overall response rate of 31.6%, compared with 9.4% with gemcitabine ( $P = 0.0001$ ). The overall disease control rate (response plus stable disease) was 70.2% with FOLFIRINOX and 50.9% with

\* Indicates unlabeled/investigational use of commercial products.

gemcitabine ( $P = 0.0003$ ). Median PFS was 6.4 months with the experimental therapy and 3.3 months with gemcitabine, representing a 53% reduction in HR ( $P < 0.0001$ ). Similarly, patients treated with FOLFIRINOX had a significantly longer median survival of 11.1 months versus 6.8 months with gemcitabine, a 43% reduction in HR ( $P < 0.0001$ ).<sup>20</sup>

Results of the French trial have generated unparalleled optimism that the prognosis for this terrible disease can be improved. To put the findings into proper context, consider that the PFS with the experimental FOLFIRINOX regimen was similar to the OS with gemcitabine. Already, some pancreatic cancer specialists have begun discussions about using the FOLFIRINOX regimen as neoadjuvant therapy for patients with resectable disease.

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# Meshing the new and the traditional in lymphoma therapy

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The field of lymphoma has entered an era of rapid evolution, fueled in large part by ongoing advances in biochemistry that continually reveal pathways to new targets for therapeutic development. Several promising therapeutic candidates have emerged, particularly in the field of antibody conjugates. However, tradeoffs between clinical response and adverse events have yet to be fully defined. Moreover, traditional therapies, such as rituximab, will continue to play a role in the management of lymphoma. Future therapeutic developments will build on the progress of the past 2 decades, which has seen 10-year survival for low-grade lymphoma improve from 52% during 1990–1992 to 72% during 2002–2004 (Table 1).<sup>1</sup>

## Key results from recent studies

### *Asymptomatic follicular lymphoma*

Investigators in an intergroup trial compared rituximab\* with a strategy of watchful waiting in 462 patients with asymptomatic, nonbulky, stages II–IV follicular lymphoma.<sup>2</sup> Patients allocated to rituximab received four weekly doses, and half of the patients received rituximab maintenance therapy once every 2 months for 2 years. The primary endpoint was the time to initiation of chemotherapy or radiation therapy.

The time to new therapy and progression-free survival (PFS) favored the rituximab groups. However, the results showed no difference in overall survival as of December 2010, as reported at the American Society of Hematology (ASH) annual meeting.<sup>2</sup> Quality-of-life data were not reported. The results did show a 5% incidence of adverse events among patients treated with rituximab, including hypogammaglobulinemia associated with chronic sinusitis. The observation raised the question of whether such patients require monitoring and periodic measurement of gamma globulin levels. Of note, patients allocated to watchful waiting had a 33-month median time to new therapy, providing useful information about that clinical management strategy.

**TABLE 1**

Ten-year survival for low-grade lymphoma

Age, yr	Survival, %	
	1990–1992	2002–2004
15–44	64	84
45–54	59	81
55–64	54	73
65–74	49	70
≥ 75	31	49
Total	52	72

Adapted, with permission, from Pulte et al<sup>1</sup>

### *Relapsed/refractory lymphoma*

The clinical activity of the anti-CD40 antibody lucatumumab (HCD122) was assessed in patients with relapsed or refractory lymphoma, either Hodgkin's lymphoma or non-Hodgkin's lymphoma (NHL).<sup>3</sup> All 43 patients in the study had received more than one prior regimen. Objective responses were observed in 4 of 12 patients with follicular lymphoma, 2 of 13 patients with diffuse large B-cell lymphoma (DLBCL), and 3 of 18 patients with Hodgkin's lymphoma, resulting in an overall response rate (ORR) of 22% (9 of 41 patients). The therapy was associated with minimal toxicity.

### *Combination therapy for lymphomas*

Investigators in a multicenter randomized clinical trial evaluated two rituximab-containing combinations in 219 patients with relapsed follicular, indolent, and mantle cell lymphomas.<sup>4</sup> Patients received either bendamustine or fludarabine\* paired with rituximab. The bendamustine regimen led to

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\* Indicates unlabeled/investigational use of commercial products.

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striking improvement in outcomes compared with fludarabine-rituximab: PFS, 30 months vs 11 months; ORR, 83% vs 52%; complete response (CR) rate, 38% vs 16%. The type, frequency, and severity of adverse events did not differ between treatment groups.

Investigators performed an unplanned analysis of 40 patients who received rituximab maintenance therapy, independently of randomized therapy. The analysis showed a trend toward improved survival with maintenance rituximab.

#### *Treatment-refractory indolent lymphoma*

The antibody conjugate inotuzumab ozogamicin (CMC-544) was evaluated in 43 patients with indolent B-cell NHL refractory to rituximab, rituximab plus chemotherapy, or radioimmunotherapy.<sup>5</sup> The conjugate consists of an anti-CD22 antibody linked to the calicheamicin toxin and induces double-stranded DNA breaks.

Eighteen of the 43 patients had proved refractory or resistant to more than three prior regimens. Six-month results showed an ORR of 53%, including CRs in 19%, and a PFS of 59%. The principal toxicities were myelosuppression and abnormal liver function tests. About one-fourth of the patients had to stop therapy because of the toxicities, as prescribed in the study protocol, but the conditions resolved spontaneously upon discontinuation of therapy.

#### *Radioimmunotherapy for follicular lymphoma*

Patients with previously untreated symptomatic, stages II–IV follicular lymphoma received a single dose of <sup>90</sup>yttrium ibritumomab tiuxetan.<sup>6</sup> Analysis of 6-month data on 59 patients showed CRs in 25 patients and partial responses (PRs) in 22, resulting in an ORR of 85%. The response rate was 72% at 1 year, con-

sisting of CRs in 52% of patients and PRs in 20%. After a median follow-up of 23 months, the median PFS was 17.9 months.

The study is noteworthy because clinicians tend to reserve radioimmunotherapy until late in the clinical course of a patient with lymphoma. These results suggest that radioimmunotherapy deserves earlier consideration, possibly even as first-line therapy.

#### *Advanced DLBCL*

Patients with advanced DLBCL received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus rituximab (R-CHOP) chemotherapy plus the angiogenesis inhibitor bevacizumab.<sup>7</sup> The bevacizumab-containing regimen resulted in a 1-year PFS of 77% among 64 patients, about the same as what would be expected with the standard R-CHOP regimen. However, the addition of bevacizumab to R-CHOP was associated with severe adverse events that included 2 sudden deaths, 5 gastrointestinal perforations, 5 cases of deep-vein thrombosis, 7 cases of severe hypertension, and 13 cases of left ventricular dysfunction. Consequently, no further studies of this regimen are planned.

#### *Peripheral T-cell lymphoma*

Investigators enrolled 131 patients with progressive or relapsed peripheral T-cell lymphoma (PTCL) in a phase II evaluation of the histone deacetylase (HDAC) inhibitor romidepsin, one of two drugs with FDA approval for PTCL (the other being pralatrexate, an antifolate).<sup>8</sup> Romidepsin was administered by IV infusion three times every 28 days for a maximum of six cycles of therapy.

The ORR of 27% was not particularly impressive, but the response duration was. With a median follow-up of 8.2 months, the median duration of response had yet to be reached. Prominent adverse events included nausea,

**TABLE 2**

#### Dasatinib in relapsed or refractory NHL

- Inhibits BCR-ABL, SRC, c-KIT, PDGF receptors ( $\alpha$  and  $\beta$ ), and ephrin (EPH) receptor kinases
- 100–200 mg daily
- N = 27 patients
- Two patients with T-cell NHL: both achieved a complete response and remained in remission for over 2 years
- Adverse events: pleural effusion, myelosuppression

NHL = non-Hodgkin's lymphoma

Adapted, with permission, from William et al<sup>9</sup>

vomiting, myelosuppression, gastrointestinal disturbances, and fever, which led to a treatment discontinuation rate of 17%.

#### *Targeted therapy for relapsed/refractory NHL*

Dasatinib,\* a multitargeted tyrosine kinase inhibitor, was evaluated in a phase I/II clinical trial involving patients with relapsed or refractory NHL (Table 2).<sup>9</sup> Investigators enrolled 27 patients who had progressive or recurrent disease in response to treatment with one or more prior regimens. Of 19 patients evaluable for response, 2 patients (11%), both with PTCL, had a CR that lasted for more than 2 years. Additionally, four patients (21%) had a PR, and eight patients (42%) had stable disease. The PFS was 17% at 1 year and 13% at 2 years. Overall survival was 60% at 1 year and 50% at 2 years. Notable adverse events included myelosuppression and pleural effusion.

#### *Early, unfavorable Hodgkin's lymphoma*

The German Hodgkin Study Group conducted a multicenter trial involving 1,655 patients with stages I–IIA Hodgkin's lymphoma with unfavorable characteristics (bulky disease, elevated sedimentation rate).<sup>10</sup> Patients were randomized to receive either four cycles of the multidrug ABVD (doxorubicin, bleomycin, vin-

blastine, dacarbazine) chemotherapy regimen or two cycles of dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy followed by two cycles of ABVD. All patients received involved-field radiation therapy.

The BEACOPP regimen was associated with an ORR of 95%, compared with 89% with ABVD. However, dose-escalated BEACOPP proved to be considerably more toxic, with an adverse event rate of 87%, compared with 51% with four cycles of ABVD. Despite the added toxicity, the investigators proclaimed the BEACOPP regimen the new standard of care in Germany for unfavorable Hodgkin's lymphoma.

