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ORIGINAL RESEARCH

Common Cabozantinib Adverse Events: Management and Impact on Outcomes and Treatment Duration in Advanced Renal Cell Carcinoma, Hepatocellular Carcinoma, and Radioiodine-Refractory Differentiated Thyroid Cancer

STEVEN LEE-RAMOS,[1] MS, RN, AGACNP-BC, VIRGINIA SEERY,[2] MSN, RN, ANP-BC, AOCNP, DIANE ANDRESEN,[3] MSN, APN-C, AOCNP, DENISE WILLIAMSON,[4] MPH, NICHOLAS BERRY,[4] PhD, TASHA HALL,[4] PhD, RN, and BRENDA MARTONE,[5] MSN, ANP-BC, AOCNP

From [1]Enloe Health Gonzales Comprehensive Cancer Center, Chico, California; [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [3]John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, New Jersey; [4]Exelixis, Inc., Alameda, California; [5]Robert H. Lurie Cancer Center, Northwestern Medicine, Chicago, Illinois

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Steven Lee-Ramos, Enloe Health Gonzales Comprehensive Cancer Center, 2390 E. 20th Street, Chico, CA 95928

E-mail: steven.lee-ramos@enloe.org

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Abstract

Background: Cabozantinib, a tyrosine kinase inhibitor, is a standard-of-care therapy for previously treated advanced renal cell carcinoma, hepatocellular carcinoma, and radioiodine-refractory differentiated thyroid cancer. We evaluated the impact of cabozantinib-associated adverse events (AEs) on treatment outcomes in these populations. Here we report our findings and discuss AE management. **Methods:** In this post-hoc analysis of three cabozantinib monotherapy pivotal studies (METEOR, CELESTIAL, and COSMIC-311), we compared progression-free survival (PFS) and treatment duration between patients who experienced ≥ 1 any-cause grade ≥ 3 AE and the overall population in the cabozantinib arm of each study. We characterized the most common any-cause AEs leading to dose modification, and advanced practitioner authors provided AE management strategies. **Results:** Of 923 cabozantinib-treated patients across the studies, the most common grade 3/4 AEs occurring in ≥ 10% of patients in all three studies combined were hypertension (15%), palmar-plantar erythrodysesthesia syndrome (13%), diarrhea (10%), and fatigue (10%). In each trial, median PFS was similar in patients with a grade ≥ 3 AE vs. the respective overall study populations; treatment durations were also similar.

Among the four most common any-grade AEs leading to dose modifications, discontinuation rates due to each event were low (< 3%). Advanced practitioner–led AE management strategies included prophylaxis, monitoring, supportive care, and dose modifications. **Conclusions:** Cabozantinib has a consistent safety profile across indications. With proactive management, patients experiencing grade ≥ 3 AEs had similar PFS outcomes and treatment durations as the overall study populations. Advanced practitioner–led proactive AE management can allow patients to remain on therapy and maximize clinical benefits.

Cabozantinib (Cabometyx) is an oral, small-molecule inhibitor of multiple tyrosine kinases (TKI), including vascular endothelial growth factor receptor (VEGFR), MET, and the TAM family of kinases (TYRO3, AXL, and MER); these kinases are involved in tumor growth, metastasis, angiogenesis, and drug resistance (Bergerot et al., 2019; Exelixis, 2025; Yakes et al., 2011). Among its indications (Exelixis, 2025), cabozantinib, as monotherapy, is a standard-of-care therapy in previously treated patients with advanced renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), and radioiodine-refractory or ineligible differentiated thyroid cancer (RAIR-DTC; Gordan et al., 2024; Rathmell et al., 2022; Ringel et al., 2025). Regulatory approvals of cabozantinib monotherapy in these settings were based on three pivotal randomized, controlled studies: METEOR (RCC; NCT01865747; Choueiri et al., 2015, 2016), CELESTIAL (HCC; NCT01908426; Abou-Alfa et al., 2018), and COSMIC-311 (RAIR-DTC; NCT03690388; Brose et al., 2021, 2022). Cabozantinib significantly improved progression-free survival (PFS) vs. control in these studies, with significant improvements in overall survival in patients with RCC and HCC.

Cabozantinib has a known, consistent safety profile. Adverse events (AEs) associated with cabozantinib in pivotal studies include hypertension, diarrhea, palmar-plantar erythrodysesthesia syndrome (PPES), and fatigue (Abou-Alfa et al., 2018; Brose et al., 2021; Choueiri et al., 2015). In each study, cabozantinib was initiated at 60 mg once daily, and AEs were actively managed with individualized supportive care, dose holds, and/or dose reductions as necessary for each patient. Appropriate management of AEs is important for patient comfort and safety, and for helping patients remain on treatment. Advanced practitioners (APs) are typically the first point of contact for patients experiencing AEs associated with cancer treatments; they therefore play an essential role in the proactive management of AEs, both allowing patients to maintain their treatment schedule and optimizing clinical outcomes.

This retrospective analysis of the pivotal phase III METEOR, CELESTIAL, and COSMIC-311 studies, selected for their large sample sizes and rigorous study conduct, was performed to evaluate the impact of appropriately managed high-grade AEs on efficacy outcomes and treatment duration, and to characterize the most common AEs leading to dose modifications in previously treated patients with advanced RCC, HCC, or RAIR-DTC treated with cabozantinib monotherapy. The AP authors also describe strategies for managing these AEs to maximize clinical outcomes for patients.

