MEDICAL MUTUAL®

Drug Policy

Policy:	**201518-CC**	**Initial Effective Date: 07/30/2015**
Code(s):	**HCPCS J9308**	**Annual Review Date: 07/19/2018**
SUBJECT:	**Cyramza® (ramucirumab injection for intravenous use)**	**Last Revised Date: 07/19/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

Cyramza, a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist, is approved for the following indications:[1]

1) Gastric or gastroesophageal (GE) junction adenocarcinoma, as a single agent or in combination with paclitaxel injection for the treatment of patients with advanced or metastatic disease with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy;
2) Metastatic non-small cell lung cancer (NSCLC), in combination with docetaxel intravenous injection (Docefrez™, Taxotere®, generics) for the treatment of patients with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.
3) Metastatic colorectal cancer (mCRC), in combination with FOLFIRI (irinotecan, leucovorin, and 5-fluorouracil [5-FU]) for the treatment of patients with disease progression on or after prior therapy with Avastin® (bevacizumab intravenous injection), oxaliplatin, and a fluoropyrimidine.

Cyramza is available as preservative-free, solution at a concentration of 10 mg/mL in either 100 mg or 500 mg single-dose vials.[1] The calculated dose is further diluted with 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. The diluted Cyramza is given over 60 minutes intravenously. Prior to each Cyramza infusion, the patient is premedicated with an intravenous histamine H1 antagonist (e.g., diphenhydramine). Patients who experience Grade 1 or 2 infusion-related reactions, are also premedicated with dexamethasone (or equivalent) and acetaminophen before each Cyramza dose.

POLICY STATEMENT

This policy involves the use Cyramza infusion. Prior authorization is recommended for medical benefit coverage of Cyramza. Approval is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy**, and **Labs/Diagnostics** for the diagnosis provided. The requirement

that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Cyramza as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cyramza to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Cyramza is recommended in those who meet one of the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Colorectal Cancer.

Criteria. *The patient must meet the following criteria (A, B, and C):*
A) Cyramza is prescribed by or in consultation with an oncologist; AND
B) The patient has advanced or metastatic colorectal cancer (mCRC) that has progress on or after therapy with Avastin, oxaliplatin, and a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine (Xeloda®, generics); AND
C) Cyramza will be used in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil [5-FU]).

Cyramza is indicated in combination with FOLFIRI for the treatment of patients with mCRC with disease progression on or after prior therapy with Avastin, oxaliplatin, and a fluoropyrimidine[1] (e.g., FOLFOX plus Avastin; CapeOX [capecitabine, oxaliplatin] plus Avastin; FOLFOXIRI [5-FU, leucovorin, oxaliplatin, and irinotecan] plus Avastin).

The National Comprehensive Cancer Network (NCCN) guidelines on colon cancer (version 2.2018) and rectal cancer (version 1.2018) recommend Cyramza for the following uses: 1) as primary therapy for patients with unresectable metachronous metastases and previous adjuvant FOLFOX (5-FU, leucovorin, oxaliplatin) or CapeOX (capecitabine, oxaliplatin) within the past 12 months in combination with either irinotecan or FOLFIRI regimen (category 2A), and 2) as subsequent therapy ~~after first~~ for progression of unresectable advanced or metastatic disease in combination with either irinotecan or FOLFIRI regimen in patients not previously treated with irinotecan-based regimens(category 2A).[2-3,11] For either of these uses, Avastin is the preferred anti-angiogenic therapy based on toxicity and/or cost.[2-3] There are no data that suggest activity of FOLFIRI plus Cyramza in patients who have progressed on FOLFIRI plus Avastin or vice versa. There are no data suggesting activity of Cyramza as a single-agent. Cyramza has only shown activity when given with FOLVIRI in FOLVIRI-naïve patients. Cyramza should not be used as adjuvant therapy in patients with Stage II or III colon cancer outside the setting of a clinical trial.