#### *Extensive/advanced Hodgkin's lymphoma*

The ABVD regimen emerged from a cooperative group trial as the continued standard of care for locally extensive and advanced-stage Hodgkin's lymphoma.<sup>11</sup> Conducted by the Eastern Cooperative Oncology Group, the trial compared ABVD and the multimodality Stanford V regimen in 812 patients (Table 3). Both regimens resulted in CR rates of about 70%, with PRs in 7%–8% of patients and stable disease in 8%–10% of patients. The Stanford V regimen was associated with a higher incidence of grade 3 lymphopenia and of grade 3/4 peripheral neuropathy.

#### *Older patients with Hodgkin's lymphoma*

Investigators from the German Hodgkin Study Group analyzed data on subgroups of 68 and 49 patients older than 60 years who participated in two clinical trials of early-stage Hodgkin's lymphoma.<sup>12</sup> Patients older than 60 years account for about 20% of all Hodgkin's lymphoma patients. All patients received four cycles of ABVD chemotherapy.

The ORR was 90%–92%, and the

**TABLE 3**

#### ECOG E2496: ABVD vs Stanford V

- N = 812 patients
- ABVD given for 6–8 weeks vs Stanford V for 12 weeks (XRT > 5 cm)
- Complete response rate (~ 70%) same
- Five-year overall survival: 88% for ABVD vs 87% for Stanford V
- Adverse events: Stanford V associated with more grade 3 lymphopenia and grade 3/4 peripheral neuropathy
- Conclusion: ABVD remains the standard of care

ECOG = Eastern Cooperative Oncology Group; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; XRT = X irradiation

Adapted, with permission, from Gordon et al<sup>11</sup>

number of patients who achieved a CR was similar to that observed in younger patients. However, the older patients had high rates of adverse events, which frequently were severe. During a median follow-up of 92 months, 37% of the over-60-year-old patients in one of the trials and 22% in the other died of the disease or treatment-related toxicity. The 5-year PFS was 79% for the older patients versus 96% among younger patients in the same trials.

#### *Relapsed/refractory Hodgkin's lymphoma*

Although Hodgkin's lymphoma represents a success story in oncology, some patients do relapse or develop treatment-refractory disease. Patients with relapsed or refractory Hodgkin's lymphoma receive a variety of therapies, but no clear standard exists. Investigators in a multinational trial evaluated the antibody-drug conjugate brentuximab vedotin (SGN-35) in 102 patients, 70% of whom had relapsed within 3 months.<sup>13</sup> All of the patients had previously undergone autologous stem cell transplantation.

Brentuximab vedotin consists of an anti-CD30 antibody fused to the toxin monomethyl auristatin E. The antibody binds to the surface of malignant CD30-positive cells and releases the toxin inside the cells.

The treatment resulted in an ORR of 95%, including CRs in 34% of patients. More than 80% of patients treated with brentuximab vedotin had a decrease in constitutional symptoms. The median time on study was 27 weeks. Adverse events included peripheral neuropathy, myelosuppression, diarrhea, and fever, none of which proved to be dose limiting.

#### *Relapsed/refractory anaplastic large-cell lymphoma*

Investigators in another multinational trial reported results from an evaluation of brentuximab vedotin in patients with relapsed or refractory anaplastic large-cell lymphoma.<sup>14</sup> The report included 30 of 58 patients enrolled thus far. The ORR was 87%, including CRs in 57% of patients. The patients in the trial had received a median of two prior regimens, and eight had an unsuccessful autologous stem cell transplant. Adverse events included peripheral neuropathy and myelosuppression, which was not dose limiting.

#### *Heavily pretreated relapsed/refractory Hodgkin's lymphoma*

This phase II study included 129 patients, all of whom had undergone autologous stem cell transplantation. Most had relapsed or progressed on more than four prior regimens.<sup>15</sup> The patients received panobinostat,\* a potent HDAC inhibitor, three times weekly. The ORR was 27%, and the time to response averaged 7.4 weeks. PFS was 5.7 months. The somewhat modest activity should be considered within the context of a heavily pretreated patient population with limited treatment options.

#### *Relapsed/refractory NHL*

The oral PI3-kinase inhibitor CAL-101 was evaluated in 55 patients with relapsed or refractory NHL.<sup>16</sup> The therapy resulted in an ORR of 62% in a population that included patients with indolent and mantle cell

lymphoma. The PFS was 6–16 months in patients with indolent lymphoma and 1–8 months in patients with mantle cell lymphoma. The therapy was well tolerated.

## Conclusion

Results of these and other clinical trials reported at the 2010 ASH meeting reflect the view of lymphoma emerging from ongoing basic and clinical research. Evolving treatment paradigms increasingly will integrate immunotherapeutic agents without discarding the potential benefits afforded by traditional chemotherapy.

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# Emerging therapeutic options for advanced non-small cell lung cancer

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**S**ystemic therapy for non-small cell lung cancer (NSCLC) has evolved rapidly within the past decade. Clinicians have multiple options for first-line therapy, and the standard of care continues to change as new agents and new data become available. The concept of maintenance therapy has followed the expansion of options for first-line treatment. Although maintenance therapy has supporters in oncology, the topic remains controversial because, until recently, no clinical trial has demonstrated a survival advantage with maintenance therapy. The discovery that NSCLC often expresses the epidermal growth factor receptor (EGFR) has established a therapeutic role for EGFR inhibitors, which have been shown to extend survival in patients with EGFR-positive NSCLC. Despite the advances in therapy, the long-term prognosis remains poor for most patients and fuels the ongoing search for more effective treatments.

## First-line treatment options

Although the long-term outlook remains poor for lung cancer, advances in treatment have improved survival in the short term. Prior to 1980, treatment was limited to alkylating agents, which were associated with a 1-year survival of 12%–15%. During the 1980s, cisplatin-based doublets improved 1-year survival to about 25%. In the 1990s, new platinum-based doublets were associated with further improvement in 1-year survival to about 35%. Since the middle of the past decade, other agents have begun to show promise for improving the long-term outlook in NSCLC.

### *The role of histology*

The histology of NSCLC has established a dividing point for treatment options. About 25% of NSCLCs are squamous cell cancers, and the remaining 75% have a nonsquamous histology. In most cases, squamous cell cancers are best treated with platinum-based therapy. Commonly used doublets include cisplatin or carboplatin paired with paclitaxel, docetaxel,\* gemcitabine,\* or vinorelbine.

For patients with nonsquamous NSCLC, the treatment pathway begins with *EGFR* mutation status. About 20% of nonsquamous tumors have *EGFR* mutations and will be treated with *EGFR* tyrosine kinase inhibitors. The 80% of patients with wild-type *EGFR* are further divided into those with and without hemoptysis. Patients with no hemoptysis often receive carboplatin plus paclitaxel and bevacizumab or a platinum agent plus pemetrexed. Nonsquamous NSCLC with hemoptysis usually is treated most effectively with the combination of a platinum agent and pemetrexed.

### *Bevacizumab*

In the middle of the past decade, the introduction of bevacizumab for treatment of nonsquamous NSCLC represented another advance. Half of patients treated with platinum-based chemotherapy combined with this angiogenesis inhibitor are alive at 1 year. Two randomized clinical trials played a pivotal role in establishing bevacizumab as a component of first-line therapy for NSCLC: Eastern Cooperative Oncology Group (ECOG) 4599 and the Avastin in Lung Cancer (AVAIL) trial.

In ECOG 4599, patients in both arms of the trial received paclitaxel-carboplatin chemotherapy and were randomized to receive bevacizumab or placebo.<sup>1</sup> The primary outcome was overall survival (OS). The results showed that the addition of bevacizumab was associated with significant improvement in survival at 12 months compared with placebo (51.0% vs 44.4%) and 24 months (22.0% vs 15.4%). The difference translated into a 20% reduction in the risk of death (hazard ratio [HR], 0.80;

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$P = 0.003$ ). Median OS was 12.3 months with bevacizumab and 10.3 months without it.

The AVAIL trial had a design similar to that of ECOG 4599 but employed a cisplatin-gemcitabine doublet.<sup>2</sup> Patients were randomized to receive bevacizumab (7.5 or 15 mg/kg) or placebo in addition to chemotherapy, and the primary endpoint was progression-free survival (PFS). When the trial ended, median PFS was 6.7 months in the bevacizumab 7.5 mg/kg arm and 6.5 months in the bevacizumab 15 mg/kg arm, both of which were significantly better than the 6.1-month median PFS for patients who received placebo ( $P = 0.00026$  and  $P = 0.0301$ , respectively). Median OS, the secondary endpoint, did not differ significantly, ranging from 13.1 months to 13.6 months in the three groups.

#### *Pemetrexed*

Another recent development has been the emergence of pemetrexed as a potential option for first-line treatment of NSCLC. Pemetrexed is a multitargeted antifolate agent that primarily targets thymidylate synthase. Encouraging results have come from a phase II trial that evaluated carboplatin-pemetrexed chemotherapy plus bevacizumab.<sup>3,4</sup> Patients initially received bevacizumab maintenance therapy, which later was changed to maintenance with both bevacizumab and pemetrexed. Although small ( $n = 51$ ), the trial demonstrated a 55% overall response rate (ORR) and a median OS of 14 months. The regimen was associated with a fairly modest amount of grade 3/4 toxicity, including hematologic and nonhematologic toxicities.

An ongoing 900-patient randomized trial should provide answers about the role of pemetrexed in first-line therapy for advanced NSCLC. In one group, patients receive pemetrexed, carboplatin, and bevacizumab, followed by maintenance therapy with both pemetrexed and bevacizumab. The second

group receives paclitaxel, carboplatin, and bevacizumab, followed by maintenance therapy with bevacizumab alone. The primary endpoint is OS. The trial began enrollment in December 2008 and has an anticipated completion date of January 2012.