Methods

We conducted a post-hoc exploratory analysis of data from the three pivotal, randomized, controlled, phase III studies that evaluated the efficacy and safety of cabozantinib in advanced RCC, HCC, and RAIR-DTC (METEOR, CELESTIAL, and COSMIC-311, respectively). The study designs and eligibility criteria have been described previously (Abou-Alfa et al., 2018; Brose et al., 2021; Choueiri et al., 2015). Briefly, METEOR was an open-label study evaluating cabozantinib vs. everolimus (Afinitor) in adults with advanced RCC with a clear-cell component who had disease progression after VEGFR-TKI therapy (Choueiri et al., 2015). CELESTIAL was a double-blind, placebo-controlled study evaluating cabozantinib in adults with HCC who were not amenable to curative treatment and had previously received sorafenib (Nexavar; Abou-Alfa et al., 2018). COSMIC-311 was a double-blind, placebo-controlled study evaluating cabozantinib in patients aged ≥ 16 years with RAIR-DTC who had previously received lenvatinib

(Lenvima) and/or sorafenib and had disease progression on or after treatment with VEGFR-TKI therapy (Brose et al., 2021). In each of the three studies, AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (National Cancer Institute, 2017; Table 1). Study protocols were approved by the institutional review board or ethics committee at each center, and the studies were conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Cabozantinib Dosing and Management in Clinical Studies

In each study, the starting dose for oral cabozantinib was 60 mg once daily. Dose modifications were managed per protocol, with recommendations generally consistent with the prescribing information (Table 2; Exelixis, 2025; Ipsen, 2025). Generally, AEs were managed with supportive care at the earliest signs of toxicity. When necessary, dose holds or reductions were considered to prevent worsening of toxicity. Dose holds could occur at any time. Dose reductions to 40 mg/day (first decrease) and 20 mg/day (second decrease) were allowed. Importantly, all patients with grade 3 or 4 AEs were to have cabozantinib withheld (grade 3/4) or dose reduced (grade 3). If cabozantinib was withheld, it could be resumed with dose reduction upon resolution of the AE; patients receiving 20 mg/day could resume at the same dose. If the 20 mg/day dose was not tolerated, cabozantinib was discontinued. Certain AEs required permanent discontinuation, and cabozantinib was generally discontinued after dose holds of > 6 to 8 weeks. The consistency in AE management guidance across all three studies for patients with grade ≥ 3 AEs facilitated analysis of this subgroup.

Outcomes and Analysis

Using data from the three pivotal studies, we assessed PFS and treatment duration in patients who experienced at least one grade ≥ 3 AE of any cause and compared these outcomes to those for the overall population in each study. For PFS, the overall population consisted of all randomized patients (intention-to-treat [ITT] population); the analysis was based on the treatment a patient was randomized to receive. For treatment duration, the overall population comprised all patients who received at least one dose of study treatment (safety population); the analysis was based on the treatment the patient actually received. We also assessed the incidence, time to onset, and rates of dose holds, dose reductions, and treatment discontinuations associated with AEs of any cause that led to dose modifications of cabozantinib in ≥ 10% of patients in the three studies combined.

Progression-free survival was analyzed using Kaplan–Meier methods and the same data cutoffs as the primary study analyses. Between-group differences were assessed using stratified hazard ratios and 95% confidence intervals. Analyses were performed on data from all patients randomized to cabozantinib and are presented using descriptive statistics unless otherwise stated. The AP authors (SL-R, VS, DA, and BM) provided their supportive care strategies, as well as examples of the education provided to patients for the management of the most common AEs of any cause leading to dose modifications.

Table 1. Grades by Common Terminology Criteria for Adverse Events

Grade	Description
Grade 1	Mild; does not require intervention
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; may interfere with some activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization indicated; unable to take care of themselves
Grade 4	Severe with life-threatening consequences; urgent intervention indicated
Grade 5	Death related to an adverse event

Note. Information from National Cancer Institute (2017).

Table 2. Examples of Dose Modification Guidance for Cabozantinib-Associated AEs in METEOR, CELESTIAL, and/or COSMIC-311

AE	Severity	Recommended guidelines
General guidance	Intolerable grade 2, or grade 3 or 4	• Withhold cabozantinib until grade ≤ 1 • Resume at reduced dose[a]
Hypertension and hypertensive crisis	Grade 3	• Withhold cabozantinib until hypertension is adequately controlled to grade ≤ 2 • Resume at reduced dose[a] • Permanently discontinue cabozantinib for hypertension that cannot be controlled
	Grade 4	• Permanently discontinue cabozantinib
PPES	Intolerable grade 2 or grade 3	• Withhold cabozantinib until grade ≤ 1 • Resume at reduced dose[a]
Diarrhea	Grade 2, 3, or 4	• Withhold cabozantinib until grade ≤ 1 • Resume at reduced dose[a]

Note. PPES = palmar-plantar erythrodysesthesia syndrome. Information from Exelixis (2025); Ipsen (2025).
[a]Two dose reductions are recommended with a starting dose of 60 mg/day: to 40 mg/day (first reduction) and 20 mg/day (second reduction). Cabozantinib should be discontinued if 20 mg/day is not tolerated.

