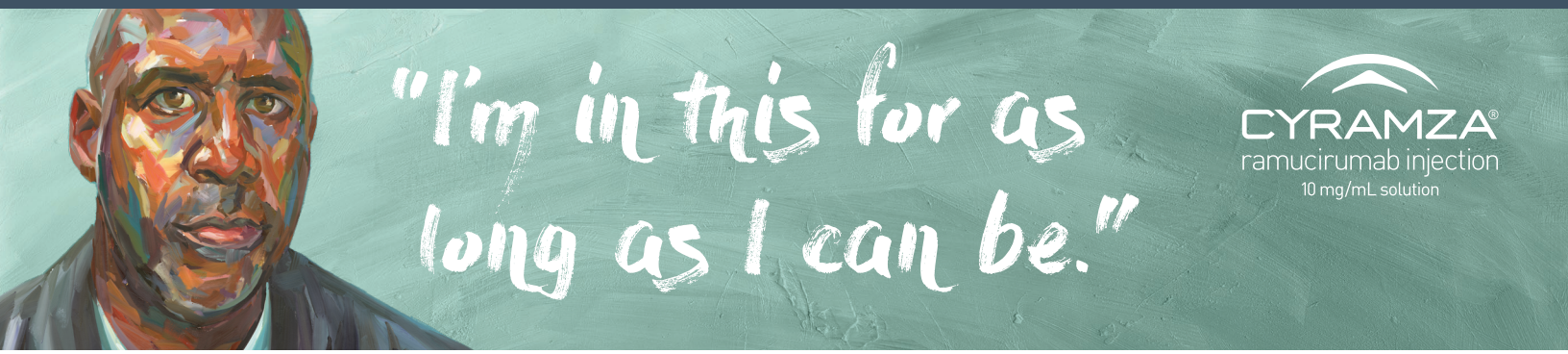
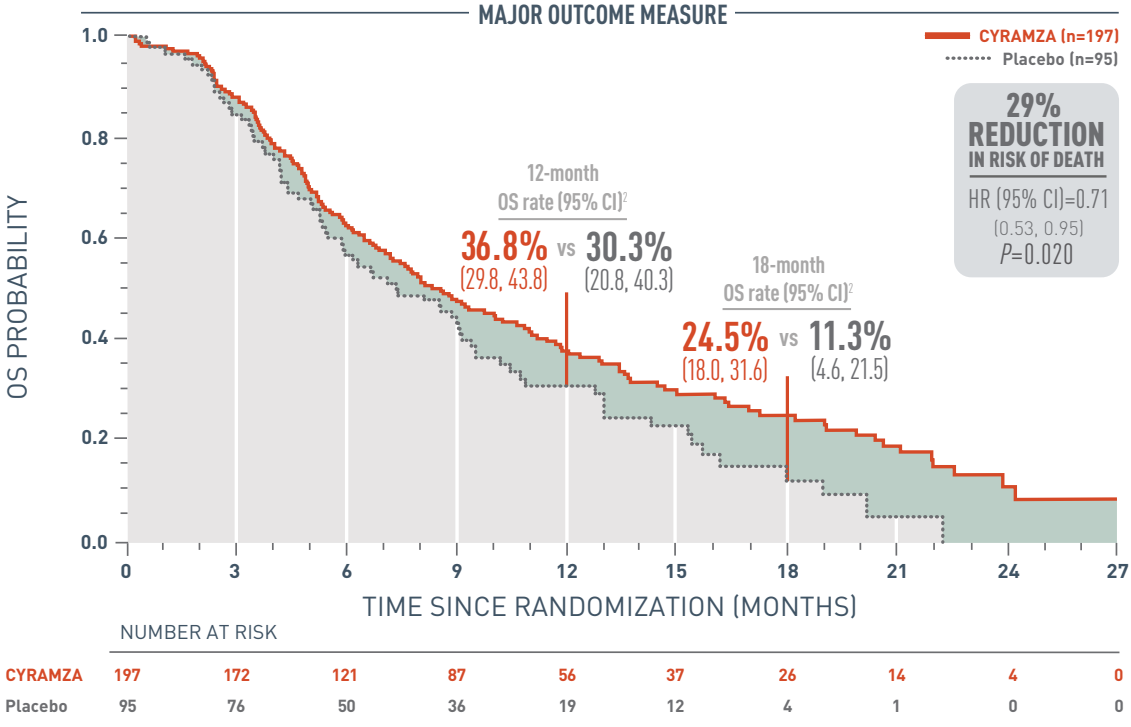


INDICATION

CYRAMZA, as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have an alpha-fetoprotein (AFP) of ≥400 ng/mL and have been treated with sorafenib.