### Contemporary issues

The search for optimal first-line chemotherapy for advanced NSCLC has addressed several key questions along the way. Each answer has helped provide focus for future investigations.

#### *Cycles of therapy*

Multiple studies extending back more than 20 years have addressed this issue with respect to platinum-based chemotherapy. Most often, the studies have compared three or four cycles of therapy versus six. To date, no trial has shown a survival benefit with extended-duration chemotherapy, either individually or with pooled data from all of the trials.

#### *Nonplatinum maintenance therapy*

Four trials have addressed this issue since 2003: one evaluated paclitaxel maintenance, two evaluated gemcitabine maintenance, and one evaluated maintenance with either gemcitabine or erlotinib.<sup>5-8</sup> Two of the trials showed that maintenance therapy with the nonplatinum agent slowed the progression of NSCLC,<sup>6,8</sup> but none of them demonstrated a survival benefit.

#### *Other maintenance options*

Other nonplatinum options for maintenance therapy have been examined in five clinical trials, some of which have yielded encouraging and important results.<sup>9-13</sup> Four of the five trials showed significant improvement in PFS when patients received a different drug from the ones used during induction.<sup>10-13</sup> More important, two of the trials demonstrated significant improvement in OS when patients received a different drug during maintenance therapy.<sup>11,13</sup> One of the two

trials that showed improved survival compared maintenance therapy with pemetrexed versus observation after induction with regimens that did not include pemetrexed.<sup>11</sup> The other trial (ATLAS) evaluated two different chemotherapy regimens plus bevacizumab followed by maintenance therapy with bevacizumab alone or in combination with erlotinib.<sup>12</sup>

The trial of pemetrexed maintenance constituted a landmark development in the treatment of NSCLC.<sup>11</sup> Patients received induction with a platinum agent plus a taxane or gemcitabine. They were randomized to receive pemetrexed maintenance therapy or observation. The intention-to-treat analysis showed a 40% reduction in the risk of disease progression and a 21% reduction in the risk of death in patients treated with pemetrexed. Subgroup analysis showed that the overall benefits were due entirely to pemetrexed's activity against tumors with nonsquamous histology. That subgroup had a 53% reduction in the risk of disease progression ( $P < 0.00001$ ) and a 30% reduction in the risk of death ( $P = 0.002$ ).

In the SATURN trial of erlotinib maintenance therapy,<sup>13</sup> almost 2,000 patients received platinum-based chemotherapy, and those who did not have progressive disease on treatment were randomized to receive maintenance therapy with erlotinib or placebo. The intention-to-treat analysis showed a 29% reduction in the risk of disease progression with erlotinib maintenance therapy ( $P < 0.0001$ ) compared with placebo.

Subgroup analyses revealed two specific types of patients who derived particular benefit from erlotinib: those who were positive for EGFR expression by immunohistochemistry and those who had wild-type EGFR tumors as opposed to tumors with EGFR mutations (a 23% reduction in the risk of disease progression in both subgroups). EGFR mutation carriers had substantial improvement in PFS,

but more than 70% of patients in the control arm crossed over to erlotinib in second-line treatment. As a result, OS did not improve significantly in that subgroup of patients.

Two key issues in maintenance therapy remain unresolved: (1) the value of pemetrexed maintenance after first-line treatment with pemetrexed and (2) the potential benefit of extending maintenance with bevacizumab. Both of the issues are being addressed in ongoing clinical trials.

#### *First-line use of EGFR inhibitors*

Five randomized clinical trials have compared EGFR tyrosine kinase inhibitors with chemotherapy as first-line treatment for NSCLC.<sup>14-18</sup> Four trials evaluated gefitinib,<sup>\*14-17</sup> and one trial evaluated erlotinib.<sup>\*18</sup> Two of the trials initially enrolled patients who were nonsmokers or light former smokers.<sup>14,15</sup> Investigators in both trials collected tissue samples to evaluate the subset of patients with *EGFR* mutations. The other three trials limited enrollment to patients with *EGFR* mutations.<sup>16-18</sup>

All five studies showed a profound impact of EGFR inhibition on PFS, at least a doubling of PFS in most cases. Additionally, treatment with EGFR inhibitors was associated with about a twofold increase in objective response rates, from 35%–45% with chemotherapy to 70% or higher with the targeted therapy. One-year survival exceeded 80% in some cases.

The overwhelming majority of patients initially treated with chemotherapy in these trials eventually crossed over to the EGFR inhibitor. Results from most of the studies suggested that patients had better outcomes when treated initially with an EGFR inhibitor, reserving chemotherapy for second-line treatment. An ongoing meta-analysis of the trials will show whether starting treatment with an EGFR inhibitor is superior to first-line chemotherapy.

These trial results have made a

strong case for EGFR tyrosine kinase inhibitors as first-line treatment options in advanced NSCLC. However, none of the agents has received US Food and Drug Administration approval for that indication, even though EGFR inhibitors have become a worldwide standard for first-line therapy.

#### **Inhibiting signal transduction**

The importance of EGFR in NSCLC comes from the fact that only 12 signal transduction pathways are known to exist, and the EGFR receptor complex (ErbB1 and ErbB2) employs 5 of them. The pathways are activated as a result of cross-phosphorylation of internal constituents and the intracellular domain of EGFR. Some of the pathways drive proliferation; others inhibit apoptosis.

Several years ago, scientists discovered that a substantial proportion of patients with NSCLC harbor mutations in the adenosine triphosphate (ATP)-binding domain of EGFR. Inhibition of ATP prevents phosphorylation and activation of the intracellular domain of EGFR. In experiments involving mutated and normal (wild-type) EGFR, gefitinib demonstrated 200-fold greater binding avidity for mutated EGFR.<sup>19</sup> The increased binding avidity translates into 100-fold greater inhibition of ATP in mutated versus wild-type EGFR.

In the clinical setting, the increased avidity of drugs such as gefitinib and erlotinib for mutated EGFR has led to dramatic responses. Such was the case with one of the first patients with NSCLC in the United States treated with gefitinib. The patient, who had never smoked, had a massive hepatic lesion that decreased to less than half its size within 3 weeks of beginning treatment with gefitinib.

About 20 years ago, oncology researchers learned that cancer is a disease not only of abnormal cellular pro-

liferation but also of abnormal cellular survival. Arguably, development of therapies that target abnormal survival and induce apoptosis has had a greater impact on cancer survival than has the ability to control cell proliferation.

Apoptosis involves both extrinsic and intrinsic pathways, which terminate in a common pathway.<sup>20</sup> Many chemotherapeutic agents work by triggering the intrinsic pathways of apoptosis, ultimately inhibiting anti-apoptotic signaling in both types of pathways. The five signaling pathways activated by ErbB1 and ErbB2 become antiapoptotic pathways in the presence of receptor mutations. Inhibition of aberrant signaling by an EGFR inhibitor restores normal signaling and allows apoptosis to proceed.<sup>21</sup>

Some agents target the extrinsic pathways of apoptosis, such as the monoclonal antibody cetuximab. The results are not the same as those achieved with agents that target the intrinsic pathways. The relative activity of gefitinib and cetuximab\* was evaluated in NSCLC cell lines with normal and mutated EGFR.<sup>22</sup> The two agents had similar activity in cells with wild-type EGFR, but cetuximab demonstrated only modest activity, at best, in cells with mutated EGFR. In contrast, gefitinib robustly induced apoptosis in cells with mutated EGFR.

Inhibition of EGFR also has relevance because of a phenomenon known as oncogene addiction, which might be considered the Achilles heel of cancer. Despite the presence of multiple genetic and epigenetic abnormalities, cancer cells remain dependent on—or addicted to—a few genes for survival.<sup>23</sup> Evidence of this phenomenon has come from transgenic mouse models of human cancer, studies of human cancer cell lines, and clinical trials of molecularly targeted drugs.<sup>23</sup> Clinical studies of NSCLC have consistently shown that inhibition of mutated EGFR slows disease progression and may confer an OS advantage.

## Beyond EGFR

About 20% of NSCLC tumors have *EGFR* mutations. Recent studies have identified other mutations, which will continue to fuel the search for more specific and effective therapies. Even more common are mutations in *KRAS*, occurring in 25% of NSCLC cases. Thus far, efforts to develop therapies that target *KRAS* mutations have met with little success. However, identification of other types of mutations in NSCLC has provided new opportunities for therapeutic development.

Another subgroup of NSCLC has mutations in *EML4-ALK*. Seven variants have been identified. The investigational drug crizotinib targets *EML4-ALK* transversion, and early clinical trials have yielded encouraging results. In one study, 10 of 18 patients with heavily pretreated NSCLC had an objective response to crizotinib, including some profound responses that occurred as early as 4 weeks.<sup>24</sup>

Unfortunately, tumor cells develop resistance to once-effective therapy. Oncogene addiction exerts strong selective pressure for emergence of mutated cells that restore the abnormal downstream signaling to which the cells originally were addicted. Any of the five signal transduction pathways involved in aberrant signaling may render cells resistant to therapy. Ultimately, combination therapy that simultaneously targets more than one pathway will be needed for more effective control of NSCLC.

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# Progress in the management of metastatic melanoma

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**M**elanoma has the fastest-rising incidence of all cancers. The disease poses multiple challenges that distinguish it from other solid tumors, including early age at onset, early metastatic potential, early involvement of the central nervous system (CNS), and a historic lack of effective nonsurgical therapies.