RESULTS

Patients

Across the three studies, 925 patients were randomized to cabozantinib (METEOR, *n* = 330; CELESTIAL, *n* = 470; COSMIC-311, *n* = 125) and comprised the ITT population for the current analysis; 923 patients received at least one dose of cabozantinib (METEOR, *n* = 331; CELESTIAL, *n* = 467; COSMIC-311, *n* = 125) and were included in the safety analyses (one patient who was randomized to everolimus in METEOR received cabozantinib instead and is included here; Abou-Alfa et al., 2018; Brose et al., 2021; Choueiri et al., 2015). Overall, 613 (66%) cabozantinib-treated patients had a grade 3/4 AE (68% of patients with RCC [METEOR], 68% with HCC [CELESTIAL], and 57% with RAIR-DTC [COSMIC-311]). The most common grade 3/4 AEs (occurring in ≥ 10% of patients in the three studies combined) were hypertension (15%), PPES (13%), diarrhea (10%), and fatigue (10%; Abou-Alfa et al., 2018; Brose et al., 2021; Choueiri et al., 2015). At the individual study level, grade 3/4 AEs occurred at similar rates across the different tumor types; grade 3/4 hypertension was reported in 9% to 16%, PPES in 8% to 17%, diarrhea in 7% to 11%, and fatigue in 8% to 10% of patients, respectively (Appendix A). Of these grade 3/4 events, all cases were grade 3 except for grade 4 hypertension in one patient each with HCC and RAIR-DTC and diarrhea in one patient with HCC, with no grade 5 events. As protocol-mandated, patients with grade 3/4 AEs were required to have cabozantinib withheld and/or dose reduced.

Efficacy and Treatment Duration in Patients With Grade ≥ 3 AEs

A comparison of the PFS analyses between patients who experienced grade ≥ 3 AEs and those in the ITT populations showed that, for all studies, the benefit of cabozantinib vs. control was maintained in those experiencing grade ≥ 3 AEs with the appropriate management outlined in the respective study protocols (Figure 1A–C). Among patients assigned to cabozantinib, for those who experienced grade ≥ 3 AEs vs. the ITT populations, median PFS was 7.3 vs. 7.4 months (METEOR), 5.4 vs. 5.2 months (CELESTIAL), and 7.4 vs. not reached (COSMIC-311).

Cabozantinib treatment duration was also similar for patients who experienced grade ≥ 3 AEs vs. the safety populations, with median treatment duration of 7.5 vs. 7.4 months (METEOR), 3.9 vs. 3.8 months (CELESTIAL), and 4.9 vs. 4.4 months (COSMIC-311; Table 3).

AEs Leading to Dose Modifications

Adverse events of any grade that led to dose modifications of cabozantinib in ≥ 10% of patients in the three studies combined were PPES (23%), diarrhea (21%), fatigue (14%), and hypertension (10%; Table 4). For these AEs, the median time to first onset was

