Ramucirumab (Cyramza)
A Breakthrough Treatment for Gastric Cancer
Amrita D. Singh, PharmD candidate, and Sapna Parmar, PharmD, BCOP

INTRODUCTION
Gastric cancer is the fourth most common malignancy in men and the fifth most common malignancy in women worldwide.¹ It is a common cancer in Japan, China, Southern and Eastern Europe, and South and Central America. In the United States, higher diagnosis rates are seen among Hispanic-Americans, African-Americans, Asians, and Pacific Islanders than in non-Hispanic whites.² An estimated 22,220 new cases of gastric cancer and 10,990 deaths occurred in the United States in 2014.³ The median age at diagnosis is 69 years, and five-year survival following diagnosis is 28.3%.²

Gastric carcinoma is defined as tumors originating in the distal stomach that are greater than 5 cm from the gastroesophageal junction (GEJ), the lower part of the esophagus that connects to the stomach, or within 5 cm of the GEJ but not crossing over into the GEJ or esophagus.⁴ Approximately 90% to 95% of gastric carcinoma is adenocarcinoma in histology, arising from the epithelial cells of the gastric mucosa. Histological transformation of the gastric mucosa slowly progresses over time from chronic nonatrophic gastritis to multifocal atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately to invasive adenocarcinoma. These adenocarcinomas are classified as intestinal or diffuse. Intestinal-type tumors are well differentiated and usually develop secondary to Helicobacter pylori infection. Diffuse-type carcinomas are undifferentiated and result from a genetic defect of the intracellular adhesion molecules. This may be due to germline or somatic mutations, loss of heterozygosity, or epigenetic silencing of gene transcription, which results in the loss of epithelial cadherin (E-cadherin) protein expression, encoded by CDH1. In addition, gastric carcinoma may be nonadenocarcinoma in origin, which includes GIST (gastrointestinal [GI] stromal tumors), MALT (mucosa-associated lymphoid tissue) lymphomas, and carcinoids.⁵

The exact cause of gastric cancer is unknown. However, certain risk factors are thought to play a role in its development, including infection with H. pylori bacteria; a diet high in salt or nitrates; tobacco use; obesity; occupations associated with exposure to coal, metal, and rubber; and a family history of gastric cancer or inherited genetic disorders (e.g., familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer).⁶ An estimated 5% to 10% of gastric cancers have a familial component, and 3% to 5% are associated with inherited cancer predisposition syndromes. Screening for gastric cancer is not routinely performed in the U.S. because of a lack of evidence to show that screening would be cost-effective or would result in decreased mortality.⁶

Patients with gastric cancer generally develop nonspecific symptoms, including weight loss, abdominal pain, and nausea, and they typically present with advanced disease. Cancer originating in the GEJ usually presents as dysphagia. Occult GI bleeding is also common; however, overt bleeding is typically unusual, occurring in only 20% of cases.³ Following clinical presentation, diagnosis is confirmed through endoscopy and biopsy. Endoscopic ultrasound is preferred if there is no evidence of distant metastatic disease. In the case of documented or suspected metastatic adenocarcinoma, HER2/new testing using immunohistochemistry and fluorescence in situ hybridization is recommended to assess eligibility for therapy with trastuzumab (Herceptin, Genentech).

Staging from the American Joint Committee on Cancer is based upon primary tumor (T), regional lymph nodes (N), and distant metastasis (M) classification. Anatomic stage and prognostic group ranges from stage 0 to stage IV depending on the TNM stage. Clinical staging based on findings from endoscopic ultrasound directs the initial approach to therapy. Following the initial workup, patients are classified as Tis or T1a, locoregional (stages I–III or M0), or metastatic (stage IV or M1). Treatment choice is then based on whether the patient is deemed medically fit or medically unfit to undergo surgery. Patients who are medically fit with stage Tis or T1a undergo endoscopic resection or surgery. Those with locoregional disease may either go straight to surgery or receive neoadjuvant chemotherapy or chemoradiation prior to surgery. Following surgery, patients may be observed or receive adjuvant chemotherapy and/or chemoradiation depending upon margins post-resection and whether or not they received neoadjuvant treatment. Those with advanced stage IV disease are referred to palliative management, which includes chemotherapy, a clinical trial, or best supportive care depending on the patient’s Karnofsky performance status or Eastern Cooperative Oncology Group (ECOG) performance status.