Also, in contrast to other solid tumors, melanoma has proven to be largely refractory to conventional chemotherapy, which has rarely produced complete responses (CRs). Biologic agents have shown some promise, and chemoimmunotherapeutic strategies even more. Unfortunately, the inability to inhibit CNS seeding has limited the success of even the most promising therapies—until recently. Within the past year, the emergence of ipilimumab and agents that target BRAF has amounted to a breakthrough in the treatment of melanoma. Not surprisingly, the new therapies appear to have an effect on CNS seeding.

The largely ineffective therapies of the past have given way to a new generation of agents and strategies that appear to offer promise for better disease control. The new therapies fall into several broad categories: targeted chemotherapy, angiogenesis inhibition, targeted immunotherapy, and targeted MAP kinase therapy.

## Targeted chemotherapy

The leader in this category is nanoparticle albumin-bound (*nab*) paclitaxel.\* The therapy makes use of nanotechnology to deliver a cytotoxic drug directly to the tumor. The first real test of the therapy came in a phase II trial involving 74 patients with previously treated and untreated metastatic melanoma.<sup>1</sup> Few patients had a CR, but about half had a durable partial response (PR) and stable disease. The results immediately distinguished *nab*-paclitaxel from any prior single-agent therapy for melanoma.

As compared with historic data, the results of the phase II study showed improvement in progression-free survival (PFS) and overall survival (OS).

**TABLE 1**

Phase II results of *nab*-paclitaxel in melanoma

Outcome	Prior treatment (n = 37)	No chemotherapy (n = 37)
Progression-free survival, months		
Median duration	3.5	4.6
Normal LDH level	3.6	8.1
Elevated LDH level	1.8	3.5
Overall survival, months		
Median duration	12.1	9.6
Normal LDH level	> 20.6	21.3
Elevated LDH level	8.5	5.6

LDH = lactate dehydrogenase

Adapted, with permission, from Hersh et al<sup>1</sup>

The drug appeared to be especially active in patients who had normal levels of lactate dehydrogenase (LDH), resulting in a median OS of about 21 months (Table 1).

The encouraging results of the phase II study led to a much larger phase III randomized clinical trial comparing *nab*-paclitaxel with dacarbazine in more than 500 patients with untreated metastatic melanoma. If the results resemble those of the phase II trial, *nab*-paclitaxel could win approval in the near future as a treatment for metastatic melanoma.

## Angiogenesis inhibition

Bevacizumab\* in combination with chemotherapy has demonstrated activity in several types of solid malignancies, creating interest in evaluating this therapeutic strategy in melanoma. The interest

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\* Indicates unlabeled/investigational use of commercial products.

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led to a phase II randomized trial to compare carboplatin-paclitaxel chemotherapy with or without bevacizumab in 200 patients with untreated metastatic melanoma.<sup>2</sup>

Patients were randomized 2:1 to receive chemotherapy plus bevacizumab or placebo, and the primary endpoint was PFS. The objective response rate was modest in both treatment arms (25.5% with bevacizumab, 16.4% without), and only 1%–2% of patients in each arm had a CR. Half of the patients in the bevacizumab group had stable disease or better response at 6 months, compared with 37% in the placebo group.

Patients who received bevacizumab had a trend toward improved PFS (5.6 months vs 4.2 months in those who received placebo), but the difference did not achieve statistical significance ( $P = 0.14$ ). Although lacking statistical power to evaluate survival, the trial showed almost a 4-month difference in median survival favoring the bevacizumab arm in a preliminary analysis (12.3 months vs 8.6 months). The difference translated into a 33% reduction in the risk of death ( $P = 0.04$ ). With longer follow-up, however, the statistically significant survival advantage disappeared (12.3 months vs 9.2 months; hazard ratio [HR], 0.79;  $P = 0.19$ ), although the trend in improved survival persisted.

Although subgroup analysis can create misleading impressions, bevacizumab appeared to perform especially well in poor-prognosis patients, ie, those with extensive visceral tumor involvement and elevated levels of LDH. A trial limited to high-risk patients is still in the proposal stage.

### Targeted immunotherapy

Great care should be taken in using the term “breakthrough” in the field of medicine, particularly oncology. However, the emergence of the targeted immunotherapeutic agent ipilimumab has qualified for that de-

scriptive term by shifting the treatment paradigm. The agent is the first therapy to demonstrate a survival advantage in metastatic melanoma.

Ipilimumab blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) to potentiate the antitumor T-cell response. Costimulation of CD28 and B7 leads to T-cell activation in response to a virus or other threat. CTLA-4 acts as a kind of biologic brake by downregulating the T-cell response after the threat has been neutralized. In melanoma, maintaining T-cell activation and response is desirable, and ipilimumab does that by inhibiting CTLA-4.

In phase I–II clinical trials involving patients with advanced melanoma, ipilimumab resulted in durable responses (objective response plus stable disease) in 20%–30% of patients. Durable late responses occurred in 10% of patients. Because targeted immunotherapy constitutes a shift in the clinical paradigm, objective responses have less importance for this type of therapy than for other types of cancer therapy.

The primary goal of targeted immunotherapy is to contain the cancer, not eradicate it. That objective assumes great importance in melanoma because of the disease's propensity to spread quickly to the liver and CNS. In early studies involving melanoma patients, ipilimumab treatment achieved long-term disease control about a third of the time, and in many cases the control lasted for years, not months.

As would be expected, toxicity characteristic of an overactive immune system correlated with clinical benefit. In fact, emergence of autoimmunity is desirable because it indicates the therapy has a higher chance of working. Treatment with an immunosuppressive agent to control autoimmune toxicity does not interfere with the antitumor response.

A dose-escalation study showed that higher doses of ipilimumab resulted in

few objective responses, a maximum of 11% with the highest dose.<sup>3</sup> However, the highest dose (10 mg/kg) led to a disease-control rate of about 30%. Investigators had to adjust to the de-emphasis on objective responses and the increased importance of disease control. The 10 mg/kg dose of ipilimumab also resulted in the best survival, a median of 11.4 months. The 1-year survival was almost 50%, and 30% of patients were still alive at 2 years.<sup>3</sup>

A trial of ipilimumab as second-line therapy for metastatic melanoma yielded similar encouraging results.<sup>4</sup> Patients treated with the 10 mg/kg dose had a median OS of 10.2 months.

Delayed response is another unusual aspect of treatment with this monoclonal antibody. About 10% of patients have disease progression during the first 12 weeks of treatment, and then the lesions begin to regress. In some cases, late responses have been dramatic. Intuitively, the observation makes sense because the immune system requires time to achieve a level of T-cell activation sufficient to control cancer growth. Delayed responses occur independently of early disease control, meaning that the overall rate of disease control could be in the range of 40%.

Immune-related toxicity affects four organ systems: the skin, gastrointestinal tract, pituitary gland, and liver. The skin toxicity typically manifests as a maculopapular rash, which may resolve without treatment. Persistent rash can be managed effectively with topical corticosteroids. About 30% of patients develop colitis, which is severe enough to require treatment about half of the time.<sup>5,6</sup> Patients might have as many as 10 loose or watery bowel movements a day. The colitis usually responds to high-dose corticosteroids (1 mg/kg), continued for 4–6 weeks and then tapered. Between 5% and 15% of patients develop pituitary toxicity, which presents as fatigue, headache, or vision

disturbances.<sup>6</sup> Most patients respond to corticosteroids or thyroid replacement hormone, and men can be treated with testosterone therapy. Some patients may require lifelong hormone therapy, but the trade-off is often control of the cancer.

A pivotal phase III trial of ipilimumab involved patients with previously treated, poor-prognosis melanoma: pretreated, unresectable, stage III/IV disease, 70% frequency of visceral metastases, and 40% frequency of an elevated LDH level.<sup>7</sup> Almost 700 patients were randomized 3:1:1 to receive ipilimumab plus the gp100 vaccine, ipilimumab plus placebo, or the gp100 vaccine plus placebo.

The primary endpoint was survival. Ipilimumab with or without the gp100 vaccine reduced the risk of death by more than 30% compared with the gp100 vaccine plus placebo (ipilimumab plus gp100,  $P = 0.0004$ ; ipilimumab alone,  $P = 0.0026$ ). Treatment with ipilimumab was associated with a median OS of more than 10 months, which is a large increase for a disease that typically has a median survival of 6 months. About 45% of ipilimumab-treated patients were alive at 1 year, and 2-year survival exceeded 20% in both ipilimumab arms. The study was historic as the first randomized, phase III clinical trial to show improved survival in metastatic melanoma.

Ipilimumab represents a new class of T-cell potentiators and an important advance in the field of immunoncology. Clinical development of ipilimumab is ongoing and includes evaluation in a variety of other cancer types and settings, studies of al-

ternative combination regimens, and refinements in dose and schedule.

### Targeted MAP kinase therapy

The MAP kinase (MAPK) pathway comprises several attractive targets for therapy in melanoma, including BRAF, c-Kit, and Mek. About one-half of cutaneous melanomas have *BRAF* mutations, making BRAF an important proliferative and survival pathway. Recognition of *BRAF* mutations did not occur until 1992. Sorafenib was one of the first known inhibitors of BRAF, but the activity is fairly weak compared with the new generation of inhibitors in development. Preliminary clinical studies with sorafenib in metastatic melanoma concluded with negative results.

In contrast to the experience with sorafenib, the first results in melanoma with the selective BRAF inhibitor vemurafenib (PLX4032) were impressive, as 19 of 27 patients (70%) had objective responses, some of which were dramatic.<sup>8</sup> Only two patients had tumor growth during treatment with vemurafenib, and the growth was minimal in one patient. Unfortunately, the durability of responses frequently has been less than desired, a median of 6–9 months.