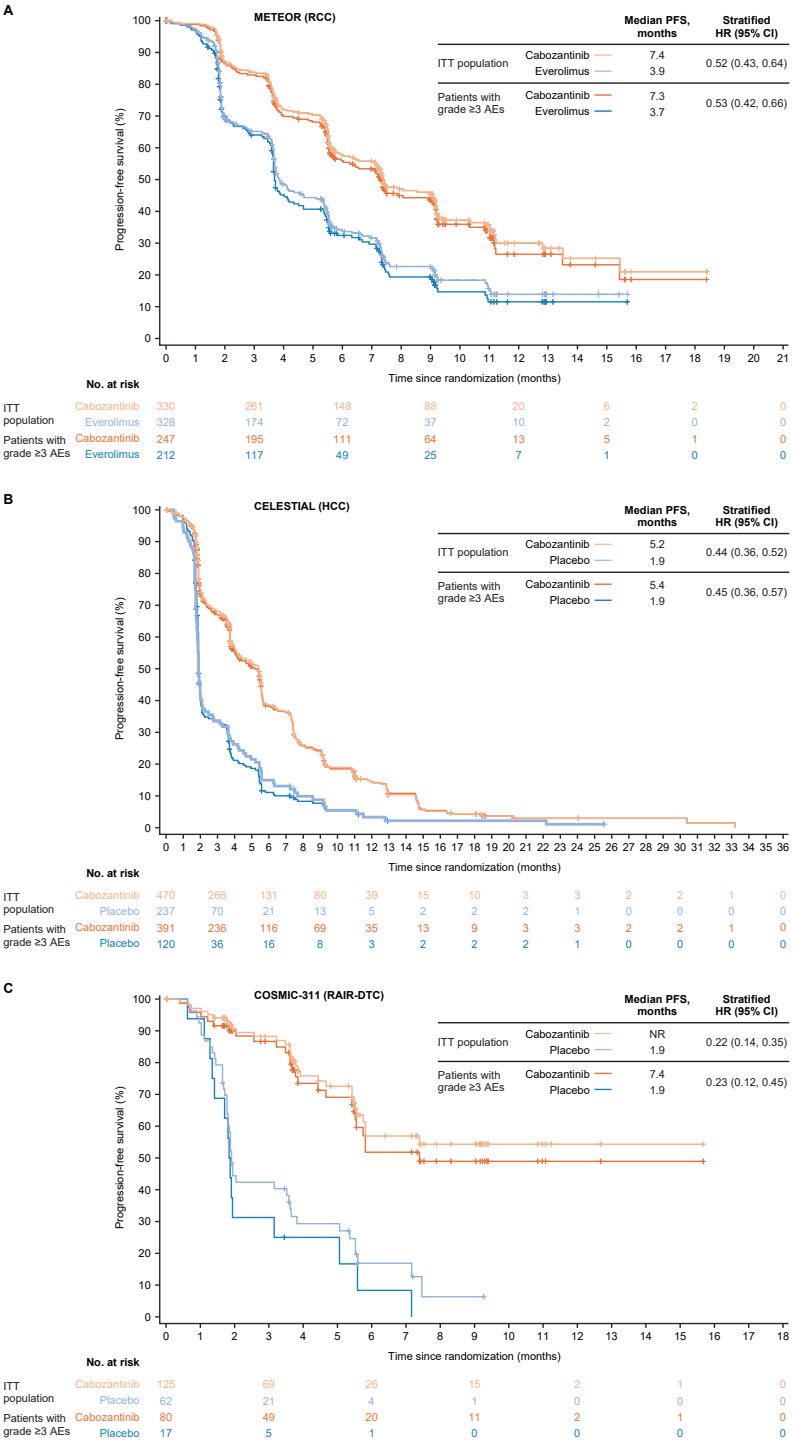


Figure 1. Kaplan–Meier analyses of PFS in patients with a grade ≥ 3 AE and the ITT population in (A) METEOR (RCC), (B) CELESTIAL (HCC), and (C) COSMIC-311 (RAIR-DTC). AE = adverse event; CI = confidence interval; HCC = hepatocellular carcinoma; HR = hazard ratio; ITT = intention-to-treat; NR = not reached; PFS = progression-free survival; RAIR-DTC = radioiodine-refractory or ineligible differentiated thyroid cancer; RCC = renal cell carcinoma.

Table 3. Median Cabozantinib Treatment Duration in METEOR, CELESTIAL, and COSMIC-311

Study (cancer type)	Patients with grade ≥ 3 AE, mo (range)	Safety population, mo (range)
METEOR (RCC)	*n* = 248 7.5 (0.3–18.4)	*n* = 331 7.4 (0.3–20.5)
CELESTIAL (HCC)	*n* = 391 3.9 (0.3–37.3)	*n* = 467 3.8 (0.1–37.3)
COSMIC-311 (RAIR-DTC)	*n* = 80 4.9 (0.4–15.7)	*n* = 125 4.4 (0.0–15.7)

Note. AE = adverse event; HCC = hepatocellular carcinoma; RAIR-DTC = radioiodine-refractory or ineligible differentiated thyroid cancer; RCC = renal cell carcinoma.

generally consistent across the studies, with hypertension developing earlier and diarrhea presenting later. Median times to onset ranged from 2.1 to 2.7 weeks for hypertension, 2.1 to 3.6 weeks for fatigue, 3.1 to 4.0 weeks for PPES, and 4.1 to 4.9 weeks for diarrhea (Appendix B). The proportions of patients experiencing dose holds, dose reductions, or treatment discontinuations due to these AEs were similarly consistent (Table 5). A discontinuation rate of < 3% was associated with each of these AEs, indicating that the vast majority of patients were able to remain on treatment with appropriate AE management.

Perspectives on AE Management

Supportive care strategies and examples of patient education for AE management related to the four most common AEs leading to dose modification, as provided by the AP authors, are outlined here.

PPES

Palmar-plantar erythrodysesthesia syndrome is one of the most clinically significant dermatologic AEs for patients treated with VEGFR-targeted multikinase inhibitors. It can progress quickly from a mild condition (tingling and numbness) to a painful ailment (lesions and hyperkeratosis) that can limit daily activities and impact quality of life (Belum et al., 2015; Gerendash & Creel, 2017; Kwakman et al., 2020). Hence, a full assessment of a patient's hands, feet, and nails should be conducted prior to initiating cabozantinib, and any preexisting skin conditions should be treated by a dermatologist (Gerendash & Creel, 2017; Kwakman et al., 2020). Patients are advised to use preventative skin care and avoid extreme temperatures and repetitive activities for hands and feet. If PPES occurs, proactive management should be instituted to prevent the worsening of skin symptoms. For supportive care, recommendations include daily use of urea and clobetasol creams, with pain medications for grade 2/3 PPES (Table 6). Patients with grade 2 PPES that is intolerable or does not resolve with treatment and those with grade 3 PPES should be referred to a dermatologist. Palmar-plantar erythrodysesthesia syndrome that cannot be managed with supportive care typically resolves with cabozantinib dose holds or reductions; however, cabozantinib should be discontinued if necessary.

Diarrhea

Prior to starting cabozantinib, it is important to establish the patient's baseline bowel habits and assess current medications for potential impact on bowel function. Patients with diarrhea should be advised to seek medical attention if they have an increase of four or more movements a day over pretreatment baseline, blood or mucus in stools, fever, abdominal cramps/pain/bloating, dizziness, or an inability to drink adequate amounts of fluid.

Strategies for managing diarrhea during cabozantinib treatment include providing dietary education, appropriate administration of one or more antidiarrheal or antimotility medications, isotonic hydration, and correction of fluid and electrolyte abnormalities (Table 6). Patients should be advised to log their dietary intake to help identify and remedy potential nontreatment causes of diarrhea, such as an infection or bowel obstruction. A tailored diet should be discussed with patients to help them avoid foods that may increase bowel movements (Colombo et al., 2022).