Currently, there is no single standard first-line regimen for metastatic or locally advanced unresectable gastric cancer. The decision on which regimen to use depends on the patient’s performance status, access to frequent evaluation for toxicity, and the toxicity profile of the regimen. Standard cytotoxic chemotherapy used in the first-line setting for advanced gastric or GEJ adenocarcinoma is typically administered as a two-drug regimen of fluoropyrimidine (fluorouracil [Adrucil, Teva] or capecitabine [Xeloda, Genentech]) and cisplatin (Plati-
nol, Bristol-Myers Squibb). Three-drug regimens of DCF (docetaxel [Taxotere, Sanofi-Aventis], cisplatin [Platinol, Bristol-Myers Squibb], and fluorouracil; DCF modifications; ECF (epirubicin [ElleSciences, Pfizer], cisplatin, and fluorouracil); or ECF modifications (epirubicin, oxaliplatin [Eloxatin, Sanofi-Aventis], and fluorouracil; epirubicin, cisplatin, and capetitabine; or epirubicin, oxaliplatin, and capetitabine) may be considered in patients with good performance status and access to frequent monitoring for toxicity. Trastuzumab is given as first-line therapy in the setting of HER2-positive disease in combination with cisplatin and fluorouracil or in combination with other chemotherapy agents. Median survival following first-line treatment ranges from eight to 10 months. Second-line salvage chemotherapy for eligible patients, typically with a single agent such as irinotecan or a taxane (paclitaxel or docetaxel), may extend survival by one to two months.

In an effort to address the lack of effective second-line treatment options for gastric cancer, a new, targeted systemic drug that acts on the angiogenesis pathway has been developed. Angiogenesis is the physiological formation and development of new blood vessels from pre-existing blood vessels. Tumors, including gastric adenocarcinomas, depend on this path-way for growth and metastasis. In April 2014, the Food and Drug Administration (FDA) approved ramucirumab (Cyramza, Eli Lilly and Company), making it the first drug approved as second-line therapy for patients with advanced stomach cancer or GEJ adenocarcinoma.

**INDICATIONS AND USAGE**

Ramucirumab is approved as a single agent or in combination with paclitaxel for the treatment of advanced or metastatic gastric or GEJ adenocarcinoma in patients with disease progression on or after prior fluoropyrimidine or platinum chemotherapy regimens. Following its approval for gastric cancer, the FDA expanded the approved use of ramucirumab to non–small-cell lung cancer (NSCLC) and colorectal cancer. Ramucirumab is indicated for use in combination with docetaxel for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should exhibit disease progression on FDA-approved therapy for these mutations prior to receiving ramucirumab.

Ramucirumab is also approved for use in combination with FOLFIRI (folinic acid, fluorouracil, and irinotecan) for the treatment of patients with metastatic colorectal cancer with disease progression on or after prior therapy with bevaci-zumab (Avastin, Genentech), oxaliplatin, and a fluoropyrimidine.

**PHARMACOLOGY**

**Mechanism of Action**

Vascular endothelial growth factor A (VEGF-A) is a proangiogenic factor that promotes blood-vessel dilation and permeability along with new blood-vessel formation. Studies have shown that many tumors overexpress this factor, and multiple studies in gastric cancer patients demonstrate an association between VEGF-A levels and overall survival or disease stage. VEGF-A acts as a ligand primarily for two tyrosine kinase receptors: vascular endothelial growth factor receptor (VEGFR)-1 and VEGFR-2. VEGFR-2 is associated with stronger signal transmission and is responsible for most of the proangiogenic actions of VEGF-A. Selective VEGFR-1 stimulation transmits weak signals, but VEGFR-1 can heterodimerize with VEGFR-2 to produce enhanced downstream signaling. Animal studies have shown that inhibition of VEGF-A signaling effectively suppresses tumor angiogenesis. VEGF-C and VEGF-D are ligands for VEGFR-3, which mediates lymphatic penetration, growth, and development processes that lead to tumor metastasis to lymph nodes (demonstrated in Figure 1).