In one multinational, double-blind, Phase III study (RAISE), patients with mCRC who had disease progression on or after first-line therapy with Avastin, oxaliplatin, and a fluoropyrimidine were randomized to receive Cyramza 8 mg/kg

intravenously (n = 536) or placebo (n = 536) in combination with FOLFIRI given every 2 weeks.[1,4] Patients had disease progression within 6 months of the last dose of first-line therapy. Patients who discontinued one or more components of treatment because of an adverse event (AE) could continue therapy with the other treatment component(s) until disease progression or unacceptable toxicity. Median age was 62 years; 49% of patients had ECOG performance status 0; 49% of patients had *KRAS* mutant tumors; and 24% of patients had < 6 months from time to disease progression after beginning first-line treatment. Median overall survival was 13.3 months (95% confidence interval [CI]: 12.4, 14.5) in patents on Cyramza plus FOLFIRI and 11.7 months (95% CI: 10.8, 12.7) in patients on placebo plus FOLFIRI (hazard ratio [HR] 0.85; 95% CI: 0.73, 0.98; P = 0.023 stratified log-rank). Median progression-free survival (PFS) was 5.7 months (95% CI: 5.5, 6.2) with Cyramza plus FOLFIRI and 4.5 months (95% CI: 4.2, 5.4) with placebo plus FOLFIRI (HR 0.79; 95% CI: 0.70, 0.90; P < 0.001 stratified log-rank). Grade 3 or worse treatment emergent AEs were higher in the Cyramza group (79% of patients; n = 418/529) than in the placebo group (62% of patients; n = 329/528). These were mainly Grade 3 events. AEs that were Grade 3 or worse that occurred in > 5% of patients were neutropenia, hypertension, diarrhea, and fatigue.

Studies directly comparing Cyramza to the other antiangiogenesis agents, Avastin and Zaltrap, in combination with FOLFIRI or other chemotherapy in the second-line setting are not available.

Dosing in mCRC in Adults. *Dosing must meet the following*: 8 mg/kg as an intravenous infusion over 60 minutes every 2 weeks prior to administration of FOLFIRI (irinotecan, folinic acid, and 5-FU).

The recommended dose is 8 mg/kg every 2 weeks given as an intravenous infusion over 60 minutes prior to FOLFIRI administration.[1] Cyramza is continued until disease progression or unacceptable toxicity. Dose modifications are recommended in the prescribing information for infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, gastrointestinal perforation, or Grade 3 or 4 bleeding. Therapy with Cyramza is interrupted before scheduled surgery until the wound is fully healed. Management of AEs may require that Cyramza be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.

A) *Initial Approval*: Approve for 6 months.

B) *Extended Approval*: Approve at 6-month intervals if the patient has a response as determined by the prescribing physician.

Duration of Therapy in mCRC in Adults. Indefinite if the patient is responding to therapy.

In the Phase III RAISE study, the median number of infusions was 8 (interquartile range [IQR], 3 to 15 infusions), and the median duration of therapy was 19.0 weeks (IQR, 8.0 to 34.3 weeks).[4]

Labs/Diagnostics. None required.

2. Gastric, Esophagogastric Junction Cancer, or Esophageal Cancer.

Criteria. *The patient must meet the following criteria (A, B, C, AND D)*:

A) Cyramza is prescribed by or in consultation with an oncologist; AND

B) The patient has locally advanced or metastatic gastric, esophagogastric junction, or esophageal adenocarcinoma;[5-6] AND

C) Cyramza will be used alone or in combination with paclitaxel; AND

D) The patient has received chemotherapy with at least ONE of the following (i or ii):

- **i.** 5-Fluorouracil (5-FU) or capecitabine (Xeloda®, generics); OR
- **ii.** Cisplatin, carboplatin, or oxaliplatin.

The NCCN guidelines on gastric cancer (version 2.2018) recommend Cyramza as palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic adenocarcinoma and Karnofsky performance score (KPS) ≥ 60% or ECOG performance score ≤ 2 as second-line or subsequent therapy in combination with paclitaxel (preferred) or as a single agent (both are category 1).[5,11] The NCCN guidelines on esophageal and esophagogastric junction cancers (version 2.2018) recommend Cyramza as palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic esophageal (category 2A) or esophagogastric junction (category 1) adenocarcinoma and KPS ≥ 60% or ECOG performance score ≤ 2 as second-line or subsequent therapy in combination with paclitaxel (preferred) or as a single agent.[6,11]

