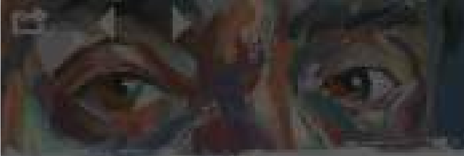
CYRAMZA: Adverse Events Were Generally Manageable

Adverse Reactions Occurring with CYRAMZA in Combination with Paclitaxel (at Incidence Rate of ≥5% and ≥2% Higher than Placebo):[1]

Adverse events	All grades		Grade 3/4	
	CYRAMZA + paclitaxel	Placebo + paclitaxel	CYRAMZA + paclitaxel	Placebo + paclitaxel
Fatigue/asthenia	56.9%	43.8%	11.9%	5.5%
Neutropenia	54.4%	31.0%	40.7%	18.8%
Leukopenia	33.9%	21.0%	17.4%	6.7%
Diarrhea	32.4%	23.1%	3.7%	1.5%
Epistaxis	30.4%	7.0%	0.0%	0.0%
Hypertension	25.1%	5.8%	14.7%	2.7%
Peripheral edema	25.1%	13.7%	1.5%	0.4%
Stomatitis	19.4%	7.3%	0.6%	0.6%
Proteinuria	16.8%	6.1%	1.7%	0.0%
Thrombocytopenia	13.1%	6.1%	1.5%	1.8%
Hypoalbuminemia	11.6%	4.9%	1.2%	0.9%
Gastrointestinal hemorrhage events	10.1%	6.1%	3.7%	1.5%

- Data from the RAINBOW trial
- **Although the incidence of grade 3 or 4 neutropenia was higher in the CYRAMZA plus paclitaxel group, the incidence of grade 3 or greater febrile neutropenia was similar in both groups (10 [3%] vs. 8 [2%])[1]**
- In the CYRAMZA plus paclitaxel treatment arm, the median duration of exposure to CYRAMZA was 18 weeks and to paclitaxel was 17.7 weeks[1]
- In the placebo plus paclitaxel treatment arm, the median duration of exposure was 12 weeks[1]

CYRAMZA in combination with paclitaxel resulted in significantly increased rates of grade 3/4 neutropenia (40.7% vs. 18.8%), **though this did not translate into higher incidence of febrile neutropenia.**[1]



Tell me what I might expect

CYRAMZA: Adverse Events Were Generally Manageable

Adverse Reactions Occurring with CYRAMZA in Combination with Paclitaxel (at Incidence Rate of ≥5% and ≥2% Higher than Placebo)[1]

Reference:

1. Ramucirumab (Cyramza) India Prescribing Information.
2. Wilke H, 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, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224-1235.
3. Wilke H, 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, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224-1235. Supplementary appendix: 1-37. Available at: http://www.thelancet.com/journals/lanonc/article/PI-IS1470-2045(14)70420-6/supplemental. Accessed December 2017.
4. Salati M. et al. Second-line treatments: moving towards an opportunity to improve survival in advanced gastric cancer? *ESMO Open* 2017;2:e000206. doi:10.1136/esmoopen-2017-000206.

CYRAMZA: Adverse Events Were Generally Manageable

Adverse Reactions Occurring with CYRAMZA Monotherapy (at Incidence Rate of ≥5% and ≥2% Higher than Placebo):[1]

	CYRAMZA		Placebo	
Adverse events	All grades	Grade 3/4	All grades	Grade 3/4
Hypertension	16.1%	7.6%	7.8%	2.6%
Abdominal pain	28.8%	5.9%	27.8%	2.6%
Diarrhea	14.4%	0.8%	8.7%	1.7%
Headache	9.3%	0%	3.5%	0%
Hyponatremia	5.5%	3.4%	1.7%	0.9%

- Data from the REGARD trial
- Median duration of exposure was 8 weeks[1]

Combination Monotherapy

Tell me what I might expect

CYRAMZA: Adverse Events Were Generally Manageable

Adverse Reactions Occurring with CYRAMZA Monotherapy (at Incidence Rate of ≥5% and ≥2% Higher than Placebo)[1]

	CYRAMZA		Placebo	
Hyponatremia	5.5%	3.4%	1.7%	0.9%

- Data from the REGARD trial
- Median duration of exposure was 8 weeks[2]

Combination Monotherapy

X

References:

1. Ramucirumab (Cyramza) India Prescribing Information.
2. Fuchs CS, et at. 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(99111:31-39.

