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ADIS DRUG EVALUATION

Cabozantinib: A Review of Its Use in Patients with Medullary Thyroid Cancer

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Abstract Cabozantinib (Cometriq®) is an orally administered small molecule inhibitor of multiple tyrosine kinase receptors, including those involved in the pathogenesis of medullary thyroid cancer (MTC) [i.e. rearranged during transfection (RET), MET and vascular endothelial growth factor receptor (VEGFR)-2]. Cabozantinib is indicated for the treatment of adults with progressive, unresectable locally advanced (in the EU) or metastatic (in the EU and USA) MTC. Compared with placebo, cabozantinib significantly prolonged progression-free survival, reflecting a 72 % reduction in the risk of disease progression or death, in patients with unresectable, locally advanced or metastatic MTC participating in a multinational, phase III study. A significantly higher proportion of patients receiving cabozantinib than those receiving placebo achieved an objective response or disease stabilization (i.e. a complete or partial response, or stable disease). The overall survival benefit with cabozantinib is as yet unclear, with no significant benefit observed in two interim analyses (one prespecified, and one unplanned and conducted at the request of the US FDA). The tolerability profile of oral cabozantinib is typical for a small molecule targeting the VEGFR and other tyrosine kinase-mediated pathways, with adverse events associated with the inhibition of the VEGF pathway (e.g. gastrointestinal perforation, haemorrhage, hypertension and venous thrombosis) reported in the phase III study. Treatment-emergent adverse events were generally managed with supportive therapy, dose reductions and/or dose interruptions. Although final overall survival data are awaited, current evidence suggests cabozantinib to be a valuable treatment option for adults with progressive, unresectable locally advanced or metastatic MTC.

Cabozantinib in the management of medullary thyroid cancer (MTC): a summary

Orally administered small molecule inhibitor of multiple tyrosine kinase receptors, including rearranged during transfection (RET), MET and vascular endothelial growth factor receptor-2 (VEGFR-2)

Significantly prolongs progression-free survival in adults with unresectable, locally advanced or metastatic MTC

Associated with adverse events (e.g. fistulas, perforations, haemorrhage, hypertension and venous thrombosis) secondary to its inhibition of the VEGF pathway

Most frequently reported grade 3 or 4 adverse events and laboratory abnormalities included diarrhoea, lymphopenia, palmar-plantar erythrodysesthesia syndrome, hypocalcaemia, fatigue and hypertension

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1 Introduction

Medullary thyroid cancer (MTC) is an uncommon (accounting for 5–8 % of all thyroid malignancies) histological subtype of thyroid cancer originating from the calcitonin-secreting parafollicular (C) cells of the thyroid [1, 2]. The majority (up to 80 %) of MTC cases occur sporadically; the remainder arise as inherited autosomal dominant syndromes (multiple endocrine neoplasia [MEN] type 2A [MEN 2A], MEN 2B and familial MTC) [1, 2].

Germline mutations in the rearranged during transfection (*RET*) proto-oncogene appear to initiate at least 95 and 88 % of inherited MEN 2A and familial MTC cases, respectively, and have been identified in approximately 6 % of patients with clinically sporadic MTC [1, 3]. *RET* codes for a cell membrane-associated tyrosine kinase receptor (RET), which is thought to modulate intracellular signalling pathways involved in the regulation of cell proliferation, differentiation and survival [1, 3, 4]. At least 25 % of sporadic MTC cases are characterized by acquired somatic mutations in RET, particularly M918T, which can also be present in hereditary MEN 2B; the M918T mutation is associated with a poor prognosis [1, 3]. Other tyrosine kinase receptors that may also play a role in MTC are MET (the receptor for hepatocyte growth factor; coded for by the *MET* proto-oncogene), which is important in tumourigenesis, the vascular endothelial growth factor receptor (VEGFR), specifically VEGFR-2, which is often overexpressed in both MTC cells and the supporting vascular endothelium and plays a role in tumour angiogenesis, and the epidermal growth factor receptor (EGFR), which mediates the actions of different growth factors [4, 5].

The abnormal activation of various tyrosine kinases and signalling pathways in MTC has led to their identification as valid therapeutic targets [2–4], with the simultaneous inhibition of various tyrosine kinases potentially preventing the compensatory activation of other tyrosine kinases if only one tyrosine kinase receptor is inhibited [4]. Cabozantinib (Cometriq®) is an inhibitor of multiple tyrosine kinase receptors, including RET, MET and VEGFR-2 [1]. This article reviews pharmacological, therapeutic efficacy and tolerability data relevant to the utilization of oral cabozantinib in the treatment of patients with unresectable, locally advanced or metastatic MTC.

