

## **Management of Adverse Events Associated with Cabozantinib Treatment in Patients with Advanced Hepatocellular Carcinoma**

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### **Declarations:**

**Funding:** Medical writing assistance was provided by Karen O'Leary, PhD, and Michael Raffin (Fishawack Communications Inc., Conshohocken, PA, USA) and was funded by Exelixis, Inc.

**Conflicts of interest/Competing interests:** **GS** reports advisory board or speaker bureau fees from Exelixis, Eisai, and Amgen (all outside of the submitted work); **JOD** reports advisory board fees from Exelixis, Bayer, and Lilly (all outside of the submitted work); **MM** and **LD** have nothing to disclose.

**Supplementary Tables and Figures**

**Supplementary Table 1** Child-Pugh classification [125, 126]

Assessment	Degree of abnormality	Score
Encephalopathy	None	1
	Moderate	2
	Severe	3
Ascites	Absent	1
	Slight	2
	Moderate	3
Bilirubin (mg/dL)	<2	1
	2.1–3	2
	>3	3
Albumin (g/dL)	>3.5	1
	2.8–3.5	2
	<2.8	3
Prothrombin time (seconds > control)	0–3.9	1
	4–6	2
	>6	3



Total score	Child-Pugh classification	Severity of impairment
5–6	A	Mild
7–9	B	Moderate
10–15	C	Severe

**Supplementary Table 2** Examples of substrates, inhibitors, and inducers of cytochrome P450 3A4 [97, 101]

Inhibitors	Inducers
<b>Strong<sup>a</sup></b>	HIV antiviral: efavirenz nevirapine Antiepileptic/antiseizure: carbamazepine oxcarbazepine phenytoin Antimycobacterials: rifabutin rifampin rifapentin Thiazolidinediones: pioglitazone troglitazone Miscellaneous: barbiturates (eg, phenobarbital) glucocorticoids (eg, dexamethasone) modafinil (diphenylmethane, promotes wakefulness) St. John's wort
HIV antivirals: indinavir nelfinavir ritonavir saquinavir Macrolide antibiotics: clarithromycin telithromycin Antifungals: itraconazole ketoconazole Miscellaneous: nefazodone (antidepressant)	
<b>Moderate<sup>b</sup></b>	
Calcium channel blockers: diltiazem verapamil NK-1 antagonists (antiemetic): aprepitant netupitant/palonosetron Antifungals: fluconazole voriconazole Miscellaneous: erythromycin (macrolide antibiotic) grapefruit juice	
<b>Weak<sup>c</sup></b>	
Proton pump inhibitors: esomeprazole omeprazole pantoprazole Miscellaneous: cimetidine (histamine H2 receptor antagonist) lesinurad (urate transporter inhibitor) atomoxetine (norepinephrine reuptake inhibitor)	

This list is not exhaustive. Further information can be found in The Flockhart Table (available at <https://drug-interactions.medicine.iu.edu/MainTable.aspx>). Before prescribing medication to patients receiving cabozantinib, providers should consult the label to check for potential drug-drug interactions.

<sup>a</sup>Strong inhibitor: Causes >5-fold increase in the plasma AUC values or >80% decrease in clearance

<sup>b</sup>Moderate inhibitor: Causes >2-fold increase in the plasma AUC values or 50–80% decrease in clearance

<sup>c</sup>Weak inhibitor: >1.25-fold but <2-fold increase in the plasma AUC values or 20–50% decrease in clearance  
 AUC area under the curve, HIV human immunodeficiency virus, NK-1 neurokinin

**Supplementary Table 3** AE symptom grading derived from CTCAE 5.0. AEs are color coded by system: ■ gastrointestinal; ■ skin and subcutaneous tissue; ■ constitutional; ■ hepatic disorders; ■ cardiovascular/hematological disorders

