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Clinical Pathways for Advanced Stage Gastric Cancer:

Standardizing Practice to Decrease Variability and Improve Outcomes

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EXECUTIVE SUMMARY

Gastric cancer is the fifth most diagnosed cancer worldwide and the third leading cause of cancer deaths. In the United States and other countries with low rates of gastric cancer, the population is not routinely screened for the disease, so it is diagnosed at later stages and has worse prognosis. For patients with advanced gastric cancer, the median overall survival rate is less than 5 months with best supportive care management.

Palliative therapy with chemotherapy and other agents can improve overall survival and quality of life for patients with advanced or recurrent disease. The 2016 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Gastric Cancer (Version 3.2016) note that first-line therapy using two chemotherapy agents is preferable for patients with advanced disease, though a combination with three agents is a good option for patients who are medically fit. The choice of a second-line therapy for stage IV or recurrent gastric cancer depends on first-line treatment and the patient's performance status. Data on the cost-effectiveness of these treatments are limited, and there is evidence of high variability in treatment for patients with advanced stage gastric cancer.

Clinical pathways are frequently used to support treatment decision-making for oncology, weighing clinical benefit, toxicity, and cost considerations to arrive at the highest value treatment pathway. Given that gastric cancer does not have a widely accepted standard treatment for either first- or second-line treatment, clinical pathways have the potential to standardize practice, decrease variability, and improve outcomes for this disease.

INTRODUCTION

Gastric cancer is the fifth most diagnosed cancer worldwide and the third leading cause of cancer deaths. The prevalence is much higher in Asian countries than in Western ones, with the highest incidence in China. While the incidence is low in the United States, as the 16th most diagnosed cancer in the country,[1] there were an estimated 26,370 new gastric cancer diagnoses (1.3% of all newly diagnosed cancers),[2] and an estimated 10,730 deaths from disease, in 2016. Gastric cancer primarily affects older adults, at 39.4 diagnoses per 100,000 people for individuals aged 65 years and older, vs 2.9 diagnoses per 100,000 in those younger than 65 years.[3] Risk factors for developing gastric cancer include obesity,[4] infections from *Helicobacter pylori*,[5] as well as lifestyle and dietary factors like smoking, high salt intake, and possibly heavy alcohol use.[6] Men are twice as likely to be diagnosed with gastric cancer as women, and up to 10% of gastric cancer cases may have a familial genetic link predisposing to the disease.[7]

Diagnosis of gastric cancer is typically made from a surgical or gastroscopic biopsy, reviewed by a pathologist.[7] A postdiagnosis work-up for initial risk assessment and staging includes a complete history and physical examination, complete blood count, and comprehensive chemistry profile. Imaging includes a computed tomography (CT) scan of the chest, abdomen and pelvis, with contrast for preoperative staging; positron emission tomography (PET)/CT for detecting lymph node involvement or metastases;[7] and an endoscopic ultrasound to help determine tumor invasion depth[6] and assess the depth of primary tumor invasion (T-stage) and number of positive nodes (N-stage).[7] If metastases are suspected or found, testing for human epidermal growth factor receptor 2 (HER2) expression is recommended.[6]

In the United States and other countries with low rates of gastric cancer, the population is not routinely screened for the disease. Thus, gastric cancer is usually detected at a later stage.[6] Detecting gastric cancer during the more easily treated early stages is challenging, because patients experience no symptoms or nonspecific symptoms. By the time patients are diagnosed, 34% have distant metastases, 30% have regional spread, and 25% have localized disease, with the remaining patients not yet staged.[8]

A number of factors help determine a patient's prognosis, including T-stage,[9] N-stage, presence or absence of metastases (M-stage),[10] and surgical resectability.[6] Surgery may be curative in cases in which gastric cancer is diagnosed early; 5-year survival is 64.1% for those with localized disease. However, patients who undergo surgery to remove the lesion generally still often experience metastasis or recurrence. Once the cancer advances, the 5-year survival rate decreases to 4.2% for patients with advanced stage metastatic disease.[1] For these patients, the median overall survival rate (OS) is less than 5 months when getting best supportive care management. With newer first- and second-line chemotherapy and treatment combinations, the OS is typically up to 12 months.[8]