When medical attention is sought, patients should be assessed to determine the severity

Table 4. AEs That Led to Dose Modifications (Dose Holds or Reductions) in ≥ 5% of Patients Who Received Cabozantinib in METEOR, CELESTIAL, or COSMIC-311

AE leading to dose modifications	METEOR (RCC) *n* = 331, *n* (%)	CELESTIAL (HCC) *n* = 467, *n* (%)	COSMIC-311 (RAIR-DTC) *n* = 125, *n* (%)	All studies combined *n* = 923, *n* (%)
PPES	53 (16)	132 (28)	28 (22)	213 (23)
Diarrhea	87 (26)	84 (18)	22 (18)	193 (21)
Fatigue	50 (15)	71 (15)	11 (9)	132 (14)
Hypertension	30 (9)	48 (10)	10 (8)	88 (10)
Decreased appetite	29 (9)	40 (9)	11 (9)	80 (9)
Nausea	35 (11)	35 (7)	8 (6)	78 (8)
Asthenia	16 (5)	37 (8)	9 (7)	62 (7)
AST increase	10 (3)	47 (10)	4 (3)	61 (7)
Vomiting	27 (8)	20 (4)	5 (4)	52 (6)
ALT increase	13 (4)	28 (6)	7 (6)	48 (5)
Stomatitis	20 (6)	15 (3)	6 (5)	41 (4)
Mucosal inflammation	13 (4)	18 (4)	7 (6)	38 (4)
Proteinuria	16 (5)	11 (2)	8 (6)	35 (4)
Dyspnea	6 (2)	11 (2)	9 (7)	26 (3)
Hypocalcemia	2 (1)	4 (1)	7 (6)	13 (1)

Note. AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma; PPES = palmar-plantar erythrodysesthesia syndrome; RAIR-DTC = radioiodine-refractory or ineligible differentiated thyroid cancer; RCC = renal cell carcinoma.

(grade) and cause of diarrhea, including details on the onset and duration, number of episodes in 24 hours, consistency, color, and associated symptoms. Prior to cabozantinib dose modifications for diarrhea, APs should ensure that patients understand and are correctly implementing the recommended antidiarrheal strategies.

Fatigue

Fatigue refers to the subjective, persistent, and distressing sense of tiredness or exhaustion related to cancer or cancer treatments and is known to reduce patients' quality of life and willingness to complete treatment; hence, the occurrence and severity of fatigue should be regularly assessed (Kang et al., 2023). Prior to starting cabozantinib, patients should be advised to seek medical attention if they are unable to get out of bed for a 24-hour period, feel confused or have memory problems, have problems waking up, cannot catch their breath or have dizziness when active, or start to experience poor balance or coordination. The importance of daily physical activity, adequate rest, a regular sleep/wake cycle, and calling their healthcare provider if they experience confusion, dizziness, imbalance, or falls should be discussed.

Supportive care starts with ruling out common causes of fatigue, such as hypothyroidism, after which psychostimulant medications and/or dose holds may be considered (Table 6). Early intervention with cabozantinib dose reduction for fatigue of grade 2 severity may be considered (Jimenez et al., 2024). Management strategies include exercise regimens, tailored to the patient's abilities and preferences to optimize adherence (Bower et al., 2024), and educating the patient about drinking plenty of fluids (avoiding caffeine) and eating protein-rich foods. Cognitive behavioral therapy or mindfulness-based programs may also reduce fatigue severity (Bower et al., 2024).

Hypertension

The early onset of hypertension observed in this analysis (Appendix B) highlights the need to counsel patients about the risk of developing new or worsening hypertension, so they can participate

Table 5. Incidence of Cabozantinib Dose Holds, Dose Reductions, and Treatment Discontinuations due to PPES, Diarrhea, Fatigue, and Hypertension in METEOR (RCC; *n* = 331), CELESTIAL (HCC; *n* = 467), and COSMIC-311 (RAIR-DTC; *n* = 125)

AE	Dose holds, *n* (%)	Dose reductions, *n* (%)	Treatment discontinuations, *n* (%)
PPES			
METEOR	46 (14)	38 (11)	1 (< 1)
CELESTIAL	119 (25)	101 (22)	11 (2)
COSMIC-311	20 (16)	24 (19)	0
Diarrhea			
METEOR	72 (22)	54 (16)	3 (1)
CELESTIAL	69 (15)	47 (10)	5 (1)
COSMIC-311	20 (16)	13 (10)	1 (1)
Fatigue			
METEOR	41 (12)	33 (10)	4 (1)
CELESTIAL	63 (13)	35 (7)	7 (1)
COSMIC-311	6 (5)	9 (7)	3 (2)
Hypertension			
METEOR	17 (5)	25 (8)	0
CELESTIAL	31 (7)	35 (7)	4 (1)
COSMIC-311	9 (7)	1 (1)	1 (1)

Note. Percentages are based on the total safety population in the cabozantinib arm for each study. AE = adverse event; HCC = hepatocellular carcinoma; PPES = palmar-plantar erythrodysesthesia syndrome; RAIR-DTC = radioiodine-refractory or ineligible differentiated thyroid cancer; RCC = renal cell carcinoma.

in blood pressure monitoring and understand the potential need to initiate or escalate antihypertensive therapy (Pandey et al., 2023). Prior to starting cabozantinib, APs should document the patient's blood pressure and ensure underlying hypertension or cardiac conditions are appropriately managed. Strategies for managing hypertension include educating patients about when and how to measure blood pressure, optimizing antihypertensive medications, and monitoring for hypotension (Table 6). Patients should be advised to take and log blood pressure medications as instructed, and to call their health-care provider for elevated blood pressure; patients should be given systolic and diastolic parameters for calling their provider, based on their baseline blood pressure, comorbidities, and available guidelines (Jones et al., 2025; Unger et al., 2020). Cabozantinib should be held for grade 3 hypertension (> 160/100 mmHg; Exelixis, 2025; National Cancer Institute, 2017). Where necessary, APs should consider electronic adherence aids, such as text messaging services, for monitoring and medication reminders (Unger et al., 2020).