Ramucirumab is a recombinant human IgG1 monoclonal antibody that binds to VEGFR-2 and acts as an antagonist to VEGF-A, VEGF-C, and VEGF-D. Inhibition of receptor activation impedes VEGF-A–stimulated proliferation and migration of endothelial cells, which ultimately results in reduced tumor vascu-larity and growth.

**Pharmacokinetics**

Ramucirumab is administered as a one-hour intravenous (IV) infusion, ensuring complete bioavailability. The area under the curve (AUC) (mean ± standard deviation) observed in patients at 8 mg/kg was 43,824 ± 10,341 h•mcg/mL after the first infusion and 132,789 ± 47,746 h•mcg/mL after the last infusion in a four-week cycle. Mean maximum concentration (C_{max}) was 325 ± 62.2 mcg/mL after the first infusion and 497 ± 168 mcg/mL after the last infusion.

![Figure 1 The VEGF Signaling Pathway](image-url)
infusion. Results from phase 1 pharmacokinetic studies showed a disproportionate increase in $C_{\text{max}}$ and AUC following administration of the first and last infusions in cycle 1 as the dose increased from 2 to 16 mg/kg. Mean trough concentrations measured seven days after treatment were 93.4 ± 21 mcg/mL following the first infusion and 176 ± 57.9 mcg/mL following the last infusion, both of which were in the target trough value of at least 20 mcg/mL. Negligible accumulation of ramucirumab was noted over a minimum of 32 treatment cycles.11

Clearance of ramucirumab decreases disproportionately as doses increase from 2 to 16 mg/kg, suggesting saturation of the clearance mechanism. Clearance from phase 1 studies was 0.190 ± 0.038 mL/h/kg and 0.067 ± 0.025 mL/h/kg following first and last infusions of 8 mg/kg. The decrease in clearance rate after initial and final infusions in cycle 1 implies patients were approaching steady state. The mean half-life at an 8 mg/kg dose was 123 hours for the first infusion and 318 hours for the last infusion.11

Pharmacodynamics
Post-treatment analysis of serum biomarkers showed increased VEGF-A concentrations as well as decreased VEGFR-1 and VEGFR-2 concentrations almost immediately following treatment; these effects were sustained throughout extended cycles and were independent of dose. Post-treatment assessment with dynamic contrast-enhanced MRI showed decreased tumor perfusion and vascularity.11

PIVOTAL CLINICAL TRIALS IN GASTRIC CANCER
Clinical studies of ramucirumab in patients with metastatic or unresectable, locally recurrent gastric or GEJ adenocarcinoma began in October 2009. Published literature includes efficacy and safety studies for other malignancies as well. This article will primarily highlight the use of ramucirumab for patients with gastric or GEJ adenocarcinoma.

The REGARD trial was a phase 3, international, randomized, double-blind, placebo-controlled trial conducted to demonstrate improvement in overall survival (OS). Secondary endpoints included progression-free survival (PFS), response rate (RR), and duration of response (DOR). Patients with metastatic gastric or GEJ adenocarcinoma following disease progression on first-line platinum or fluoropyrimidine-containing combination therapy were eligible; 355 patients received either ramucirumab or placebo at 8 mg/kg once every two weeks in combination with best supportive care. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal from the trial.