TREATMENT OPTIONS FOR ADVANCED STAGE METASTATIC GASTRIC CANCER

For patients with metastatic gastric cancer, surgery is not a curative option.[11] Palliative chemotherapy—whether single agent or in combination—can significantly improve patients' OS and quality of life (QOL) compared with best supportive care alone.[6] The 2016 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Gastric Cancer (Version 3.2016) recommend that a patient's performance status be used to determine whether they are offered best supportive care alone or in combination with palliative care in the form of chemotherapy and other agents (see ***Gastric Cancer Treatment Algorithm***).[6]

The NCCN Guidelines note that first-line therapy using two chemotherapy agents is preferable for patients with advanced or recurrent disease because of lower toxicity, although a combination with three agents is a good option for patients who are medically fit.[6] In the United States, a combination of cisplatin and a fluoropyrimidine (fluorouracil or capecitabine) is commonly recommended, though cisplatin may be substituted for oxaliplatin.

In addition to chemotherapy agents, physicians may add targeted systemic therapies if warranted. Patients testing positive for HER2 overexpression benefit from the first-line addition of trastuzumab, a humanized monoclonal antibody.[12] Trastuzumab improves overall survival in patients whose tumors are immunohistochemistry (IHC) 2+ and fluorescence in situ hybridization–positive or IHC 3+.[6]

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> ***—Jeffrey William Clark, MD***

The choice of a second-line therapy for advanced gastric cancer depends on first-line treatment and the patient's performance status.[6] Ramucirumab as a single agent or in combination with paclitaxel are considered preferred second-line treatment options for locally advanced or metastatic gastric adenocarcinoma.[13] Irinotecan and docetaxel are also recommended for second-line treatment.[6]

"Standard of care includes combinations of taxols, irinotecan, and ramucirumab, of course depending upon whatever treatment patients initially received and what residual side effects they have sustained," said Valerie Lee, MD, a gastric oncologist at The Sydney Kimmel Comprehensive Cancer Center at Johns Hopkins (Baltimore, MD). "However, clinical trials should also be considered early on."