For medical management of hypertension, current guidelines recommend initial treatment with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, calcium-channel blocker, or thiazide-like diuretic, to achieve a target blood pressure of < 130/80 mmHg for patients aged < 65 years and < 140/90 mmHg for those aged ≥ 65 years; however, it is important to consider each patient on an individual basis, accounting for frailty, independence, and expected treatment tolerability (Unger et al., 2020). Health-care providers must exercise caution to avoid choosing antihypertensive agents known to interact with cabozantinib; for example, some calcium-channel blockers are strong cytochrome P450 3A4 (CYP3A4) inhibitors and the coadministration of cabozantinib with a strong CYP3A4 inhibitor increases cabozantinib plasma levels, potentially raising the risk of exposure-related AEs (Exelixis, 2025; Pandey et al., 2023).

Table 6. Advanced Practitioner-Led Management Strategies for Common AEs Leading to Cabozantinib Dose Modifications[a]

AE	Supportive care strategy	Patient education
PPES	• Recommend use of 20% urea cream twice daily and 0.05% clobetasol cream once daily • Suggest pain medications (e.g., NSAIDs, GABA agonists) for grade 2 and 3 PPES • Adequate intervention is necessary to prevent worsening » Aggressively manage skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas » Refer early to a dermatologist	• Use preventative skin care: supportive shoes, gel inserts, thick socks and gloves, and cold packs • Avoid exposing hands and feet to extreme temperatures • Avoid repetitive activities with hands and feet
Diarrhea	• Administer antidiarrheal or antimotility agent at first sign of diarrhea (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea, up to 16 mg per day) • More than one agent may be necessary; maximize dose • Continuous oral isotonic hydration • Correction of fluid and electrolyte abnormalities	• Eat small, frequent meals • Stay well hydrated • Follow BRAT diet: bananas, rice, applesauce, and toast • Avoid lactose-containing products, high fat meals, and alcohol
Fatigue	• Rule out common causes such as anemia, deconditioning, emotional distress, poor nutrition, sleep disturbance, and hypothyroidism • Consider psychostimulants, such as methylphenidate, after disease-specific morbidities have been excluded • Withholding or reducing the dose may be considered for fatigue despite optimal management, at the HCP's discretion	• Participate in daily physical activity • Get adequate rest and fluids and maintain sleep/wake cycle • Call HCP in case of confusion, dizziness, imbalance, or falls
Hypertension	• Educate patients on how to take blood pressure accurately • Confirm accuracy of patient's home blood pressure monitor • Instruct patients to monitor blood pressure regularly during cabozantinib treatment and maintain a record • Optimize antihypertensive medication by: » Adding new or additional antihypertensive medications » Increasing dose of existing medication and monitoring closely for hypotension	• Take blood pressure medications as instructed • Call HCP for elevated blood pressure • Keep home blood pressure log and bring to clinic appointments

Note. AE = adverse event; GABA = gamma-aminobutyric acid; HCP = health-care provider; NSAIDs = nonsteroidal anti-inflammatory drugs; PPES = palmar-plantar erythrodysesthesia syndrome.
[a]For additional information related to cabozantinib-related warnings and precautions, as well as specific management strategies, please refer to prescribing information.

DISCUSSION

Findings from this retrospective analysis indicate that grade ≥ 3 AEs, when properly managed, do not impact clinical outcomes or treatment duration in patients receiving cabozantinib for previously treated, advanced RCC, HCC, or RAIR-DTC. Patients who initiated cabozantinib at the approved dose of 60 mg once daily in the pivotal phase III studies and experienced grade ≥ 3 AEs had similar PFS outcomes and cabozantinib treatment durations as the overall population in each study. These data demonstrate that early recognition and appropriate management of AEs with individualized dose modifications maintains treatment duration and allows patients to obtain the clinical benefits associated with cabozantinib in these tumor types.

Cabozantinib has a consistent, predictable safety profile across the three cancers. Palmar-plantar

erythrodysesthesia syndrome, diarrhea, fatigue, and hypertension were the most common grade 3/4 AEs and the most frequent AEs leading to cabozantinib dose modifications in the three studies combined. Despite the dose modifications observed, cabozantinib discontinuations due to each of these AEs occurred in < 3% of patients in each study. The time to first onset for each of these AEs was also similar across the studies. The consistency in type, frequency, and timing of cabozantinib-associated AEs for patients with different tumor types allows APs to effectively plan management strategies for their cabozantinib-treated patients.

Strategies for the management of AEs associated with TKIs, including cabozantinib, in advanced RCC, HCC, and thyroid cancer, have been previously published (De Leo et al., 2021; Gerendash & Creel, 2017; Rimassa et al., 2019; Schmidinger & Danesi, 2018; Schwartz et al., 2020; Tahara, 2018). Recommendations have included early assessment of risk factors and identification of AEs (De Leo et al., 2021), patient education, prophylactic and supportive care, and dose modifications (Gerendash & Creel, 2017; Schwartz et al., 2020; Tahara, 2018). Here, the AP authors have provided evidence-informed, AP-led, cabozantinib-specific AE management strategies for the four most common AEs leading to dose modifications. In routine practice, APs are typically the first point of contact for patients experiencing AEs associated with cancer treatments; hence, they play an essential role in the timely and proactive management of AEs, allowing patients to maintain their treatment schedule and optimizing clinical outcomes. The benefit of proactive management is supported by the low rates of cabozantinib-related discontinuations due to these most common AEs and the maintained efficacy among patients with grade ≥ 3 AEs observed in the pivotal studies.