In one multicenter, placebo-controlled, Phase III trial (REGARD), patients with advanced gastric or GE junction adenocarcinoma that progressed after first-line platinum- or fluoropyrimidine-containing chemotherapy were randomized to best supportive care plus either Cyramza (n = 238) or placebo (n = 117).[7] In patients receiving Cyramza, median overall survival was 5.2 months (95% CI: 4.4, 5.7) vs. 3.8 months (95% CI: 2.8, 4.7) for patients on placebo (HR 0.78; 95% CI: 0.60, 0.998; P = 0.047). In another Phase III trial (RAINBOW), patients with metastatic gastric or GE junction adenocarcinoma progressing on first-line chemotherapy with platinum- and fluoropyrimidine-containing combination therapy were randomized to Cyramza plus paclitaxel (n = 330) or paclitaxel alone (n = 335).[8] In patients receiving Cyramza plus paclitaxel, median overall survival was 9.6 months (95% CI: 8.5, 10.8) vs. 7.4 months (95% CI: 6.3, 8.4) with paclitaxel alone (HR 0.807; 95% CI: 0.678, 0.962; P = 0.017). Median PFS was 4.4 months and 2.9 months, respectively (P < 0.0001).

Dosing in Gastric, Esophagogastric Junction, or Esophageal Cancer Cancer in Adults. *Dosing must meet the following*: 8 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.

The recommended dose, either as a single agent or in combination with weekly paclitaxel, is 8 mg/kg every 2 weeks given as an intravenous infusion over 60 minutes.[1] Cyramza is continued until disease progression or unacceptable toxicity. When used in combination, Cyramza is given before administering paclitaxel. Dose modifications are recommended in the prescribing information for infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, gastrointestinal perforation, or Grade 3 or 4 bleeding. Therapy with Cyramza is interrupted before scheduled surgery until the wound is fully healed. Management of AEs may require that Cyramza be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.
A) *Initial Approval*: Approve for 6 months.
B) *Extended Approval*: Approve at 6-month intervals if the patient has a response as determined by the prescribing physician.

Duration of Therapy in Gastric, Esophagogastric Junction, or Esophageal Cancer in Adults. Indefinite if the patient is responding to therapy.

Median duration of treatment with Cyramza plus paclitaxel, in one study, was 18 weeks (IQR, 10.0 to 31.1 weeks).[8] In another study, the median duration of treatment with Cyramza alone was 8 weeks (IQR, 6 to 16 weeks).[7]

Labs/Diagnostics. None required.

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3. Non-Small Cell Lung Cancer (NSCLC).

Criteria. *The patient must meet the following criteria (A, B, C, D, and E)*:
A) Cyramza is prescribed by or in consultation with an oncologist; AND
B) The patient has advanced or metastatic NSCLC; AND
C) Cyramza will be used in combination with docetaxel intravenous injection (Docefrez™, Taxotere®); AND
D) The patient has tried a platinum-based chemotherapy (e.g., cisplatin, carboplatin); AND
E) The patient has one of the following histologic subtypes of NSCLC (i or ii):
- **i.** Non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) AND the following condition is met (a):
  - i. Testing has been completed for epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) fusions, AND the patient meets the ONE of the following (1 or 2):
    - **(1)** The patient's tumor is sensitizing *EGFR* mutation positive or *ALK* positive and the patient has received targeted drug therapy for the specific mutation; OR
    - **(2)** *EGFR* and *ALK* tests are negative;

  OR
- **ii.** Squamous cell carcinoma.

Cyramza is indicated in combination with docetaxel for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy.[1] Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.

The NCCN guidelines on NSCLC (version 4.2018) recommend Cyramza as subsequent therapy (if not already given) in combination with docetaxel for metastatic disease for patients with performance status 0 to 2 who have not previously received docetaxel either following progression on initial cytotoxic therapy (category 2A) or for further progression on a systemic immune checkpoint inhibitor or other systemic therapy (category 2B).[9,11] Cyramza is

recommended in patients with adenocarcinoma (with mixed subtypes), squamous cell carcinoma, or large cell carcinoma.

In patients with metastatic non-squamous cell NSCLC or NSCLC not otherwise specified, the NCCN guidelines recommend testing for *EGFR* mutations and *ALK* gene rearrangements (category 1) so that patients with genetic abnormalities can receive therapy with targeted agents.[9] Testing for *ROS1* rearrangements, *BRAF* mutations, and PD-L1 expression is also recommended (all are category 2A recommendations). Testing for *EGFR* mutations and *ALK* rearrangements, can be considered in patients with squamous cell histology if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported. In patients with squamous cell carcinoma, *ROS1* and *BRAF* also should be considered. *EGFR*, *ALK*, and *ROS1* genetic alterations do not usually overlap. *BRAF* mutations typically do not overlap with *EGFR* mutations or *ALK* rearrangements. Programmed death-ligand 1 (PD-L1) testing is recommended before first-line treatment in patients with metastatic NSCLC with negative or unknown test results for *EGFR* mutations, *ALK* rearrangements, *BRA*F V600E mutations, and *ROS1* rearrangements. Currently, testing for PD-L1 expression is the best available biomarker to assess whether a patient is a candidate for Keytruda® (pembrolizumab intravenous injection) therapy. Regardless of PD-L1 expression levels, immunotherapy seems to be less effective in tumors with an actionable mutation (e.g., *EGFR* mutations, *ALK* rearrangements). The NCCN panel strongly advises broader molecular profiling to identify rare driver mutations to identify rare driver mutations for which effective drugs may be available or to appropriately counsel patients on the availability of clinical trials. Broad molecular testing is a key component of the improvement of care of patients with NSCLC. First-line therapies are recommended based on the testing results.