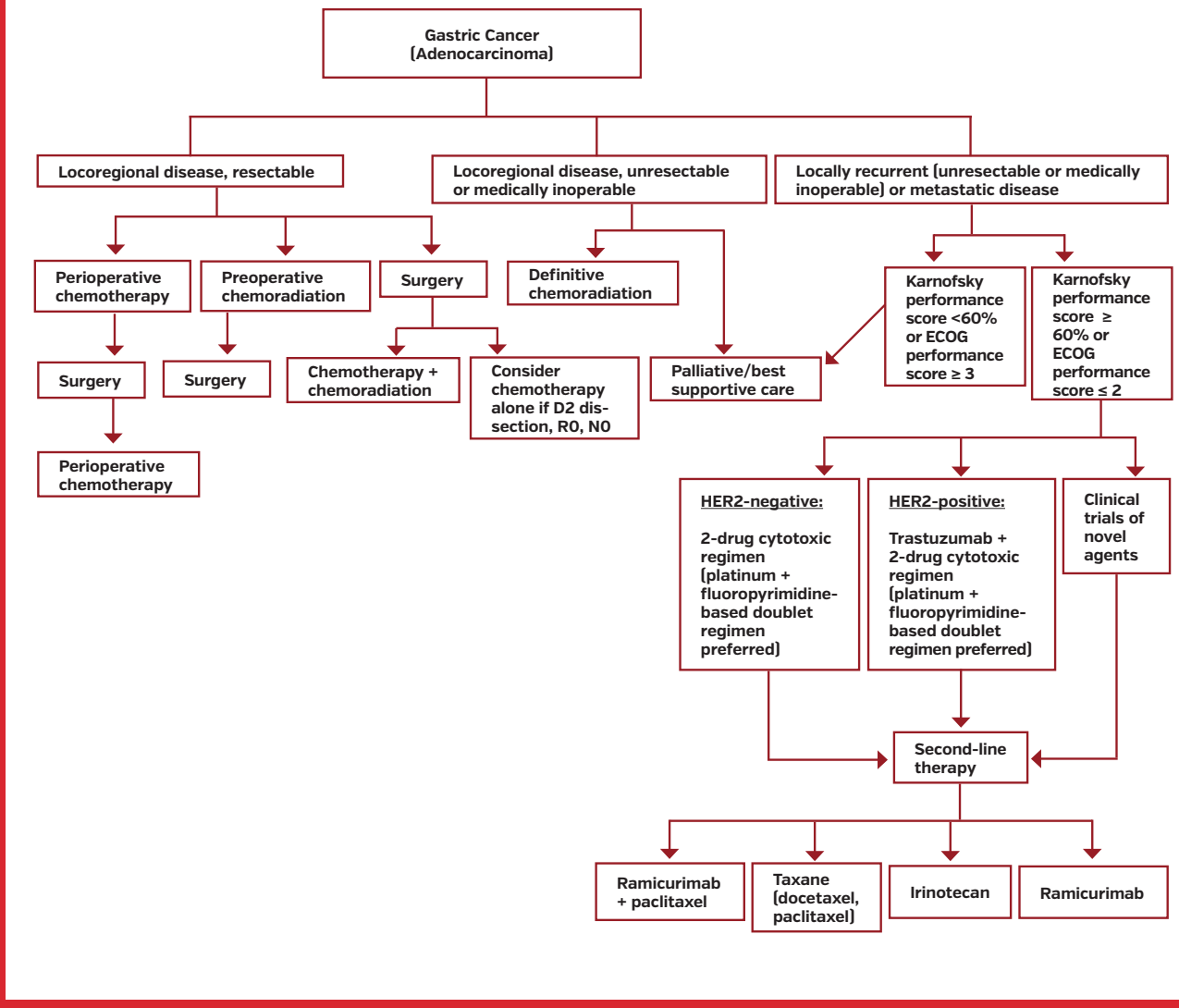
Ramucirumab is a monoclonal antibody that targets the vascular endothelial growth factor pathway. One randomized, phase 3 international trial included 355 patients who received second-line treatment after platinum- or fluoropyrimidine-based treatment failed. They were randomly assigned (2:1) to receive ramucirumab and best supportive care or placebo and best supportive care. Results showed that use of ramucirumab significantly improved median OS (5.2 vs 3.8 months) and progression-free survival (PFS; 2.1 vs 1.3 months). Ramucirumab was well tolerated; the only relevant side effect in the ramucirumab group was hypertension (15% for ramucirumab, 8% for placebo).[14]

The international RAINBOW phase 3 trial randomly assigned 665 metastatic gastric cancer patients to paclitaxel plus ramucirumab or paclitaxel plus placebo after they received the same first-line therapies of a platinum therapy plus fluoropyrimidine. Researchers found that ramucirumab improved OS in both groups (9.6 months for ramucirumab/paclitaxel; 7.4 months for paclitaxel/placebo). Increased side effects for the ramucirumab/paclitaxel group and paclitaxel/placebo group were grade 3 or 4 neutropenia (40.7% vs 18.8%), hypertension (14.1% vs 2.4%) and fatigue (11.9% vs 5.5%). Even with increased side effects, researchers concluded that ramucirumab plus paclitaxel could be seen as a new standard second-line treatment for patients with advanced gastric cancer.[15]

The chemotherapy drug irinotecan was compared with best supportive care in a prospective, multicenter, open label, randomized, phase 3 study to evaluate the impact of second-line chemotherapy on survival. A total of 40 patients with metastatic or locally advance gastroesophageal junction or gastric adenocarcinoma were included in the study. Second-line chemotherapy with irinotecan significantly prolonged median OS compared with best supportive care (4 months in the irinotecan arm compared with 2.4 months in the best supportive care arm). The study was closed prematurely due to poor accrual.[16]

A South Korean phase 3 study with 223 patients compared irinotecan to paclitaxel as a second-line treatment after first-line therapy with a fluoropyrimidine plus a platinum agent. The median OS was 9.5 months for paclitaxel patients, vs 8.4 months for the irinotecan group, and both groups experienced side effects including neutropenia (28.7% in the paclitaxel group; 39.1% in the irinotecan group), anemia (21.3% vs 30.0%), and anorexia (7.4% vs 17.3%). Two patients in the irinotecan group suffered treatment-related deaths. Many study patients subsequently received third-line chemotherapy (89.8% for the paclitaxel group; 72.1% for the irinotecan group). Researchers concluded that both agents are reasonable options for second-line treatment.[17]