CYRAMZA+BSC significantly reduced the risk of death by 29% in patients with advanced HCC and AFP ≥400 ng/mL[1]

REACH-2 OS: Median—Months (95% CI)[1]



NUMBER AT RISK

CYRAMZA	197	172	121	87	56	37	26	14	4	0
Placebo	95	76	50	36	19	12	4	1	0	0

The percentage of deaths at the time of analysis was 75% (147 patients) and 78% (74 patients) in the CYRAMZA and placebo treatment arms, respectively.[1]

Median OS: CYRAMZA+BSC 8.5 months (7.0, 10.6) vs **placebo+BSC 7.3 months** (5.4, 9.1)[1]

See more REACH-2 data

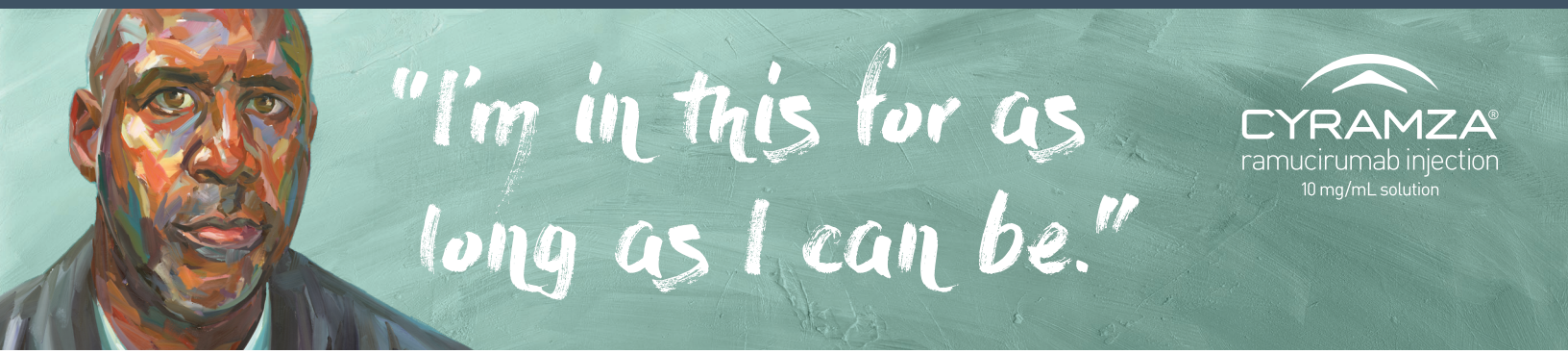
SELECT IMPORTANT SAFETY INFORMATION

HEMORRHAGE

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

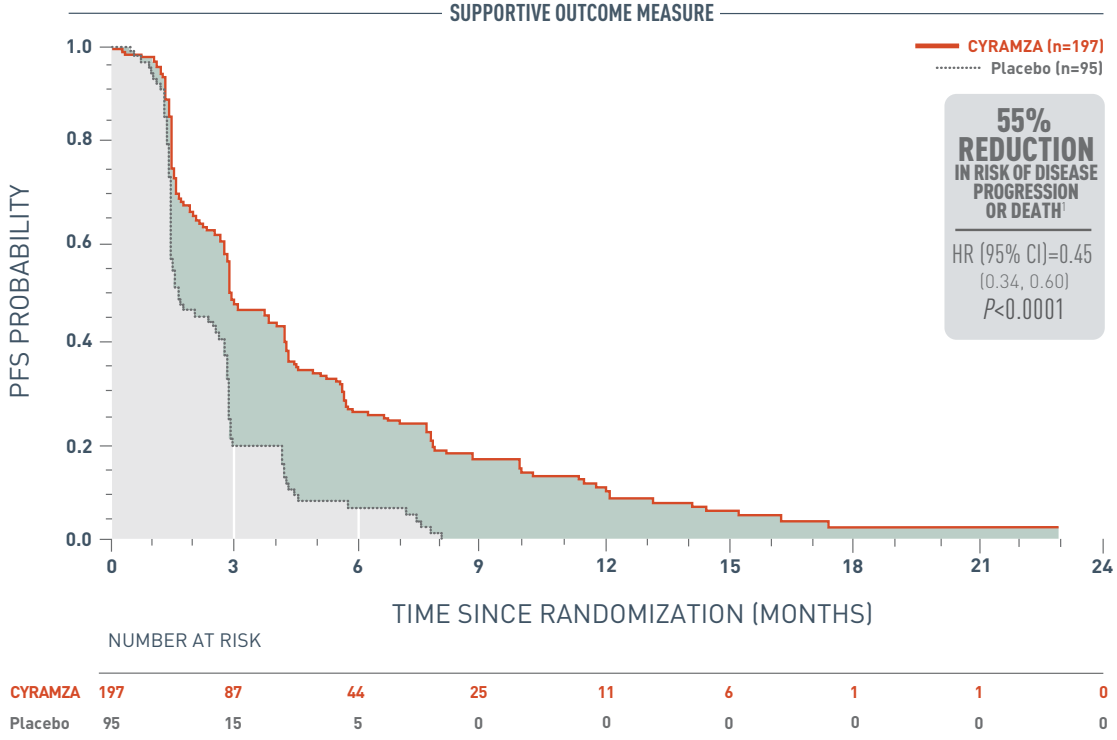
BSC=best supportive care; CI=confidence interval; HR=hazard ratio; OS=overall survival.