Blocking the BRAF pathway alone might not be sufficient to achieve prolonged responses with consistency. Downstream from BRAF, Mek appears to be upregulated and may play a role in the development of resistance to BRAF inhibition. Studies of combination therapy with inhibitors of BRAF and Mek have just begun,

and the goal is to achieve durable responses with greater frequency.

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# Prostate cancer and biologics

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**M**en with early-stage prostate cancer have multiple treatment options, including radical prostatectomy, radiation therapy, active surveillance, and cryotherapy. If the disease progresses after local treatment, the number of options dwindles.

Treatment options for advanced prostate cancer consist primarily of hormonal therapies, including gonadotropin releasing hormone (GnRH) agonists (such as leuprolide and goserelin) and antiandrogens (such as bicalutamide, flutamide, and nilutamide). Within the past year, a new hormonal option became available with the introduction of the GnRH antagonist degarelix.

Until recently, progression to castration-resistant prostate cancer (CRPC) left men with few options. That changed with the results of two clinical trials showing that docetaxel improved survival in men with advanced prostate cancer.<sup>1,2</sup> For the next 6 years, however, patients whose disease progressed during treatment with docetaxel had only the limited options available (Table 1).

Within the past year, three new therapies have been approved by the US Food and Drug Administration (FDA) for advanced prostate cancer: a new-generation tubulin-binding taxane, cabazitaxel; sipuleucel-T immunotherapy; and an androgen synthesis inhibitor, abiraterone. Additionally, denosumab received FDA approval for prevention of skeletal-related events (SREs) associated with bone metastases in patients with advanced solid tumors. In contrast to prior experience with advanced prostate cancer, the near future appears to offer reasons for optimism.

## Illustrative case: a 64-year-old man with lower back pain

The patient had refused prostate-specific antigen (PSA) assessment in the past because of a belief that the screening test offered no benefit to life expectancy. Upon development of lower back pain and at the physician's urging, due to a strong suspicion of prostate cancer, the man agreed to a PSA test, which revealed a level of 225 ng/mL. A prostate biopsy showed cancer in all six cores and a Gleason score of 8. Bone and CT scans confirmed metastat-

**TABLE 1**

### Current therapeutic options for castration-resistant prostate cancer

#### Secondary hormonal manipulations

- Abiraterone
- Antiandrogen withdrawal
- Antiandrogen administration
- Adrenal suppressives (ketoconazole)
- Corticosteroids (prednisone, dexamethasone, etc)
- Estrogens (diethylstilbestrol, etc)

#### External-beam radiation therapy

#### Intravenous bone-seeking radioisotopes

- Samarium-153-EDTMP
- Strontium-89

#### Bone-targeted agents

- Zoledronic acid and denosumab

#### Chemotherapy

- Mitoxantrone
- Docetaxel
- Estramustine
- Cabazitaxel

#### Immunotherapy

- Sipuleucel-T

ic disease in the lumbar spine, ribs, and iliac crest.

The patient began hormonal therapy, consisting of oral bicalutamide for 1 week, followed by leuprolide injection. One month later, the man's PSA level had declined to 25.2 ng/mL. A PSA nadir of 1.2 ng/mL occurred 5 months after initiation of androgen deprivation therapy (ADT) but then began to rise, and the patient reported mild pain in the lumbar spine.

Despite ADT, the patient's PSA level increased to 3.3, 4.9, and 6.8 ng/mL on three consecutive monthly measurements. A bone scan revealed increased tracer uptake in the lumbar spine, ribs, and

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iliac crest, consistent with metastatic disease. Treatment with zoledronic acid was instituted in an effort to prevent SREs.

The patient's PSA level continued to rise, and bicalutamide was stopped, with the hope of an antiandrogen withdrawal response. The patient progressed to metastatic CRPC. Eight weeks later, the patient's PSA level had risen to 15.9 ng/mL, despite antiandrogen withdrawal. Pain had worsened, and the patient began taking oxycodone with acetaminophen for pain relief. After a discussion about chemotherapy, the patient opted for secondary hormonal manipulation as the next therapeutic approach.

The patient's PSA level stabilized during the first 2 months of treatment with ketoconazole and hydrocortisone but then rose to 45 ng/mL 2 months later. The patient began taking docetaxel in combination with prednisone. The PSA level declined by 40% after 3 months but then started to rise again. After seven cycles of docetaxel therapy, the PSA level began to rise quickly and was associated with increasing pain in the lower back.

A bone scan confirmed metastatic lesions in the lumbar spine. The patient was referred for radiation therapy, and treatment with docetaxel was stopped.

The patient continues to have good performance status. Options after radiation therapy include a clinical trial of hormonal therapy or one of the newly approved therapies for advanced prostate cancer: cabazitaxel, sipuleucel-T, or abiraterone.

### The first survival benefit

Docetaxel received FDA approval on the basis of results from two randomized clinical trials involving almost 1,800 men with CRPC.<sup>1,2</sup> In one trial, patients received mitoxantrone and prednisone or one of two doses of docetaxel plus prednisone.<sup>1</sup> In the second study, patients were randomized to receive mitoxantrone

**TABLE 2**

#### Mitoxantrone vs cabazitaxel: overall survival

	Mitoxantrone/prednisone	Cabazitaxel/prednisone
Median overall survival, months	12.7	15.1
Hazard ratio (95% CI)	0.70 (0.59–0.83)	
P value	< 0.0001	

CI = confidence interval

Adapted, with permission, from Sartor et al<sup>4</sup>

and prednisone or to the combination of docetaxel, estramustine, and dexamethasone.<sup>2</sup> The primary results of both trials showed a statistically significant improvement in overall survival of about 2 months with docetaxel versus mitoxantrone.

### New options for advanced prostate cancer

#### Cabazitaxel

Cabazitaxel is a new-generation tubulin-binding taxane. Given its novel mechanism of action, the drug might offer another therapeutic option for patients after docetaxel. The viability of cabazitaxel as a post-docetaxel therapy was evaluated in an international multicenter randomized clinical trial of men with metastatic CRPC that had progressed during or after docetaxel therapy.<sup>3</sup> Investigators randomized 755 patients to receive cabazitaxel plus prednisone or mitoxantrone plus prednisone. The primary endpoint was overall survival.

When the trial ended, patients treated with cabazitaxel had a median survival of 15.1 months compared with 12.7 months with mitoxantrone, representing a statistically significant 30% reduction in the risk of death ( $P < 0.0001$ ; Table 2).<sup>4</sup> Subgroup analysis showed a consistency of the benefit across a wide range of clinical and demographic variables.

Patients treated with cabazitaxel experienced more toxicity, particularly diarrhea, fatigue, nausea, and vomiting, than did those who received mitoxantrone. Febrile neutropenia occurred in 7.5% of cabazitaxel-treated patients, which was more than five

times greater than the rate in the control arm. Most adverse events were mild or moderate in severity.

A recent analysis of the data focused on causes of death in the trial. The cabazitaxel arm had fewer deaths overall (61.2% vs 74.1%) and fewer deaths due to disease progression (53.1% vs 68.2%). However, cabazitaxel was associated with more deaths related to adverse events (4.9% vs 1.9%).<sup>4</sup>

The survival benefits demonstrated by docetaxel and cabazitaxel have altered clinical practice by creating the potential to incorporate selected chemotherapeutic agents along with hormonal therapies in the sequential treatment of advanced prostate cancer. Sequential use of available therapies offers the possibility of extending the duration of treatment response.

#### Sipuleucel-T

Characterized as immunotherapy or a vaccine, sipuleucel-T represents a new approach to the treatment of CRPC. Because the therapy is patient specific, the production process is fairly labor intensive. The patient undergoes leukapheresis for harvesting of autologous dendritic or antigen-presenting cells, which are then cultured with a fusion protein consisting of prostatic acid phosphatase and granulocyte macrophage-colony stimulating factor. The so-called antigen-loaded antigen-presenting cells are then infused back into the patient. The therapy has a paradoxical response profile. The patient's PSA level is unaffected, but survival is improved.

The phase III trial that led to FDA approval involved about 500 patients with CRPC, randomized 2:1 to re-

**TABLE 3**

## Sipuleucel-T vs placebo: overall survival

	Placebo	Sipuleucel-T	Hazard ratio	P value
Median overall survival, months	21.7	25.8	0.775	0.032

Source: Kantoff et al<sup>5</sup>

ceive sipuleucel-T therapy or best supportive care.<sup>5</sup> When the trial ended, patients treated with the adaptive immunotherapy had a median overall survival of 25.8 months, compared with 21.7 months in the control group, a 23% reduction in the risk of death ( $P = 0.032$ ; Table 3).

The potential survival benefit of this therapy will likely apply to a select group of patients. The number of eligible candidates far exceeds current production and infusion capabilities, and the situation is unlikely to improve in the near future. Additionally, the therapy is expensive, so only those patients with adequate insurance coverage or personal financial means will be able to afford the treatment.

*Abiraterone*

Abiraterone is an upstream inhibitor in the cholesterol pathway that leads to steroid hormone synthesis. Specifically, abiraterone inhibits 17- $\alpha$  hydroxylase, a key enzyme in the production of cortisol, estradiol, and testosterone.

In a study of patients with CRP-C previously treated with docetaxel, treatment with abiraterone led to a time to tumor progression of almost 281 days, which is an accomplishment in such a difficult-to-treat group of patients.<sup>6</sup> In April 2011, the FDA approved abiraterone for use in combination with prednisone to treat patients with CRPC, as an option after receiving docetaxel.