Ramucirumab demonstrated statistically significant improvement in OS and PFS after a median follow-up of 4.9 months in the ramucirumab group and 3.7 months in the placebo group. Median OS was 5.2 months in the ramucirumab group compared with 3.8 months in the placebo group ($P = 0.047$). Treatment with ramucirumab reduced the risk of disease progression or death by 32% ($P < 0.0001$). Median PFS in the ramucirumab group was 2.1 months compared with 1.3 months in the placebo group ($P < 0.0001$). There was a statistically significant difference in the disease control rate between the ramucirumab (49%) and placebo (23%) groups. DOR was 4.2 months with ramucirumab and 2.9 months with placebo ($P = 0.036$). The rates of adverse events were similar between groups; however, more patients experienced hypertension in the ramucirumab group.7

The RAINBOW study, a phase 3, randomized, multicenter, double-blind, placebo-controlled trial, compared the combination of ramucirumab 8 mg/kg on days 1 and 15 and paclitaxel 80 mg/m² on days 1, 8, and 15 of a 28-day cycle with placebo and paclitaxel for second-line treatment of gastric and GEJ adenocarcinoma in 665 patients. The primary endpoint was OS. Secondary endpoints included PFS, time to progression (TTP), and overall RR.

Median OS was 9.63 months in the ramucirumab/paclitaxel group and 7.36 months in the placebo/paclitaxel group ($P = 0.0169$). A statistically significant improvement in PFS (4.4 months versus 2.86 months; $P < 0.0001$) was reported with the ramucirumab/paclitaxel combination. The RR was significantly higher in the ramucirumab/paclitaxel group (28%) compared with the placebo/paclitaxel group (16%). TTP was also longer with ramucirumab/paclitaxel (5.5 months versus 3.0 months; $P < 0.0001$). Neutropenia was reported more frequently in the ramucirumab/paclitaxel group, but incidence of febrile neutropenia was comparable between arms.22 Based on the results of the RAINBOW trial, combination therapy with ramucirumab and paclitaxel is preferred over ramucirumab alone.6

PIVOTAL CLINICAL TRIALS IN OTHER MALIGNANCIES
Phase 2 trials have been performed to demonstrate the efficacy and safety of ramucirumab as therapy for other malignancies. Approval of ramucirumab in combination with docetaxel in NSCLC was based on a phase 3 trial (REVEL) completed with ramucirumab plus docetaxel versus docetaxel alone as second-line therapy in NSCLC patients that showed improved OS (10.5 months versus 9.1 months) with no detriment to patient-reported global quality of life. Toxicities, most commonly neutropenia, febrile neutropenia, fatigue, leukopenia, and hypertension, were managed with appropriate dose reductions and supportive care without substantial reductions in the planned dose intensity of therapy.13

Approval of ramucirumab in combination with FOLFIRI in metastatic colorectal cancer was based on a phase 3 trial (RAISE) completed with ramucirumab plus FOLFIRI versus FOLFIRI alone that resulted in significantly improved OS (13.3 months versus 11.7 months) and PFS (5.7 months versus 4.5 months). Adverse events included neutropenia, febrile neutropenia, hypertension, diarrhea, and fatigue.14

Ramucirumab was studied as first-line monotherapy in patients with advanced hepatocellular carcinoma. Median PFS was 4.0 months and OS was 12.0 months. The most common grade 3 or higher adverse reactions were hypertension, GI hemorrhage, and infusion-related reactions. Results from this trial indicate potential anticancer activity with an acceptable safety profile.15

Ramucirumab alone or in combination with dacarbazine was associated with an acceptable safety profile in patients with metastatic melanoma. Although the study was not powered for comparison between treatment arms, PFS appeared greater with combination therapy (2.6 months versus 1.7 months). Secondary end-
ADVERSE DRUG REACTIONS

The AEs reported below reflect exposure to ramucirumab in the phase 3 REGARD trial of best supportive care plus either ramucirumab or placebo. These patients were treated with 8 mg/kg of ramucirumab once every two weeks. Patients received a median of four doses of ramucirumab over a median duration of eight weeks. Thirty-two patients received ramucirumab for at least six months. The most commonly occurring AEs of any grade of severity included hypertension (16%) and diarrhea (14%). The most common serious AEs included anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were required in 11% of patients. Additional clinically relevant adverse reactions were headache (9%), proteinuria (8%), hypotension (6%), neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), and arterial thrombosis (1.7%), which included myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia. Two patients who developed proteinuria withdrew from the trial.