Subsequent therapy. In patients with performance status of 0 to 2 who have progressive disease, subsequent therapy with one of the systemic immune checkpoint inhibitor is a preferred therapy, Opdivo® (nivolumab intravenous injection), Keytruda, or Tecentriq (atezolizumab intravenous injection) [all are category 1], if Keytruda was not previously given. Other subsequent systemic therapies in patients with performance status 0 to 2 and progressive disease include docetaxel, Alimta® (pemetrexed for intravenous injection) [for non-squamous cell histology only], or gemcitabine, or the combination of Cyramza and docetaxel. Other regimens are also recommended for further progression and one of the immune checkpoint inhibitors (Opdivo, Keytruda, or Tecentriq) may be used if not already given.

In one Phase III trial (REVEL), adults (n = 1253) with squamous or non-squamous cell Stage IV NSCLC who had progressed during or after first-line platinum-based chemotherapy were randomized to docetaxel and either Cyramza or placebo on Day 1 of a 21-day cycle until disease progression, unacceptable toxicity, withdrawal, or death.[10] Median overall survival was 10.5 months (IQR, 5.1 to 21.2) for patients (n = 628) on docetaxel plus Cyramza and 9.1 months (IQR, 4.2 to 18.0) for patients (n = 625) on docetaxel plus placebo (HR 0.86; 95% CI: 0.75, 0.98; P = 0.023). Median PFS was 4.5 months (IQR, 2.3 to 8.3) for patients on docetaxel/Cyramza vs. 3.0 months (IQR, 1.4 to 6.9) for patients on docetaxel/placebo (HR 0.76; 95% CI: 0.68, 0.86; P < 0.0001). The study was not powered for subgroup analysis, but most subgroups of patients had numerically longer duration of survival on docetaxel/Cyramza than with docetaxel/placebo. For example, in patients with non-squamous NSCLC, overall survival was 11.1 months (IQR range, 5.3 to 24.3) with docetaxel/Cyramza and 9.7 months (IQR, 4.4 to 19.6) with docetaxel/placebo (HR 0.83; 95% CI: 0.71, 0.97). In patients with squamous cell NSCLC, overall survival was 9.5 months (IQR, 4.4 to 17.6) with

docetaxel/Cyramza vs. 8.2 months (IQR, 3.6 to 14.9) with docetaxel/placebo (HR 0.88, 95% CI: 0.69, 1.13). Some NCCN panel members feel that the data are statistically significant, but not clinically relevant.[9]

Dosing in NSCLC in Adults. *Dosing must meet the following:* 10 mg/kg as an intravenous infusion over 60 minutes every 3 weeks.

The approved dosing of Cyramza in NSCLC is 10 mg/kg given intravenously over about 60 minutes on Day 1 of a 21-day cycle prior to infusion of docetaxel.[1] Cyramza is continued until disease progression or unacceptable toxicity. Dose modifications are recommended in the prescribing information for infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, gastrointestinal perforation, or Grade 3 or 4 bleeding. Therapy with Cyramza is interrupted before scheduled surgery until the wound is fully healed. Management of AEs may require that Cyramza be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.
A) *Initial Approval:* Approve for 6 months.
B) *Extended Approval:* Approve at additional 6-month intervals if the patient has a response, as determined by the prescribing physician.

Duration of Therapy in NSCLC. Indefinite if the patient is responding to therapy.

In one Phase III trial, the median duration of treatment was 15.0 weeks (IQR, 6.1 to 26.6) with Cyramza, and the median number of infusions was 4.5 (IQR range, 2.0 to 8.0).[10]

Labs/Diagnostics. Detection of *EGFR* mutations and *ALK* fusions is necessary for selection of patients appropriate for targeted therapies prior to using Cyramza therapy. This applies to patients initiating therapy with Cyramza. See criteria above.