*Denosumab*

In patients with CRPC, treatment with the RANK ligand (RANKL) inhibitor denosumab can significantly

reduce the risk of SREs secondary to ADT.<sup>7</sup> However, some tumors express RANKL, raising the possibility that inhibition of RANKL might have a direct impact on tumor growth.<sup>8</sup>

Bisphosphonates in general, and zoledronic acid in particular, have been the standard for preventing SREs secondary to cancer therapy. The benefit was demonstrated in a large, multicenter, randomized, placebo-controlled clinical trial involving men with prostate cancer. The results showed that zoledronic acid extended the time to first SRE by 50% compared with placebo (16.0 months vs 10.7 months).<sup>9</sup>

Zoledronic acid remained the standard of care for preventing SREs for more than 5 years, when denosumab challenged its supremacy in a large, multicenter randomized clinical trial involving men with metastatic CRPC.<sup>10</sup> Almost 2,000 patients were randomized to receive denosumab or zoledronic acid. Time to occurrence of a first on-study SRE, the primary endpoint, was extended from 17.1 months with zoledronic acid to 20.7 months with denosumab, which translated into an 18% reduction in the risk of developing SREs.

**Conclusion**

After years of minimal progress, therapy for CRPC has greater diversity and potential for improved survival. Within the past year, four new drugs and biologics have joined docetaxel as therapies that can have a meaningful impact on the disease: cabazitaxel, sipuleucel-T, abiraterone, and denosumab. Several other novel agents are in various stages of evalu-

ation. For the first time in years, the outlook for CRPC offers reason for optimism.

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# Inhibition of DNA repair as a therapeutic strategy

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All cells face a constant risk of DNA damage from multiple sources: ultraviolet light, ionizing radiation, man-made and natural chemicals, and endogenously generated reactive oxygen species, to name some of the most common threats. An estimated 10,000 single-strand breaks occur daily in every cell. On any given day, the human body has about 100 quadrillion DNA lesions.<sup>1-3</sup>

Cells, including cancer cells, respond to DNA damage by means of a variety of reparative mechanisms, which work in concert to keep genomic fidelity intact. Cancer cells are highly susceptible to inhibition of DNA repair, a susceptibility that affords opportunities for therapeutic development. However, cancer cells also are adept at adjusting to loss of repair mechanisms by using one of the many alternative pathways. Poly(ADP-ribose) polymerase (PARP) has a key role in the repair of DNA single-strand breaks, thus making it an attractive target for inhibiting DNA repair and causing cancer cell death.

## PARP and DNA repair

PARP is an enzyme family comprising at least 12 distinct molecules, of which PARP1 appears to be the most important for DNA repair. An important component of the base excision-repair pathway, PARP binds directly to sites of DNA damage. When activated, PARP uses nicotinamide adenine dinucleotide (NAD) as a substrate to generate large branched chains of poly(ADP-ribose) polymers on multiple proteins. PARP also recruits other enzymes involved in DNA repair.<sup>4</sup>

Inhibition of PARP prevents recruitment of DNA repair proteins, resulting in accumulation of DNA single-strand damage. Ultimately, single-strand breaks degenerate into double-stranded DNA breaks. The degeneration occurs during the S phase of replication, effectively shutting down DNA synthesis.

BRCA1 and BRCA2 are necessary for efficient repair of double-stranded DNA breaks. The repair

occurs by means of a mechanism known as homologous recombination, which drives cells—normal as well as cancer cells—toward the preferred pathway for repair of double-stranded DNA breaks. The end result is an error-free repair system that maintains the fidelity of DNA and ensures cell survival.

If the preferred pathway is not operant, other pathways may be used but result in less-efficient DNA repair. The predominant alternative pathway is nonhomologous recombination, which occurs without BRCA. Nonhomologous recombination is error prone and results in gross genomic instability within a cell and, ultimately, necrosis.

Cells with *BRCA* mutations are homologous recombination-deficient and lack the ability to repair double-stranded DNA breaks efficiently. Failed and inefficient DNA repair results in synthetic lethality, a term that refers to the occurrence of two deficits that can lead to cell death.<sup>5</sup>

BRCA and PARP are therefore central to DNA repair and the ability to maintain normal cell integrity and function. Inhibition of PARP leaves the BRCA pathway to continue homologous recombination. Conversely, if BRCA becomes unavailable or nonfunctional, homologous recombination continues by PARP-related mechanisms. However, if neither PARP nor BRCA is functional, the result is synthetic lethality and cell death.

A series of laboratory experiments showed that cells with two nonfunctional copies of BRCA1 or BRCA2 (homozygotes) demonstrate exquisite sensitivity to PARP inhibition.<sup>6</sup> The observations led to rapid development of PARP inhibitors, with multiple drugs in clinical development. Although they share a common enzymatic target, the PARP inhibitors differ with respect to chemical structure,

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toxicity profiles, and schedules and routes of administration. The PARP inhibitors remain in the early stages of evaluation, with the exception of iniparib, which has completed a phase III trial.

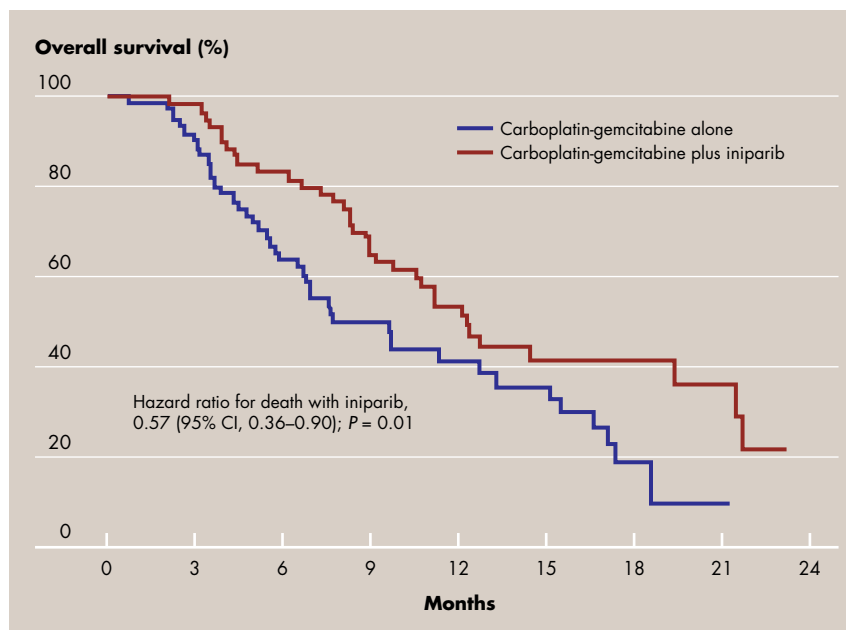
### PARP inhibitors and BRCA-mutant tumors

Patients with *BRCA*-mutant tumors represent an obvious starting point for clinical evaluation of PARP inhibitors. Phase I and II clinical trials of PARP inhibitors as monotherapy for *BRCA*-deficient tumors have yielded response rates of 13%–50%. In general, the response rates have clustered around 40%–50%.

In a phase I study of patients with *BRCA* mutations, the oral PARP inhibitor olaparib demonstrated clinical activity in 12 of 19 patients, including 1 complete response (CR) and 10 partial responses (PRs).<sup>7</sup>

A phase II evaluation of olaparib involved patients with *BRCA*-deficient metastatic breast cancer. Sequential cohorts of patients received 400 and 100 mg twice daily; the primary endpoint was overall response rate (ORR).<sup>8</sup> The higher dose was associated with objective responses in 11 of 27 patients (41%), including 1 CR. The lower dose was associated with PRs in 6 of 27 patients (22%). Median progression-free survival (PFS) was 5.7 months with the higher dose and 3.8 months with the lower dose. The most common adverse effects were fatigue, nausea, vomiting, headache, and constipation—most of which were mild or moderate.

A trial of olaparib in patients with *BRCA*-mutant ovarian cancer produced evidence that might prove useful for identifying patients most likely to respond to the PARP inhibitor.<sup>9</sup> The patients were characterized as platinum-refractory, platinum-resistant, or platinum-sensitive on the basis of the duration of the platinum-free interval. The results showed that the likelihood of response to olaparib increased



**FIGURE 1** Improvement in overall survival in patients with triple-negative breast cancer receiving iniparib in addition to carboplatin-gemcitabine chemotherapy. Adapted, with permission, from O'Shaughnessy et al.<sup>11</sup> © 2011 Massachusetts Medical Society. All rights reserved.

with the duration of the platinum-free interval. In particular, CRs tended to cluster in the subgroup of patients who had platinum-free intervals of more than 6 months ( $P = 0.03$ ).

### Beyond BRCA mutation carriers

Drugs that interfere with DNA repair have clinical potential that extends well beyond carriers of *BRCA* mutations. Several studies have examined PARP inhibitors in non-*BRCA*-deficient patient populations.

One early test involved patients with triple-negative breast cancer, which refers to a histologic subtype characterized by negative estrogen receptor, negative progesterone receptor, and negative HER2 (human epidermal growth factor receptor 2) status. Triple-negative breast cancer accounts for 10%–17% of all breast cancers and is associated with increased aggressiveness and risk of recurrence.<sup>10</sup>

In an open-label phase II clinical trial, patients with metastatic triple-negative breast cancer were randomized to receive treatment with car-

boblatin-gemcitabine chemotherapy alone or in combination with iniparib.<sup>11</sup> The primary endpoints were clinical benefit rate (objective responses plus stable disease) and safety. Patients treated with iniparib in addition to chemotherapy had a clinical benefit rate of 56%, compared with 34% for patients treated with chemotherapy alone ( $P = 0.01$ ). The ORR was 52% with iniparib and 32% without ( $P = 0.02$ ). No significant differences in adverse events were observed between the two treatment groups.