A UK study focused on docetaxel as a second-line therapy to investigate survival and QOL in patients for whom first-line treatment with a platinum and fluoropyrimidine regimen failed. The open-label, phase 3 trial enrolled 168 patients, half of whom received docetaxel plus active symptom control, and half of whom received active symptom control alone. The overall survival was 5.2 months for the docetaxel group vs 3.6 months for the active symptom control group. The docetaxel group had a higher incidence of grade 3 or 4 neutropenia (15% vs 0), infection (19% vs 3%), and febrile neutropenia (7% vs 0). However, the docetaxel group experienced less pain, nausea, constipation, dysphagia, and abdominal pain. The global QOL was similar for both groups.[18]



Gastric Cancer Treatment Algorithm. Adapted from NCCN Guidelines: Gastric Cancer, Version 3.2016[6] and Version 1.2017.[13] Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; N, number of positive nodes; R, residual tumor classification.

ECONOMIC CONSIDERATIONS

In a 2015 study in *Journal of Gastric Cancer*, the costs to Medicare for the treatment of gastric cancer were estimated to be $300 million for the 22,000 patients that researchers predicted would be diagnosed in 2014.[3] This estimate was based on data from the Surveillance, Epidemiology and End Results database between 2000 and 2009 and only included costs for patients over age 65 who presented with advanced gastric cancer and received at least first-line treatment. Researcers estimated a median per-patient average of $70,000 (±56,620) in gastric cancer-related costs. For those receiving active treatment subsequent to firstline chemotherapy vs supportive care alone, disease-related costs increased by an estimated $25,216.[3] Because the Population Reference Bureau estimates a doubling of the 65+ age group by 2060,[19] this number could drastically rise as the population continues to age.

Data on the cost-effectiveness of second-line treatments for advanced stage gastric cancer are limited. A 2017 study compared the incremental cost-effectiveness ratio, dividing the incremental cost by the number of quality-adjusted life-years (QALYs) saved, between six second-line therapy options (irinotecan, docetaxel, paclitaxel, ramucirumab, paclitaxel plus ramucirumab, and palliative care), based on direct medical costs from a third-party payer perspective.[20] The most utilized treatments in the study population were docetaxel, ramucirumab alone, and palliative

care. Researchers found the lowest lifetime cost was with irinotecan, with a QALY gain of 0.35 year. Paclitaxel and paclitaxel/ramucirumab resulted in higher QALYs gained, with an incremental cost of $86,815 and $1,056,125 per QALY gained, respectively. The researchers concluded that irinotecan alone is the most cost-effective regimen, based on a willingness-to-pay (WTP) threshold set at $50,000 per QALY gained. They estimated that paclitaxel/ramucirumab would not be cost-effective at a WTP threshold less than $400,000/QALY gained, and paclitaxel was cost-effective when using the $160,000/QALY gained WTP threshold.[20]

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> —*Valerie Lee, MD*

Jeffrey William Clark, MD, director of clinical trial support at Massachusetts General Hospital (Boston, MA), said that the way in which clinicians should consider economic issues for various second-line treatments is a difficult issue. "While there is a societal obligation to try to minimize the cost of therapy, there is an absolute obligation to the patient to optimize the clinical benefit–toxicity ratio," Dr Clark said. "If there were information directly comparing the benefit/risk/overall cost—not of just the drugs but the real-world cost of the regimen in terms of additional physician visits, hospitalizations, and need of additional support and medications—this would be much easier to integrate into decision-making. But, there has never been a phase 3 trial of FOLFIRI [folinic acid, fluorouracil, and irinotecan combination] vs paclitaxel/ramucirumab in the second-line setting, nor is there likely to be." He noted that a European phase 2 trial is randomizing these two arms, which he hopes will provide better guidance as to which option is preferable based on all the factors.

Dr Clark added, "[I]mmunotherapy is likely to be approved and that will change how treatments are delivered in the second-line setting, and potentially the first-line setting as well, so this will evolve."