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4. Patient has been Started on Cyramza. Approve if the patient meets the conditions for coverage required for **Dosing**, **Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** for an approved use in this *Cyramza Utilization Review* policy.

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5. Other Cancer-Related Indications. Forward to the Medical Director for review on a case-by-case basis. -

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Waste Management for All Indications.
Dosing for Cyramza is based on body weight (mg/kg). The dose should be calculated and the number of vials needed assessed.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cyramza has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Breast Cancer.** In one multicenter Phase III trial, patients (n = 1,144) with unresectable, locally recurrent, or metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer were randomized to docetaxel plus Cyramza or to docetaxel plus placebo once every 3 weeks.[12] Patients had not received prior cytotoxic therapy or biologic therapy for advanced disease. At baseline, 76% of patients had hormone receptor-positive and 24% of patients had triple-negative breast cancers. The primary end point was investigator-assessed PFS. Median PFS was 9.5 months (95% CI: 8.3, 9.8) in patients who received docetaxel plus Cyramza vs. 8.2 months (95% CI: 7.1, 8.5) in patients who received docetaxel plus placebo (HR 0.88; 95% CI: 0.75, 1.01; P = 0.077). At the interim analysis, median overall survival was 27.3 months (95% CI: 23.6, 29.1) in patients who received docetaxel plus Cyramza vs. with 27.2 months (95% CI: 7.9, 9.8) in patients who received docetaxel plus placebo (HR 1.01; 95% CI: 0.83, 1.23; P = 0.915). Toxicities seen at significantly higher rates in patients receiving Cyramza included fatigue, hypertension, febrile neutropenia, palmar-plantar erythrodysesthesia syndrome, and stomatitis.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Prior approval is required for HCPCS Code J9308.

HCPCS Code(s):	
J9308	Injection, ramucirumab, 5mg

REFERENCES

1. Cyramza® injection for intravenous use [prescribing information]. Indianapolis, IN: Eli Lilly and Company; March 2017.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2018 – March 14, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 22, 2018.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 1.2018 – March 14, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 22, 2018.
4. Tabernero J, Yoshino T, Cohn AL, et al; RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16:499-508.
5. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (Version 2.2018 --- May 22, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 22, 2018.

6. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (Version 2.2018 – May22, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 22, 2018.
7. Fuchs CS, Tomasek J, Yong CJ, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383:31-39.
8. Wilke H, Muro K, Van Cutsem E, et al; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15:1224-1235.
9. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 4.2018 – April 26, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 22, 2018.
10. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665-673.
11. The NCCN Drugs & Biologics Compendium. © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 19, 2018. Search term: ramucirumab.
12. Mackey JR, Ramos-Vazquez M, Lipatov O, et al. Primary results of ROSE/TRIO-12, a randomized placebo-controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. *J Clin Oncol*. 2015;33:141-148.

OTHER REFERENCES UTILIZED

- Petrylak DP, Tagawa ST, Kohli M, et al. Docetaxel as monotherapy or combined with ramucirumab or icrucumab in second-line treatment for locally advanced or metastatic urothelial carcinoma: An open-label, three-arm, randomized controlled phase II trial. *J Clin Oncol*. 2016;34:1500-1509.
- Park K, Kim JH, Cho EK, et al. East Asian subgroup analysis of a randomized, double-blind, phase 3 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy (REVEL). *Cancer Res Treat*. 2016;48(4):1177-1186.
- Yardley DA, Reeves J, Dees EC, et al. Ramucirumab with eribulin versus eribulin in locally recurrent or metastatic breast cancer previously treated with anthracycline and taxane therapy: A multicenter, randomized, phase II study. *Clin Breast Cancer*. 2016;16(6):471-479.
- Petrylak DP, de Wit R, Chi KN, et al; RANGE study investigators. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. *Lancet*. 2017;390(10109):2266-2277.
- Chau I, Peck-Radosavljevic M, Borg C, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib: Patient-focused outcome results from the randomised phase III REACH study. *Eur J Cancer*. 2017;81:17-25.
- Zhu AX, Kang Y-K, Yen C-J, et al. REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib [abstract]. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; Chicago, IL; June 1-5. Available at: https://meetinglibrary.asco.org/record/159169/abstract. Accessed on June 25, 2018.