The addition of iniparib significantly slowed cancer progression (Figure 1), a secondary endpoint of this study. The hazard ratio (HR) for disease progression in the iniparib arm was 0.59 versus the control arm, representing a 41% reduction in risk ( $P = 0.01$ ). The hazard for death was reduced by 43% in the iniparib arm (HR, 0.57;  $P = 0.01$ ).

In a phase I clinical trial, olaparib was paired with paclitaxel as first- or second-line therapy for metastatic breast cancer.<sup>12</sup> The study included 19 patients who were not selected for

*BRCA* mutations, most of whom received the combination as first-line therapy. The ORR was 33%–40%, all PRs. The median PFS was 5.2–6.3 months. Hematologic toxicity was considerable. Patients required growth factor support, and dose reductions were common.

Investigators in a small phase II study evaluated the PARP inhibitor veliparib in combination with the alkylating agent temozolomide in patients with metastatic breast cancer.<sup>13</sup> By itself, temozolomide has little or no activity in breast cancer. However, as an alkylator, the drug induces DNA damage, providing a rationale for combining it with the PARP inhibitor.

The ORR was a disappointing 7%. However, a post hoc analysis of response by *BRCA* status showed that five of six patients with *BRCA* mutations had an objective response to the combination of veliparib and temozolomide. Median PFS was 1.8 months overall, but it reached 5.5 months in patients with *BRCA* mutations.

### Future directions

Although clinical evaluation of PARP inhibitors had produced some encouraging results, evidence of drug resistance has already begun to emerge.<sup>14</sup> One mechanism of resis-

tance identified thus far involves restoration of partial function by *BRCA2*, leading to resumption of homologous recombination repair.

A key unanswered question related to the future of PARP inhibitors is whether the agents have broader application for cancer therapy, such as treatment of tumors that have specific types of DNA-repair defects. The timing of PARP inhibitor administration also requires further study to determine when these agents should be given in relation to the administration of cytotoxic therapy.

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# Current status of bone-targeted therapy for cancer patients

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**B**one loss occurs in both men and women as a natural consequence of aging. Cancer patients, however, have accelerated bone loss as a result of cancer treatment, which leads to an increased susceptibility to fracture. Additionally, bone metastases cause substantial pain and morbidity, which can result in complications or additional treatments, often referred to as skeletal-related events (SREs). Clinicians have an obligation to recognize and treat cancer therapy-induced bone loss as well as to prevent SREs in their patients.

To date, bisphosphonates have been the mainstay of treatment to prevent bone loss and SREs in cancer patients. More recently, the monoclonal antibody denosumab has also shown impressive activity in preventing SREs and in treating cancer therapy-induced bone loss. Recent trials have also explored the ability of these bone-targeted agents to prevent metastases.

## The burden of bone disease

Loss of bone mineral density (BMD) occurs as a consequence of the aging process, ranging from 0.5% per year in men older than age 50 to 2.0% per year among women in early menopause.<sup>1</sup> Many cancer therapies further accelerate bone loss. Estimates of yearly bone loss are as high as 2.6% per year with aromatase inhibitor use,<sup>2</sup> 4.6% with androgen deprivation therapy (ADT),<sup>3</sup> and up to 7.7% in the year following ovarian failure secondary to chemotherapy.<sup>4</sup>

An estimated 400,000 cancer patients develop bone metastases each year. Besides causing pain, complications of bone metastases include fracture, spinal cord compression, and hypercalcemia. In patients with advanced breast cancer, SREs or complications account for almost two-thirds of hospital costs.<sup>5</sup> Almost 70% of patients with advanced metastatic breast cancer and up to one-half of patients with advanced multiple myeloma, prostate cancer, or lung cancer develop SREs within 24 months.<sup>6</sup>

## Options for preventing bone loss

### *Bisphosphonates*

Bisphosphonates have an established role for prevention of cancer therapy-induced bone loss. Bisphosphonates have a direct apoptotic effect on osteoclasts, resulting in decreased bone resorption. To a lesser degree, bisphosphonates can also affect macrophages; osteoblasts; T cells; and, theoretically, tumor cell function.

Oral and intravenous formulations of bisphosphonates have demonstrated the ability to increase BMD in men with prostate cancer treated with ADT.<sup>7,8</sup> An integrated analysis of a large clinical trial program with zoledronic acid demonstrated significant bone preservation in patients with early breast cancer who were treated with the aromatase inhibitor letrozole.<sup>9</sup>

Patients were randomized to two clinical strategies: concurrent therapy with letrozole and zoledronic acid or delayed bisphosphonate therapy until the development of worsening osteopenia (T-score below -2.0) or fracture. Immediate bisphosphonate therapy was associated with improvement in BMD within 6 months, whereas delayed treatment was associated with a decrease in BMD. The difference in BMD between treatment groups was statistically significant at 12 months ( $P < 0.001$ ) and continued to increase through 60 months of follow-up, although no difference in clinical fractures was observed.<sup>9</sup>

### *RANK ligand inhibition*

RANK ligand (RANKL) is the primary mediator of osteoclast formation, function, and survival. The protein has a vital role in physiologic and can-

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Unlabeled/investigational use of commercial products is indicated by an asterisk (\*).

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cer-induced bone resorption. Denosumab is a fully human monoclonal antibody that binds and inhibits RANKL to prevent bone resorption. Results of phase III clinical trials show that denosumab significantly reduces markers of bone turnover, increases BMD, and prevents fractures in postmenopausal women with osteoporosis.

Denosumab also has demonstrated efficacy for preserving BMD in patients with early-stage breast cancer treated with aromatase inhibitors.<sup>10</sup> In a placebo-controlled clinical trial of early-stage breast cancer patients receiving adjuvant aromatase inhibitor therapy, patients treated with denosumab had a 5.5% absolute increase in BMD after 12 months and a 7.6% increase in BMD at 24 months ( $P < 0.001$ ), compared with patients not receiving bone-targeted therapy.<sup>10</sup>

A much larger multicenter trial involving men with prostate cancer treated with ADT yielded similar findings. At 24 months, denosumab-treated patients had a 6.4% absolute improvement in lumbar spine BMD over patients receiving placebo, and a 4.6% absolute advantage for total hip BMD.<sup>11</sup> Treatment with the RANKL inhibitor also was associated with a significantly lower rate of vertebral fractures at 12, 24, and 36 months than with placebo ( $P = 0.006$  to  $P = 0.004$ ).

### Comparisons of denosumab with zoledronic acid

Three identical, international, randomized clinical trials compared zoledronic acid and denosumab in patients with solid tumors and bone metastases or with multiple myeloma.<sup>12-14</sup> None of the patients had a history of bisphosphonate therapy for bone metastases. The primary endpoint for all three trials was time to first SRE. All three trials were statistically powered to demonstrate the noninferiority of denosumab to zoledronic acid as the primary endpoint, with superiority of denosumab tested as a secondary endpoint.

Each of the trials met the primary endpoint, and the two larger trials demonstrated superiority for denosumab over zoledronic acid.<sup>12,13</sup> Denosumab treatment decreased the risk of first SRE by 16%–18%, compared with zoledronic acid ( $P = 0.0007$  to  $P < 0.0001$ ). Focusing in particular on the breast cancer trial, patients who were treated with denosumab had a statistically significant 23% reduction in the risk of first and subsequent SREs (multiple-event analysis) compared with patients receiving zoledronic acid ( $P = 0.001$ ).<sup>15</sup>

Adverse events and serious adverse events occurred in a similar proportion of patients in each treatment group. However, zoledronic acid treatment was associated with more acute-phase reactions (especially pyrexia) and renal toxicity than was denosumab, whereas more cases of hypocalcemia were observed with denosumab treatment. Osteonecrosis of the jaw was seen infrequently in both groups, with no statistical difference observed between the treatment arms, although a slightly greater number of events occurred in the denosumab arm. Denosumab also significantly extended the time to worsening pain in patients who had no or mild pain at baseline (9.7 months vs 5.8 months;  $P = 0.0024$ ).

Each new generation of bone-targeted therapy has led to substantial reductions in the risk of SREs in patients with metastatic breast cancer. Without bisphosphonate therapy, almost two-thirds of patients with advanced metastatic disease develop SREs within 2 years.<sup>16</sup> Treatment with pamidronate reduced the SRE rate by one-third.<sup>16</sup> The introduction and use of zoledronic acid led to an additional 20% reduction in SRE incidence.<sup>17</sup> Treatment with denosumab has now achieved a further 18% reduction in the risk of SREs in this patient population.<sup>15</sup>

### Bone-targeted therapy and bone metastases

More than a century ago, Stephen Paget proposed the “seed-and-soil hy-

pothesis” of cancer metastases.<sup>18</sup> The ABCSG-12 trial has sparked renewed interest in Paget’s hypothesis by providing preliminary data suggesting a role for bone-targeting agents in altering the bone microenvironment to inhibit and prevent breast cancer progression.<sup>19</sup>

In the ABCSG-12 trial, premenopausal women with early-stage breast cancer were treated with ovarian ablation with goserelin and then randomized in a 2 × 2 design to receive treatment with tamoxifen versus anastrozole and zoledronic acid versus placebo.<sup>19</sup> Approximately 1,800 patients were randomized to receive tamoxifen or anastrozole, with or without concomitant zoledronic acid. The primary endpoint was disease-free survival (DFS), and although no difference was seen between the hormone therapy arms, patients treated with the bisphosphonate had a 36% lower incidence of breast cancer recurrence than did those who had received endocrine therapy alone ( $P = 0.011$ ). Patients who were administered zoledronic acid every 6 months had fewer distant recurrences as well as fewer locoregional recurrences.<sup>19</sup> Updated analyses showed that a statistically significant advantage was maintained during follow-up beyond 5 years.<sup>20,21</sup>

More recently, a much larger trial directly testing the potential effects of zoledronic acid\* therapy on preventing breast cancer recurrences was presented at the San Antonio Breast Cancer Symposium in December 2010. In the AZURE trial, patients with stage II or III breast cancer were randomized to receive standard chemotherapy alone or with concomitant zoledronic acid. In this trial, involving more than 3,300 patients, a difference in DFS was not observed (hazard ratio [HR], 0.98).<sup>22</sup> However, a prespecified subgroup analysis revealed an intriguing interaction between treatment and menopausal status. Women who were more than 5

\* Indicates unlabeled/investigational use of commercial products.

years postmenopausal or over 60 years of age did show an improvement in DFS (HR, 0.76) and overall survival with zoledronic acid treatment.