Dr Lee agreed. "With excitement about immunotherapy and genomic testing in gastric cancer, cost considerations will become that much more important."

REAL-WORD TREATMENT PATTERNS: FRAGMENTATION AND VARIABILITY

The 2015 *Journal of Gastric Cancer* study of Medicare patients from 2000 to 2009 found wide variability in the selection of second-line treatments. In the study population, 55% of patients received additional treatment after completing first-line therapy, while the remaining 45% received only supportive care. About 40% of patients received second-line chemotherapy, which most commonly included docetaxel, paclitaxel, or 5-fluorouracil (alone and in combination with other agents). The most popular was docetaxel, but that was only used by 8% of patients. The authors noted that the high variability may be due to limited data to support second-line chemotherapy regimens, with no randomized trials being published before 2011.[3]

In another study, researchers used the IMS Health Oncology Database to search for patients with gastric cancer aged 18 and older from 2004 to 2012.[1] Of the 1982 patients with chemotherapy data, 42% received both first- and second-line therapy. From the Truven Health MarketScan Research database for the same time period, another 5299 patients with gastric cancer receiving first-line therapy were identified, and 54.5% of those also received second-line therapy. The majority of patients from both data sets received platinum and/or fluoropyrimidine therapies for first-line treatment. In contrast, for second-line treatment, at least 350 unique treatment regimens were identified in the Truven Health data set, and 131 were identified in the IMS data set.[1]

The researchers noted that, even when the agents were grouped by therapeutic class, the variability was still high. The study authors concluded that the selection of second-line therapy regimens is not currently evidence-based and has great variability. "Few patients received treatments supported by randomized trial data, which included taxanes and irinotecan during the study period, in the setting of second-line gastric cancer," they wrote. "It may be in part the consequence of the lack of strong phase 3 data that a large amount of heterogeneity was observed during this time period."[1]

THE POTENTIAL OF CLINICAL PATHWAYS TO STANDARDIZE TREATMENT DECISION-MAKING

Given that gastric cancer does not have a widely accepted standard treatment for either first- or second-line treatment,[15] the NCCN Guidelines emphasize that it is especially important that decisions are made by a multidisciplinary team consisting of surgeons, medical and radiation oncologists, radiologists, and pathologists.[6] Clinical pathways are frequently used as a tool to support multidisciplinary treatment decision-making for oncology to standardize practice, decrease variability, and improve outcomes. Clinical pathways are developed by weighing clinical benefit, toxicity, and cost considerations to arrive at the highest value treatment pathway.

"Clinical pathways… are invaluable as they help to consolidate the large body of knowledge into a comprehensible form for us busy practitioners," said Dr Lee. "While most of us feel comfortable discussing clinical benefit and toxicity with patients, cost considerations are often more difficult. Partially [that is] because it is not as emphasized during training, but also because it is difficult to deny potentially beneficial therapies to individual patients. The NCCN Evidence Blocks are a helpful new tool, though, and help take all of these items into consideration."

Most oncologists would rely on evidence-based established treatment options that primarily resulted from randomized phase 3 trials for their metastatic gastric cancer patients, said Dr Clark. "Specific decisions about the best treatment approach for any individual patient will also depend on factors specific to that patient, such as performance status, comorbid medical conditions such as diabetic neuropathy, and patient preferences based on available options."

In a 2016 article in the *World Journal of Gastroenterology*, authors argued that second-line therapy is currently underused, citing the low rates of second-line therapy dispensation in clinical trials.[21] While practitioners have debated the risks of exposing patients to additional toxic agents when they are experiencing declining performance status, the authors note that this argument is no longer valid given the strong data showing survival benefits with active treatment. After reviewing clinical trial results, the researchers found justification in using trastuzumab in the subset of eligible patients who did not receive it in the first-line setting, as well as ramucirumab monotherapy or in combination with paclitaxel, unless otherwise contraindicated.[21]

After reviewing recent studies, authors of a 2016 meta-analysis of second-line treatments concluded that, "the lack of universally accepted standard therapies beyond first line may have contributed to the poor survival rates in advanced gastric cancer seen until relatively recently… Despite these improvements, there are still no standardized treatment approaches for those with advanced disease, and optimal management is under debate."[21] They suggest that second-line treatment with ramucirumab plus paclitaxel could be regarded as a new standard for patients with advanced gastric and/or esophageal junction cancer, if they have good Eastern Cooperative Oncology Group (ECOG) performance status and progressed after finishing first-line chemotherapy.