Table 1 Dosage Modifications for Ramucirumab for Significant Adverse Events

<table>
<thead>
<tr>
<th>Table 1 Dosage Modifications for Ramucirumab for Significant Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reactions</td>
</tr>
<tr>
<td>• Reduce infusion rate by 50% for grade 1 or 2.</td>
</tr>
<tr>
<td>• Permanently discontinue for grade 3 or 4.</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>• Hold for severe hypertension until controlled with medical management.</td>
</tr>
<tr>
<td>• Permanently discontinue for severe hypertension that cannot be controlled with antihypertensives.</td>
</tr>
<tr>
<td>Proteinuria</td>
</tr>
<tr>
<td>• Hold for urine protein levels ≥ 2 g/24 hours; re-initiate treatment at 6 mg/kg every 2 weeks or urine protein level returns to &lt; 2 g/24 hours.</td>
</tr>
<tr>
<td>• If protein level ≥ 2 g/24 hours reoccurs, hold and reduce the dose to 5 mg/kg every 2 weeks or the urine protein level returns to &lt; 2 g/24 hours.</td>
</tr>
<tr>
<td>• Permanently discontinue for urine protein level &gt; 3 g/24 hours or in the setting of nephrotic syndrome.</td>
</tr>
<tr>
<td>Wound-healing complications</td>
</tr>
<tr>
<td>• Hold prior to scheduled surgery until wound is fully healed.</td>
</tr>
<tr>
<td>Arterial thromboembolic events,</td>
</tr>
<tr>
<td>gastrointestinal perforation, or</td>
</tr>
<tr>
<td>grade 3 or 4 bleeding</td>
</tr>
<tr>
<td>• Permanently discontinue</td>
</tr>
</tbody>
</table>

Use in Specific Populations

Pregnancy

Animal reproduction studies have not been conducted with ramucirumab. Animal studies involving the VEGF pathway report that loss of the VEGFR-2 gene in mice resulted in embryofetal death, along with disorganized blood vessels and blood islands in the yolk sac. Interference with the VEGF signaling pathway is also associated with developmental abnormalities, including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels. Based on these findings, it can be assumed that ramucirumab can cause fetal harm when administered to pregnant women. The FDA has designated this medication as pregnancy category C. If ramucirumab is used during pregnancy or if the patient becomes pregnant while taking ramucirumab, a discussion should take place about the potential hazards to the fetus.

Nursing Mothers

It is not known whether ramucirumab is excreted in breast milk. However, because IgG and many drugs are excreted in human milk and because of the potential risk for serious adverse reactions in nursing infants exposed to ramucirumab, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the risk–benefit profile.

Pediatric Use

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

Geriatric Use

Clinical trials included insufficient numbers of patients 65 years of age and older to determine adequately whether these patients respond differently to ramucirumab than younger patients. Of the 236 patients who received ramucirumab in the REGARD trial, 35% were 65 and older, while 9% were 75 and older. The manufacturer does not recommend dosage adjustments in older patients.

Renal and Hepatic Impairment

Ramucirumab has not been evaluated in studies to determine the effect of renal or hepatic impairment on the pharmacokinetic profile.
Drug and Food Interactions

Ramucirumab has not been evaluated in formal drug interaction studies.

WARNINGS AND PRECAUTIONS

The manufacturer’s labeling does not include any contraindications for ramucirumab use. However, hemorrhage, arterial thromboembolic events, hypertension, infusion-related reactions, GI perforations, impaired wound healing, clinical deterioration in patients with Child-Pugh B or C cirrhosis, and reversible posterior leukoencephalopathy syndrome (RPLS) are all possible AEs that require monitoring.

Ramucirumab is associated with an increased risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Of the patients studied in clinical trials, 3.4% experienced severe bleeding. Patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment, so the risk of gastric bleeding in patients who are treated with ramucirumab for gastric cancer and are also receiving NSAIDs is not known. Ramucirumab should be permanently discontinued in patients who experience severe bleeding.