Please see Important Safety Information on pages 4–5 and click for full Prescribing Information for CYRAMZA.



CYRAMZA+BSC significantly reduced the risk of disease progression or death in patients with advanced HCC and AFP ≥400 ng/mL[1]

REACH-2 PFS: Median—Months (95% CI)[1,3]



NUMBER AT RISK

CYRAMZA	197	87	44	25	11	6	1	1	0
Placebo	95	15	5	0	0	0	0	0	0

The percentage of events at the time of analysis was 87% (172 patients) and 91% (86 patients) in the CYRAMZA and placebo treatment arms, respectively.

26 of 172 events in CYRAMZA-treated patients and 9 of 86 events in the placebo-treated patients were deaths.

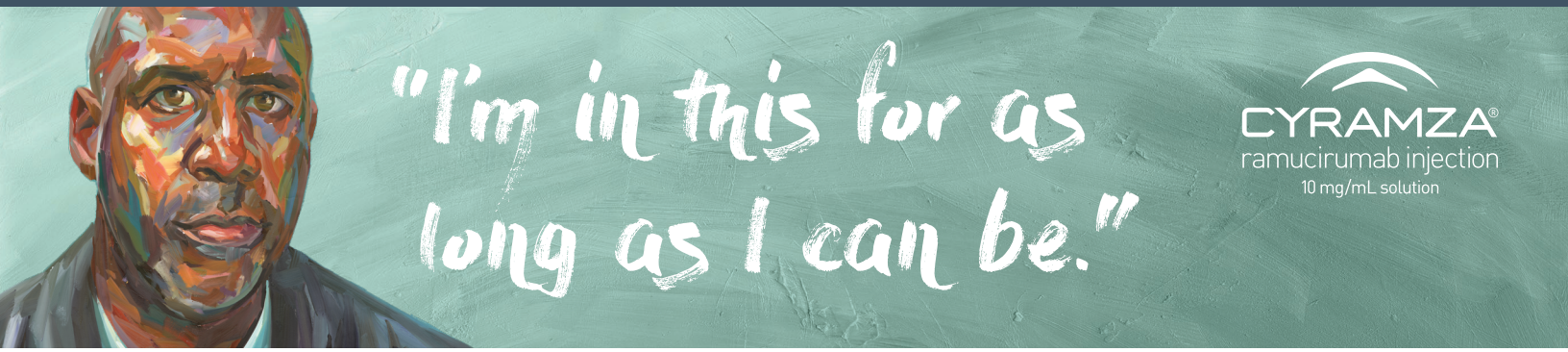
Median PFS: CYRAMZA+BSC 2.8 months (2.8, 4.1) vs **placebo+BSC 1.6 months** (1.5, 2.7)[1]

SELECT IMPORTANT SAFETY INFORMATION
GASTROINTESTINAL PERFORATIONS

- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

PFS=progression-free survival.

Please see Important Safety Information on pages 4–5 and click for full Prescribing Information for CYRAMZA.