AE	Symptoms			
	Grade 1	Grade 2	Grade 3	Grade 4
<b>PPE</b>	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis without pain)	Skin changes (eg, peeling, blisters, bleeding, fissures, edema, hyperkeratosis with pain); limiting instrumental ADL	Severe skin changes (eg, peeling, blisters, bleeding fissures, edema, or hyperkeratosis) with pain; limiting self-care ADL	–
<b>Fatigue</b>	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self-care ADL	–
<b>Diarrhea</b>	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe	Life-threatening consequences; urgent intervention indicated
<b>Decreased Appetite</b>	Loss of appetite without alteration of eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition; tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated
<b>Nausea</b>	Loss of appetite without change in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–
<b>Vomiting</b>	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences
<b>Oral mucositis</b>	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated
<b>Hypertension</b>	SBP 120–139 mmHg or DBP 80–89 mmHg	SBP 140–159 mmHg or DBP 90–99 mmHg	SBP ≥160 mmHg or DBP ≥100 mmHg	Life-threatening consequences (eg, malignant hypertension, hypertensive crisis)
<b>Increased AST</b>	>ULN –3.0 x ULN if baseline was normal; 1.5–3.0 x baseline if baseline was abnormal	>3.0–5.0 x ULN if baseline was normal; >3.0–5.0 x baseline if baseline was abnormal	>5.0–20.0 x ULN if baseline was normal; >5.0–20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
<b>Increased ALT</b>	>ULN –3.0 x ULN if baseline was normal; 1.5–3.0 x baseline if baseline was abnormal	>3.0–5.0 x ULN if baseline was normal; >3.0–5.0 x baseline if baseline was abnormal	>5.0–20.0 x ULN if baseline was normal; >5.0–20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

ADL activities of daily living, AE adverse event, ALT alanine aminotransferase, AST aspartate aminotransferase, CTCAE Common Terminology Criteria for Adverse Events, DBP diastolic blood pressure, IV intravenous, PPE palmar-plantar erythrodysesthesia, SBP systolic blood pressure, TPN total parenteral nutrition, ULN upper limits of normal, x times

**Supplementary Table 4** Resources for patients and caregivers

Resources for Patients and Caregivers
<b>AE Reporting and Management</b>
<ul style="list-style-type: none"><li>■ Cabozantinib-specific advice on AEs, when to report AEs, and AE management tips <a href="https://cabometryx.com/side-effects">https://cabometryx.com/side-effects</a> <a href="https://cabometryx.com/side-effect-management">https://cabometryx.com/side-effect-management</a> <a href="https://about-cancer.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/cabozatinib">https://about-cancer.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/cabozatinib</a> <a href="http://chemocare.com/chemotherapy/drug-info/cabozantinib.aspx">http://chemocare.com/chemotherapy/drug-info/cabozantinib.aspx</a></li><li>■ Patient education on cancer treatment–induced AEs and reporting <a href="https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/side-effects/about">https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/side-effects/about</a> (UK) <a href="https://www.cancer.gov/about-cancer/treatment/side-effects">https://www.cancer.gov/about-cancer/treatment/side-effects</a> (US) <a href="https://www.cancerca.org/tagged/side_effects">https://www.cancerca.org/tagged/side_effects</a> (US) <a href="http://chemocare.com/chemotherapy/side-effects/default.aspx">http://chemocare.com/chemotherapy/side-effects/default.aspx</a></li></ul>
<b>Mobile Apps</b>
<ul style="list-style-type: none"><li>■ Mobile app for patient education <a href="https://www.cancer.net/navigating-cancer-care/managing-your-care/mobile-applications">https://www.cancer.net/navigating-cancer-care/managing-your-care/mobile-applications</a> (Cancer.net App)</li></ul>
<b>Social Media Resources: HCC</b>
<ul style="list-style-type: none"><li>■ Patient-centered social media resources for patients with HCC and caregivers <a href="https://www.patientslikeme.com/conditions/liver-ca">https://www.patientslikeme.com/conditions/liver-ca</a> <a href="https://survivorship.cancer.gov/">https://survivorship.cancer.gov/</a> <a href="https://rarediseases.org/rare-diseases/hepatocellular-carcinoma/">https://rarediseases.org/rare-diseases/hepatocellular-carcinoma/</a> <a href="https://www.cancer.org/cancer/liver-cancer.html">https://www.cancer.org/cancer/liver-cancer.html</a> <a href="https://liverfoundation.org/">https://liverfoundation.org/</a> <a href="https://www.britishlivertrust.org.uk/">https://www.britishlivertrust.org.uk/</a> <a href="https://www.liver.ca/">https://www.liver.ca/</a> <a href="https://www.ilca-online.org/patient-information/">https://www.ilca-online.org/patient-information/</a> <a href="https://www.mayoclinic.org/diseases-conditions/hepatocellular-carcinoma/cdc-20354552">https://www.mayoclinic.org/diseases-conditions/hepatocellular-carcinoma/cdc-20354552</a> <a href="https://www.esmo.org/content/download/6615/115103/file/EN-Liver-Cancer-Guide-for-Patients.pdf">https://www.esmo.org/content/download/6615/115103/file/EN-Liver-Cancer-Guide-for-Patients.pdf</a></li></ul>

AE adverse event, HCC hepatocellular carcinoma, UK United Kingdom, US United States