Prospective evaluation of these strategies across cabozantinib indications represents an important and unmet research priority. For example, a significant improvement in overall survival associated with electronic patient-reported outcome monitoring combined with nurse-initiated early intervention was previously demonstrated in patients receiving chemotherapy (Basch et al., 2016). Although that study was conducted in a heterogeneous solid tumor population treated with intravenous therapies, it supports the mechanistic and real-world plausibility of applying similar structured, proactive care models to patients receiving oral TKIs such as cabozantinib.

Strengths and Limitations

Strengths of this analysis include the use of the randomized, controlled, phase III studies on which the analysis is based; the consistent, rigorous AE reporting and management across the analyzed populations; and the inclusion of patients with different tumor types. By applying a uniform analytical framework across multiple disease settings, the synthesized findings demonstrate reproducibility and consistency in clinically relevant outcomes associated with AEs, thereby strengthening their broader clinical relevance.

Limitations include the retrospective nature of the analysis, which negates any formal sample size and power calculations, and differences between the three studies (including design, tumor type, treatments, and patient populations), which could have led to heterogeneity of the data used to identify the most common grade 3/4 AEs. Further, owing to the strict inclusion criteria and close management of AEs in clinical studies, the data may not reflect real-world clinical practice, where the incidence of AEs and dose modifications may be higher (Johnston et al., 2023). In addition, for patients with advanced RCC, the analysis relies on data from METEOR, conducted in 2015. Since then, advances in systemic therapy, including the introduction of immunotherapy-based combination strategies such as cabozantinib plus nivolumab, have substantially altered the treatment landscape for RCC. Consequently, the findings may not fully reflect contemporary clinical practice with cabozantinib in this patient population. Nevertheless, data from subsequent trials of cabozantinib in previously treated patients, such as CONTACT-03 (Pal et al., 2023) and CaboPoint (Albiges et al., 2026), demonstrate efficacy and safety outcomes that are broadly consistent with those observed in METEOR, supporting the ongoing applicability of these data. As an exploratory analysis focused largely on identifying differences within each individual study, and when combined with insights from APs, the findings of the current analysis help elucidate the real-world impact of toxicity on patient outcomes and treatment persistence and

provide practical strategies to proactively manage AEs and optimize treatment benefit in patients receiving cabozantinib.

CONCLUSIONS

Cabozantinib has a consistent, predictable safety profile across indications. For patients with advanced RCC, HCC, or RAIR-DTC receiving cabozantinib in pivotal studies at the approved starting dose of 60 mg once daily, proactive AE management, including individualized dose modifications as appropriate, helped patients to remain on treatment and maximize their clinical outcomes. The benefit of proactive management is supported by the low rates of discontinuation due to the most common AEs observed in these studies. Advanced practitioners play an essential role in the proactive management of AEs, thereby improving treatment tolerability and helping patients remain on therapy, which in turn maximizes their clinical benefit from cabozantinib treatment. These findings support the feasibility and safety of proactive AE management and early dose modification and reinforce the role of APs in implementing supportive care strategies without delay. ●

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Disclosure

Mr. Lee-Ramos has no conflicts of interest to declare. Ms. Seery has served as a consultant for Instil Bio and has participated on advisory boards for Exelixis, Inc. and Replimune. Ms. Andresen has served as a consultant for and received honoraria and support for attending meetings and/or travel from Exelixis, Inc. Ms. Williamson, Dr. Berry, and Dr. Hall are employees of, and hold stock or stock options in, Exelixis, Inc. Ms. Martone has received honoraria from Curio Science.