REACH-2 ORR: Percentage of Patients (95% CI)[1]

SUPPORTIVE OUTCOME MEASURE

ORR[1]
(95% CI)

CYRAMZA (n=197)	Placebo (n=95)
4.6% (1.7, 7.5)	1.1% (0.0, 3.1)

- ORR was defined as CR + PR. All responses were partial[1]
- Disease progression and tumor response were assessed by investigators in accordance with RECIST 1.1[4]

ORR was not statistically significant.[1]

DCR[2]
(95% CI)

59.9% (53.1, 66.7) (n=118)	38.9% (29.1, 48.8) (n=37)
55.3% Stable Disease (n=109)	37.9% Stable Disease (n=36)

- DCR was defined as CR + PR + SD[4]

DCR was a prespecified supportive outcome measure. There was no adjustment for multiplicity; therefore, no conclusions of statistical or clinical significance can be drawn.[4]

REACH-2 Study Design

The phase III REACH-2 trial evaluated the efficacy and safety of CYRAMZA+BSC vs placebo+BSC in patients with advanced hepatocellular carcinoma after prior sorafenib therapy and high baseline serum AFP levels ≥400 ng/mL.[1] Major efficacy outcome measure was OS. Supportive efficacy outcome measures included PFS and ORR. All patients were ECOG PS 0 or 1, with Barcelona Clinic Liver Cancer stage B (and no longer amenable to locoregional therapy) or C disease, and Child-Pugh A liver disease. Patients were stratified by geographic region, macrovascular invasion, and ECOG PS. Patients were randomized 2:1 to CYRAMZA 8 mg/kg +BSC (n=197) or placebo+BSC (n=95) every 2 weeks (on days 1 and 15) of each 28-day cycle.[1,4,5]

SELECT IMPORTANT SAFETY INFORMATION

IMPAIRED WOUND HEALING

- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

AFP=alpha-fetoprotein; DCR=disease control rate; ECOG=Eastern Cooperative Oncology Group; ORR=overall response rate; PS=performance status; CR=complete response; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

Please see Important Safety Information on pages 4–5 and click for full Prescribing Information for CYRAMZA.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)

CYRAMZA®
ramucirumab injection
10 mg/mL solution

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Gastrointestinal Perforations

- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. In 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRR)

- IRR, including severe and life threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Worsening of Pre-existing Hepatic Impairment

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA 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.

Please see Important Safety Information on page 5 and click for full Prescribing Information for CYRAMZA.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA®, continued

CYRAMZA®
ramucirumab injection
10 mg/mL solution

Worsening of Pre-existing Hepatic Impairment, continued

- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatorenal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

Posterior Reversible Encephalopathy Syndrome (PRES)

- PRES (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported in <0.1% of 2137 patients with various cancers treated with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.
- Permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor for proteinuria. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- In 2137 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

Embryo-Fetal Toxicity

- CYRAMZA can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

Lactation

- Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

Adverse Reactions

REACH-2:

- The most common adverse reactions (All Grades) observed in single agent CYRAMZA-treated HCC patients at a rate of ≥10% and ≥2% higher than placebo were fatigue (36% vs 20%), peripheral edema (25% vs 14%), hypertension (25% vs 13%), abdominal pain (25% vs 16%), decreased appetite (23% vs 20%), proteinuria (20% vs 4%), nausea (19% vs 12%), ascites (18% vs 7%), headache (14% vs 5%), epistaxis (14% vs 3%), insomnia (11% vs 6%), pyrexia (10% vs 3%), vomiting (10% vs 7%), and back pain (10% vs 7%).
- The most common serious adverse reactions with CYRAMZA were ascites (3%) and pneumonia (3%).
- Treatment discontinuations due to adverse reactions occurred in 18% of CYRAMZA-treated patients, with proteinuria being the most frequent (2%).
- Clinically relevant adverse reactions reported in ≥1% and <10% of CYRAMZA-treated patients in REACH-2 were IRR (9%), hepatic encephalopathy (5%) including 1 fatal event, and hepatorenal syndrome (2%) including 1 fatal event.

Please click for full Prescribing Information for CYRAMZA.

RB-H HCP ISI 29MAY2020

CYRAMZA®
ramucirumab injection
10 mg/mL solution

References

1. CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2019.
2. Data on File, Lilly USA, LLC, DOF-RB-US-0050.
3. Data on File, Lilly USA, LLC, DOF-RB-US-0066.
4. Zhu AX, Kang Y-K, Yen C-J, et al; for REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial [published online January 18, 2019]. /Lancet Oncol/. doi:10.1016/S1470-2045(18)30937-9.
5. 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 and elevated baseline alpha-fetoprotein following first-line sorafenib. J Clin Oncol. 2018; 36(suppl; abstr 4003).

Please see Important Safety Information on pages 4–5 and click for full Prescribing Information for CYRAMZA.

Lilly