

# Alpha-fetoprotein (AFP) DESERVES ANOTHER LOOK



## AFP is a valuable clinical biomarker for patients with advanced hepatocellular carcinoma (HCC).<sup>1,2</sup>

- AFP helps monitor disease progression in advanced HCC, and it is also a clinical prognostic biomarker<sup>1,2</sup>
- High serum levels of AFP ( $\geq 400$  ng/mL) can indicate a poor prognosis<sup>3,4</sup>
- This poor prognosis is marked by increased tumor vascularization, increased tumor activity, and high tumor burden, all of which signal aggressive disease<sup>3,5</sup>

## But what does this mean to your patients?

[Learn more about AFP](#)

### INDICATION

CYRAMZA, as a single agent, is indicated for the treatment of patients with HCC who have an AFP of  $\geq 400$  ng/mL and have been treated with sorafenib.

### SELECT IMPORTANT SAFETY INFORMATION HEMORRHAGE

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade  $\geq 3$  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.

Please see Important Safety Information on pages 3–4 and click for full [Prescribing Information](#) for CYRAMZA.



# At least 40% of patients with advanced HCC are AFP-High (AFP $\geq$ 400 ng/mL)<sup>6-8</sup>

AFP-High patients have a 2X or greater risk of death than patients with AFP levels  $<$ 400 ng/mL.<sup>8,9</sup>



When you see AFP differently, you can see your AFP-High (AFP  $\geq$ 400 ng/mL) patients differently.

[Learn more about AFP](#)

## 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.

Please see Important Safety Information on pages 3-4 and click for full [Prescribing Information](#) for CYRAMZA.

# IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)



## WARNINGS AND PRECAUTIONS

### Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade  $\geq 3$  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.
- 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%).

## IMPORTANT SAFETY INFORMATION FOR CYRAMZA<sup>®</sup>, continued



### 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.

RB-H HCP ISI 29MAY2020

## References

1. Mizejewski GJ. Does alpha-fetoprotein contribute to the mortality and morbidity of human hepatocellular carcinoma? A commentary. *J Hepatocell Carcinoma*. 2016;3:37-40.
2. Chan SL, Chan ATC, Yeo W. Role of  $\alpha$ -fetoprotein in hepatocellular carcinoma: prognostication, treatment monitoring or both? *Future Oncol*. 2009;5(6):889-899.
3. Hsu C-Y, Liu P-H, Lee Y-H, et al. Using serum  $\alpha$ -fetoprotein for prognostic prediction in patients with hepatocellular carcinoma: what is the most optimal cutoff? *PLoS One*. 2015;10(3):e0118825.
4. Tangkijvanich P, Anukulkrankusol N, Suwangool P, et al. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol*. 2000;31(4):302-308.
5. Mitsuhashi N, Kobayashi S, Doki T, et al. Clinical significance of  $\alpha$ -fetoprotein: involvement in proliferation, angiogenesis, and apoptosis of hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2008;23(7, pt 2):e189-e197.
6. Bialecki ES, Di Bisceglie AM. Diagnosis of hepatocellular carcinoma. *HPB (Oxford)*. 2005;7(1):26-34.
7. Vogel A, Cervantes A, Chau I, et al; on behalf of ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv238-iv255.
8. Zhu AX, Park JO, Ryoo B-Y, et al; Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16(7):859-870.
9. Supplement to: Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54-63.

Please click for full [Prescribing Information for CYRAMZA](#)