They also suggest that oncologists need to choose first-line regimens combining good activity, good tolerability, and fewer toxic effects in order to optimize the potential benefits of second-line therapies. In that regard, the authors recommend platinum/fluoropyrimidine combination, or adding epirubicin to these two, as the best first-line regimen.[22]

"First-line treatments are fairly standardized across the board, and clinical pathways are certainly helpful in that setting, but they do become more difficult when there is no clear best treatment," Dr Lee said. Using NCCN Guidelines and other clinical pathways helps to standardize practice and decrease variability, she added, and offers great potential for supporting treatment decisions in second-line therapy. ▶

References

1. Hess LM, Michael D, Mytelka DS, Beyrer J, Liepa AM, Nicol S. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. *Gastric Cancer*. 2016;19 (2):607-615.
2. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA: A Cancer Journal for Clinicians*. 2014;64(1):9-29.
3. Karve S, Lorenzo M, Liepa AM, et al. Treatment patterns, costs, and survival among Medicare-enrolled elderly patients diagnosed with advanced stage gastric cancer: analysis of a linked population-based cancer registry and administrative claims database. *J Gastric Cancer*. 2015;15(20):87-104.
4. American Cancer Society: *Cancer Facts and Figures 2017*. Atlanta, GA: American Cancer Society; 2017.
5. Scheiman JM, Cutler AF. Helocobacter pylori and gastric cancer. *Am J Med*. 1999;106(2):222-226.
6. Ajani JA, D'Amico TA, Almhanna K, et al. NCCN Guidelines: Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(10):1286-1312.
7. Smyth EC, Verheij M, Allum W. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol*. 2016;27(suppl 5):v38-v49.
8. Wen F, Zheng H, Wu Y, et al. Cost-effectiveness analysis of fluoruracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in patients with advanced gastric adenocarcinoma. *Sci Rep*. 2016;6:36060.
9. Adachi Y, Yasuda K, Inomata M, et al. Pathology and prognosis of gastric carcinoma: well versus poorly differentiated type. *Cancer*. 2000;89(7):1418-1424.
10. Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than number? An analysis of 1038 patients. *Ann Surg*. 2000;232(3):362-371.
11. Mahar AL, El-Sedfy A, Brar SS, Johnson A, Coburn N. Are we lacking economic evaluations in gastric cancer treatment? *Pharmacoeconomics*. 2015;33(2):83-87.
12. Bartley AN, Washington MK, Colasacco C, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. *J Clin Oncol*. 2017;35(4):446-464.
13. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.1.2017.
14. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-esophageal junction adenocarcinoma (REGARD): an international, randomized, multicenter, placebo-controlled, phase 3 trial. *Lancet*. 2014;383(9911):31-39.
15. Wilke H, Muro K, Van Cutsen E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomized phase 3 trial. *Lancet Oncol*. 2014;15(11):1224-1235.
16. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer*. 2011;47(15):2306-2314.
17. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 Trial. *J Clin Oncol*. 2013;31(35):4438-4444.
18. Ford ER, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol*. 2014;15(1):78-86.
19. Mather M. Fact sheet: aging in the United States. Population Reference Bureau website. http://www.prb.org/Publications/Media-Guides/2016/aging-unitedstates-fact-sheet.aspx. January 2016. Accessed May 18, 2017.
20. Lam SW, Wai M, Lau JE, et al. Cost-effectiveness analysis of second-line chemotherapy agents for advanced gastric cancer. *Pharmacotherapy*. 2017;37(1):94-103.
21. Ghosn M, Tabchi S, Kourie HR, et al. Metastatic gastric cancer treatment: Second line and beyond. *World J Gastroenterol*. 2016;22(11):3069-3077.
22. Pericay C, Rivera F, Gomez-Martin C, Nunez I, Cassinello A, Imedio ER. Positioning of second-line treatment for advanced gastric and gastroesophageal junction adenocarcinoma. *Cancer Med*. 2016;5(12):3464-3474.

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