The reasons for the contradictory results of the AZURE and ABCSG-12 trials are unclear, but there are distinct differences between the breast cancer populations treated in the two trials. The AZURE trial included higher risk patients who were predominantly treated with chemotherapy. Of patients in the AZURE trial, 96% received chemotherapy, compared with only 5% in the ABCSG-12 trial. Thus, the role of zoledronic acid may be limited in patients who receive chemotherapy. In addition, the hormonal milieu of the bone microenvironment may play an important role in determining the effectiveness of bone-targeted agents, as suggested by the subset analyses.

Additional trials exploring the role of bisphosphonates in preventing breast cancer recurrences have been completed, and the results of these trials will hopefully provide definitive answers to this important question.

### Future directions

The role of denosumab in preventing cancer recurrence or tumor progression remains to be determined. Preclinical models have shown that inhibition of RANKL decreases the progression of established bone metastases. RANKL also appears to induce migration of RANK-expressing cancer cells to bone. An international randomized phase III clinical trial is currently actively accruing patients to determine whether denosumab treatment can impact bone metastasis-free survival in patients with high-risk stage II or stage III breast cancer.

Molecules that target other aspects of bone resorption and bone metabolism are currently in development. Eventually, oncologists will be able to offer their patients multiple choices for bone preservation and perhaps preven-

tion of bone metastases using combinations of bone-targeted therapies.

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**Conflicts of interest:** The author has been a consultant and speaker for Amgen. She also has been a consultant for Novartis and a speaker for Genomic Health.

# Highlights of the 6<sup>th</sup> Annual Community Oncology Conference

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## CME QUESTIONS Instructions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

- A pooled analysis of data from two trials of adjuvant oxaliplatin-based chemotherapy for colon cancer showed that patients older than 70:  
A. Derived the same benefit as younger patients  
B. Did not benefit from oxaliplatin  
C. Were excluded from the trials  
D. None of the above
- Which of the following achieved positive results as adjuvant therapy for colon cancer?  
A. Bevacizumab B. Irinotecan C. Cetuximab  
D. None of the agents had a positive impact
- Clinical experience in the treatment of metastatic colon cancer has shown that patients with stage IV disease:  
A. Can be cured in some cases with an interdisciplinary approach to treatment  
B. Should receive only palliative care  
C. Cannot tolerate cytotoxic chemotherapy  
D. Do not respond to treatment with targeted therapies
- Complete the following statement with the most accurate phrase. "Ten-year survival for low-grade lymphoma..."  
A. Has not improved since the early 1990s  
B. Improved during the 1990s but not since 2000  
C. Has shown an absolute improvement of 20% since 1990  
D. Has actually declined because of more instances of late diagnosis
- A randomized clinical trial comparing ABVD and the Stanford V chemotherapy regimens for advanced Hodgkin's lymphoma showed that:  
A. Stanford V is superior and should be the standard of care  
B. ABVD is superior and should be the standard of care  
C. The two regimens have similar efficacy but Stanford V is more toxic, so ABVD should remain the standard of care  
D. A regimen used in Germany is superior to ABVD and Stanford V and is less toxic
- A role for targeted therapy in the treatment of non-small cell lung cancer (NSCLC) has been established by the observation that tumors often express:  
A. PDGF B. VEGF C. HER2 D. EGFR
- A majority of NSCLCs has:  
A. Non-squamous cell histology C. Mixed histology  
B. Squamous-cell histology D. Oat-cell histology
- The addition of bevacizumab to platinum-based chemotherapy has:  
A. Proven too toxic for most patients with NSCLC  
B. Improved 1-year survival in patients with NSCLC  
C. Improved survival for patients with squamous-cell histology  
D. Had no effect on survival in NSCLC
- Which of the following is NOT true of melanoma?  
A. Early age at onset  
B. Early metastatic potential  
C. Early involvement of the central nervous system  
D. More amenable to systemic therapies, as opposed to surgery
- Which of the following is true of ipilimumab?  
A. Delayed response  
B. Initial disease progression in some patients  
C. Dramatic late responses in some patients  
D. All of the above
- Historically, treatment options for advanced prostate cancer have consisted primarily of:  
A. Chemotherapy C. Hormonal therapy  
B. Surgery D. Radiation therapy
- What therapy was the first to demonstrate an improvement in survival?  
A. Docetaxel C. Sipuleucel-T  
B. Cabazitaxel D. Abiraterone
- What type of agent is sipuleucel-T?  
A. Chemotherapy  
B. A radioactive tracer used to monitor response to therapy  
C. Immunotherapy or vaccine  
D. A tyrosine kinase inhibitor
- Iniparib, olaparib, and veliparib are examples of the drug class known as:  
A. Tyrosine kinase inhibitors C. Angiogenesis inhibitors  
B. PARP inhibitors D. EGFR inhibitors
- In patients with triple-negative breast cancer, the addition of iniparib to chemotherapy significantly improved:  
A. Clinical benefit rate C. Mortality risk  
B. Overall response rate D. All of the above
- What metabolic process is associated with treatment with an aromatase inhibitor, androgen deprivation therapy, and chemotherapy-induced ovarian failure?  
A. Alopecia C. Loss of bone mineral density  
B. Nausea/vomiting D. Secondary malignancy
- Denosumab is a member of the therapeutic class known as:  
A. RANK ligand inhibitors C. Bisphosphonates  
B. VEGF inhibitors D. PGE2 agonists
- Three randomized clinical trials comparing denosumab and zoledronic acid for prevention of skeletal-related events in cancer patients showed that:  
A. Zoledronic acid was superior  
B. Denosumab was superior  
C. The drugs had equivalent effects  
D. Both drugs were no more effective than calcium and vitamin D supplementation
- Trastuzumab emtansine (T-DM1):  
A. Targets HER2  
B. Is an antibody-drug conjugate  
C. Has activity in patients with prior exposure to trastuzumab  
D. All of the above
- In a randomized clinical trial involving patients with HER2-positive breast cancer, which therapeutic regimen led to the highest rate of pathologic complete response?  
A. Docetaxel, trastuzumab, and pertuzumab  
B. Docetaxel-trastuzumab  
C. Docetaxel-pertuzumab  
D. Pertuzumab-trastuzumab

## EVALUATION FORM We would appreciate your answering the following questions to help us plan for other activities of this type. All information is confidential.

Please print

Name: \_\_\_\_\_ Specialty: \_\_\_\_\_

Degree:  MD/DO  Nurse  NP  PA  Other healthcare provider: \_\_\_\_\_

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- How would you rate this activity overall? 5 4 3 2 1  
(5 = excellent, 1 = poor; please circle one)
- In your opinion, did you perceive any commercial bias?  Yes  No  
If yes, please explain: \_\_\_\_\_
- Do you plan to make any changes in your practice as a result of this activity?  Yes  No  
If yes, please explain: \_\_\_\_\_
- May we contact you in the future to determine if you made changes in your practice?  Yes  No
- What barriers, if any, do you anticipate encountering as you make changes in your practice? \_\_\_\_\_
- Do you feel each of the following objectives was met?  
Discuss recent developments related to integration of novel agents into the treatment of non-small cell lung cancer  Yes  No  Partially  N/A  
Describe the scientific rationale for use of PARP inhibitors to treat cancer  Yes  No  Partially  N/A  
Discuss outcomes of recent clinical trials of PARP inhibitors  Yes  No  Partially  N/A
- Recognize the role of bone-targeted therapy in clinical oncology practice  Yes  No  Partially  N/A
- Understand distinctions between bisphosphonates and RANK ligand inhibitors  Yes  No  Partially  N/A
- Describe recent developments in the treatment of melanoma  Yes  No  Partially  N/A
- Discuss novel therapies recently approved for treatment of advanced prostate cancer  Yes  No  Partially  N/A
- Describe recent clinical trial data related to Hodgkin's lymphoma and non-Hodgkin's lymphoma  Yes  No  Partially  N/A
- Review current and emerging treatment options for colon and other gastrointestinal cancers  Yes  No  Partially  N/A
- Appreciate differences between traditional and novel HER2-targeted agents  Yes  No  Partially  N/A
- Do you feel that the information in this activity was based on the best evidence available?  Yes  No  
If no, please explain: \_\_\_\_\_
- Which of the following competency areas do you feel have been improved as a result of this activity? (mark all that apply)  
 Patient Care  Professionalism  Practice Based Learning  
 Medical Knowledge  System Base Practice  Communication Skills
- Do you feel you need further education on this topic?  Yes  No  
If yes, please specify: \_\_\_\_\_
- Do you have any suggestions for future activities? \_\_\_\_\_
- Please rate the content of this activity: (5 = excellent, 1 = poor; please circle one)  
a. Timely, up to date? 5 4 3 2 1  
b. Relevant to your practice? 5 4 3 2 1
- How long did it take you to complete this activity, including this evaluation? \_\_\_\_\_ minutes

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