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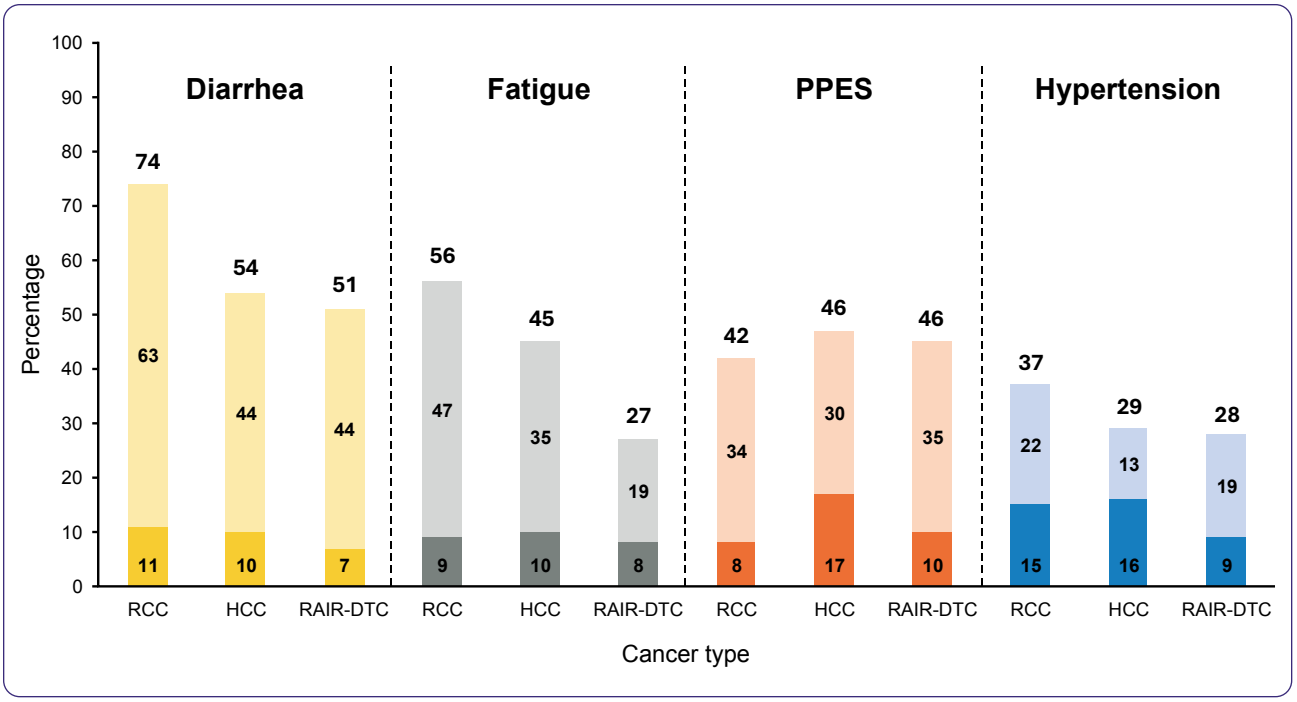
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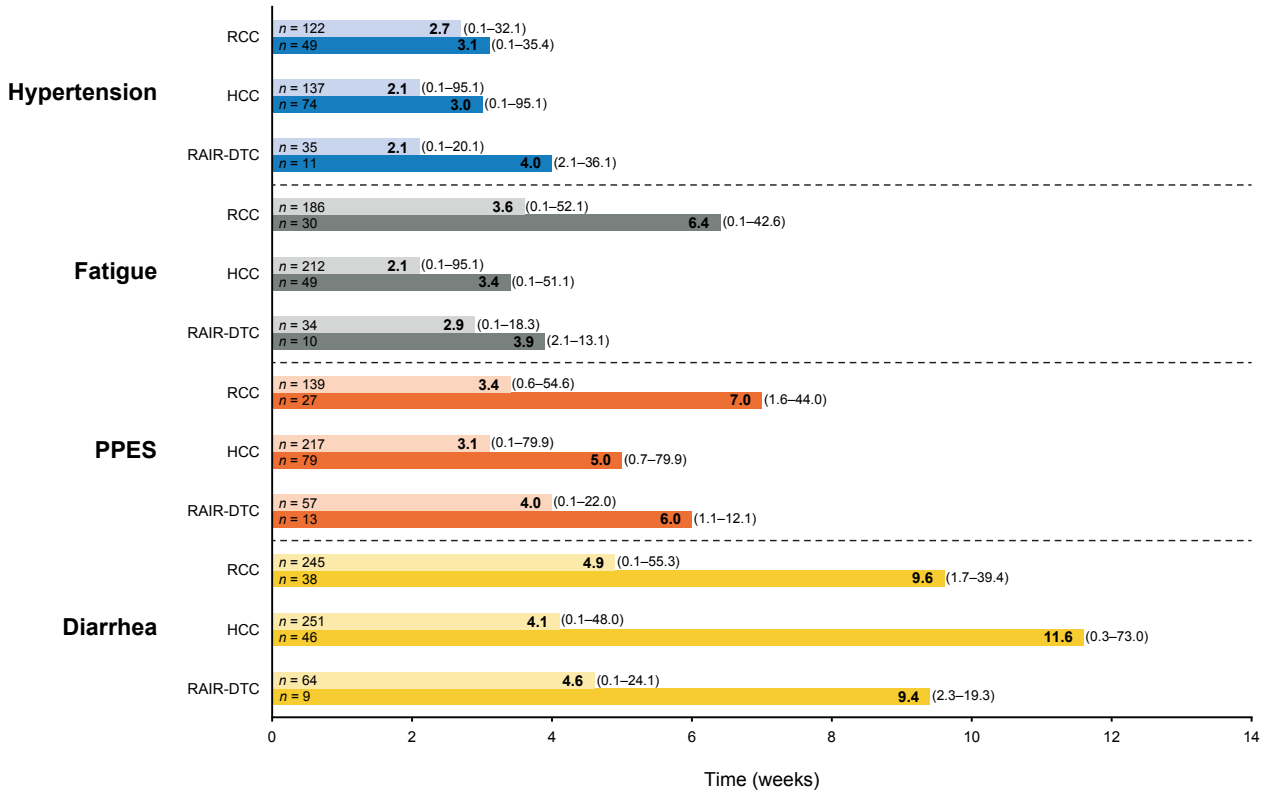
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Appendix A. The most frequent grade 3/4 AEs, occurring in ≥ 10% of patients in the three studies combined (METEOR, RCC [*n* = 331]; CELESTIAL, HCC [*n* = 467]; and COSMIC-311, RAIR-DTC [*n* = 125]). Information from Abou-Alfa et al. (2018); Brose et al. (2021); Choueiri et al. (2015). Lighter shaded parts of each bar represent the proportion of these AEs that were of grade 1/2 severity; darker shades represent the proportion that were of grade 3/4 severity. Individual values may not equal totals due to rounding. AE = adverse event; HCC = hepatocellular carcinoma; PPES = palmar-plantar erythrodysesthesia syndrome; RAIR-DTC = radioiodine-refractory or ineligible differentiated thyroid cancer; RCC = renal cell carcinoma.



Appendix B. Time to first onset of any-grade (lighter shaded bars) and grade 3/4 (darker shades) hypertension, fatigue, PPES, and diarrhea among patients receiving cabozantinib in METEOR (RCC [*n* = 331]), CELESTIAL (HCC [*n* = 467]), and COSMIC-311 (RAIR-DTC [*n* = 125]). Data are presented as median weeks (range). HCC = hepatocellular carcinoma; PPES = palmar-plantar erythrodysesthesia syndrome; RAIR-DTC = radioiodine-refractory or ineligible differentiated thyroid cancer; RCC = renal cell carcinoma.