Tell me what I might expect

CYRAMZA Safety Across Six Randomized Phase III Trials – Analysis of 4996 Patients

Summary of the Incidence and Relative Risk of AEs Across the 6 Completed Phase III Clinical Trials[1]

Adverse events	All grades			Grade ≥ 3		
	CYRAMZA (n=2768)	Control (n=2268)	Relative risk (95% CI)	CYRAMZA (n=2768)	Control (n=2268)	Relative risk (95% CI)
HTN, n (%)	585 (21.3)	147 (7.4)	2.7 (2.3, 3.2)	246 (9.0)	57 (2.5)	3.7 (2.8, 4.9)
Proteinuria, n (%)	359 (9.4)	70 (3.1)	3.4 (2.6, 4.3)	31 (1.1)	1 (0.0)†	6.5 (2.9, 24.3)
Bleeding, n (%)	1031 (37.5)	426 (19.0)	2.0 (1.8, 2.2)	74 (2.7)	62 (2.8)	1.1 (0.8, 1.5)
GI bleeding, n (%)	184 (6.8)	103 (4.6)	1.6 (1.3, 2.0)	45 (1.6)	36 (1.6)	1.1 (0.7, 1.7)
GI perforation, n (%)	30 (1.1)	7 (0.3)	3.2 (1.5, 7.0)	28 (1.0)	6 (0.3)	3.2 (1.4, 7.3)
ATE, n (%)	38 (1.4)	40 (1.8)	0.8 (0.5, 1.3)	21 (0.8)	19 (0.8)	0.9 (0.5, 1.7)
VTE,* n (%)	106 (3.9)	116 (5.2)	0.7 (0.5, 1.1)	56 (2.0)	61 (2.7)	0.7 (0.4, 1.2)
IRR, n (%)	180 (6.6)	104 (4.6)	1.4 (0.8, 2.3)	28 (1.0)	13 (0.6)	1.5 (0.8, 2.7)
Wound-healing complications, n (%)	14 (0.5)	4 (0.2)	2.0 (0.8, 5.1)	5 (0.2)	0 (0)†	1.9 (0.5, 7.5)

* For rare events (events that were not observed in at least one treatment arm in any study), the relative risk might not be reliable due to large variability.
† Random-effects analysis model utilized due to significant identified heterogeneity.
ATE=arterial thromboembolic events; CI=confidence interval; GI=gastrointestinal; HTN=hypertension; IRR=infusion-related reactions; VTE=venous thromboembolic events.

"Ramucirumab may be distinct in terms of ATE, VTE, high-grade bleeding, or high-grade GI bleeding by showing no clear evidence for an increased risk of these AEs."[1]

Tell me what I might expect

CYRAMZA Safety Across Six Randomized Phase III Trials – Analysis of 4996 Patients

Summary of the Incidence and Relative Risk of AEs Across the 6 Completed Phase III Clinical Trials[1]

Adverse events	All grades			Grade ≥ 3		
VTE† n (%)						
Wound-healing complications, n (%)						

Reference:

1. Arnold D, et al. Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. *Annals of Oncology* 2017;28(12):2932–2942.

RAINBOW Study: Discontinuation Rates Due to Adverse Events[1]

CYRAMZA + paclitaxel

12%

VS.

Placebo + paclitaxel

11%

Adapted from Miller K, et al. 2014

After discontinuation, the number of patients receiving systemic anti-neoplastic treatment was **similar** in both groups.

Tell me what I might expect

RAINBOW Study: Discontinuation Rates Due to Adverse Events[1]

CYRAMZA + paclitaxel | **Placebo** + paclitaxel

Reference:

1. Wilke H, 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, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224–1235.

After discontinuation, the number of patients receiving systemic anti-neoplastic treatment was similar in both groups.