Grading: Diarrhea

Preferred Terms Included & Related NCI CTCAE v4.03 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	**Diarrhea**	• Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	• Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	• Life-threatening consequences; urgent intervention indicated	• Death
	General Guideline	• Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated	• Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	• Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL	• Life-threatening consequences; urgent intervention indicated	• Death related to AE

Dose Adjustments for HCC

Management of Diarrhea – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including diarrhea, was done in accordance with the following instructions:[1]

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	Treatment was interrupted[c] • until resolved to Grade 0–1 or baseline	One-level dose reduction
Grade 3	Treatment was interrupted[c] • until resolved to Grade 0–1 or baseline	One-level dose reduction
Grade 4	Lenvatinib was discontinued	

- Dose reductions occurred in succession based on the previous dose level
  - Once the dose was reduced, it was not increased at a later date[2]

	Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
Actual weight ≥60 kg	12 mg once daily	8 mg once daily	4 mg once daily	4 mg every other day	Discussed with Sponsor
Actual weight <60 kg	8 mg once daily	4 mg once daily	4 mg every other day	Discussed with Sponsor	

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required sponsor's approval before treatment was resumed. During treatment interruption, AR assessment was repeated at least every 7 days (until administration was restarted).
1. CSR E7080-G000-304; 24 May 2017; Pages 46–47; Table 2.
2. Protocol E7080-G000-304; 06 Jan 2014; Pages 8–9.

Dose Adjustments for DTC

Management of Diarrhea – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including diarrhea, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	Treatment was interrupted[c] • until resolved to Grade 0–1 or baseline	One-level dose reduction
Grade 3	Treatment was interrupted[c] • until resolved to Grade 0–1 or baseline	One-level dose reduction
Grade 4	Lenvatinib was discontinued	

- Dose reductions occurred in succession based on the previous dose level
  - Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.