Serious and potentially fatal arterial thromboembolic events (ATEs), which include myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred in 1.7% of 236 patients receiving single-agent therapy with ramucirumab. Ramucirumab should be permanently discontinued in patients who experience a severe ATE.

Severe hypertension occurred in 8% of patients treated with ramucirumab as a single agent. Hypertension should be controlled prior to starting treatment with ramucirumab. Blood pressure should be monitored at least every two weeks or more often if necessary during treatment. If severe hypertension occurs, ramucirumab should be temporarily withheld until blood pressure is under control. Ramucirumab should be permanently discontinued if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-related reactions (IRRs), including two severe events, occurred in 16% of patients prior to the establishment of premedication recommendations. Most IRRs occurred during or following a first or second ramucirumab infusion. Symptoms of IRRs included rigors or tremors, back pain, back spasms, chest pain with or without tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. Severe cases of bronchospasm, supraventricular tachycardia, and hypotension have also been reported. Patients should be monitored during infusions for signs and symptoms of IRRs in a setting where resuscitation equipment is available. Ramucirumab should be immediately and permanently discontinued for grade 3 or 4 IRRs.

Due to the antiangiogenic activity of ramucirumab, risk of GI perforation, a potentially fatal event, increases during treatment. Ramucirumab-associated GI perforation occurred in 0.7% of patients. Ramucirumab should be permanently discontinued in patients who experience a GI perforation.

Ramucirumab has not been studied in patients with serious or nonhealing wounds, but based on its antiangiogenic activity, treatment may adversely affect wound healing. Ramucirumab should be held prior to surgery. Treatment with ramucirumab may be restarted following the surgical procedure based on clinical judgment of adequate wound healing. Ramucirumab should be discontinued if a patient develops wound-healing complications during therapy until the wound is fully healed.

Clinical deterioration, presenting as new-onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis. Ramucirumab should be used in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

RPLS occurred in less than 0.1% of patients during clinical studies with ramucirumab. In patients who develop RPLS, the diagnosis should be confirmed with MRI and ramucirumab should be discontinued. Symptoms typically resolve or improve within days, but some patients with RPLS can experience ongoing sequelae or death.

COST

Ramucirumab is available in single-dose, individually packaged vials of 100 mg/10 mL ($1,224) and 500 mg/50 mL ($6,120). Patients who are not eligible for copay support can be referred to Eli Lilly and Company’s PatientOne program, a patient assistance service for Lilly oncology products.

P&T COMMITTEE CONSIDERATIONS

Ramucirumab is the first single agent approved for the second-line treatment of advanced or metastatic gastric or GEJ adenocarcinoma. Approval of this agent satisfies an unmet need for this patient population. In addition, the FDA has expanded the approved use of ramucirumab to metastatic NSCLC and metastatic colorectal cancer. Hospitals should consider adding ramucirumab to their formularies.

CONCLUSION

Ramucirumab is the first FDA-approved drug for second-line therapy in patients with advanced or metastatic gastric or GEJ adenocarcinoma. Approval was based on evidence of improved OS and PFS in a multinational, randomized, double-blind, placebo-controlled study. The most common adverse reactions observed in ramucirumab-treated patients were hypertension and diarrhea. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Gastric Cancer recommend ramucirumab as monotherapy (category 1) or in combination with paclitaxel (category 2A) for second-line treatment in patients with advanced or metastatic gastric and GEJ adenocarcinoma. Since better results were seen when ramucirumab was combined with paclitaxel, ramucirumab in combination with paclitaxel is preferred over single-agent ramucirumab in the NCCN guidelines. Ramucirumab provides a new option for the effective second-line treatment of gastric cancer; it is expected to improve outcomes and transform the standard of care for gastric cancer patients with progressive disease.

REFERENCES


6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.1.2014. ©National Comprehensive Cancer Network, Inc. 2014. All rights reserved. Accessed August 6, 2014. To view the most recent and complete version of the guideline, go online to NCCN.org. National Comprehensive Cancer Network®, NCCN®, NCCN Guidelines®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.