2 Pharmacodynamic Properties

Cabozantinib (Fig. 1) is a small molecule inhibitor of multiple tyrosine kinase receptors [6]. In vitro, it has demonstrated inhibitory activity against RET (half-maximal inhibitory concentration [IC_{50}] 85 nmol/L), MET (IC_{50} 8 nmol/L) and VEGFR-2 (IC_{50} 4 nmol/L) [cellular assay] [7], and against the RET mutant M918T (IC_{50} 27 nmol/L) [biochemical assay] [8]. Cabozantinib inhibited the (auto)phosphorylation of MET, RET and VEGFR-2 in vitro and in murine tumour models, and the proliferation of cells expressing the MEN 2A mutation or the RET mutant C634 W [8–10]. It also inhibited hepatocyte growth factor-stimulated migration and invasion, and VEGF-induced endothelial cell tubule formation in vitro [9]. In a murine xenograft model of breast cancer, cabozantinib induced tumour hypoxia and apoptosis, and reduced proliferation and vascularity, inducing tumour and endothelial cell death [9].

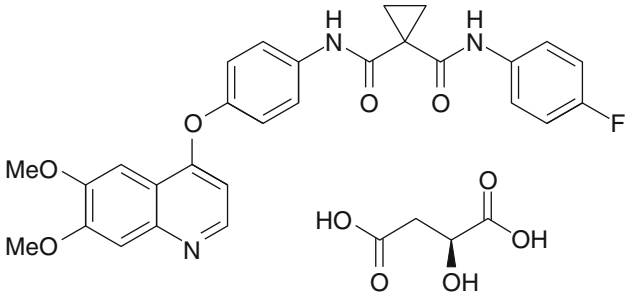

Fig. 1 Chemical structure of cabozantinib

2.1 Antitumour Effects

Antitumour activity with cabozantinib has been demonstrated in various murine xenograft tumour models (breast cancer, lung cancer, MTC and prostate cancer) [8, 9, 11]. For instance, in the murine xenograft MTC model, significant ($p < 0.01$) tumour suppression was observed following oral cabozantinib 10, 30 and 60 mg/kg once daily compared with vehicle, with the 10 and 30 mg/kg once daily dosages suppressing tumour growth in a dose-dependent manner. Moreover, an analysis of tumour cellularity demonstrated significant ($p < 0.02$) tumour regression (defined as a reduction from the start of therapy to the final measurement in mean tumour weight) following cabozantinib 10, 30 and 60 mg/kg, but not 3 mg/kg once daily versus vehicle [8].

Inhibitors that target VEGFR-2 are known to promote metastasis; this has been demonstrated in preclinical models [9]. This may be the result of increased signalling via MET, with the simultaneous targeting of MET and VEGFR-2 potentially assisting in the inhibition of alternative pathway signalling and, thus, providing a more sustained antitumour effect [12]. In a murine xenograft model of breast cancer, treatment with cabozantinib did not promote metastasis, with no differences observed in lung surface tumour burden, number of foci or whole lung wet weights compared with vehicle [9].

The antitumour effects of cabozantinib have also been observed in patients with solid tumours participating in phase I and II studies [13, 14]. Patients in a phase I, dose-escalation study received cabozantinib administered intermittently (once daily for the first 5 days of a 2-week period) at doses ranging from 0.08 to 11.52 mg/kg or continuously (once daily) at doses ranging from 175 to 265 mg [13]. Of the 35 patients who had measurable MTC in this study, 49 % experienced at least a 30 % reduction from baseline in tumour measurements and 29 % achieved an objective response (all objective responses were partial responses) [13]. In a subsequent analysis conducted after a minimum follow-up duration of 52 months [15], 11 (30 %) of 37 MTC patients achieved a confirmed partial response or were progression free at ≥24 months; all 11 patients were progression free for >24 months. Five of these 11 patients remained on treatment at the time of data cut-off, with a median duration of treatment of 55 months, with four of these patients having achieved a partial response and one stable disease at this timepoint [15].

2.2 Biomarkers

Serum calcitonin (and serum carcinoembryonic antigen [CEA] in specific cases) is a biomarker for the presence of persistent or recurrent MTC [2]. In phase I [13] and III [16] studies in patients with advanced solid tumours [13] or unresectable, locally advanced or metastatic MTC and radiographic evidence of disease progression at screening [16], therapy with cabozantinib resulted in reductions in calcitonin and CEA levels. For instance, among the 140 and 170 cabozantinib recipients and 61 and 71 placebo recipients who were evaluable for pharmacodynamic (calcitonin and CEA, respectively) responses at week 12 of the phase III study (see Sect. 5 for dosage and design details), therapy with cabozantinib was associated with significant ($p < 0.001$) reductions from baseline to week 12 in mean serum calcitonin and CEA levels versus placebo [16]. There was significant ($p < 0.0001$) correlation between the changes from baseline in serum calcitonin and CEA levels and the changes in target lesion size [17]. Moreover, calcitonin or CEA biochemical responses (i.e. a complete or partial response, or stable disease) are predictive of a longer progression-free survival (PFS) benefit with cabozantinib therapy [17].

Limited data from the phase III study (available as an abstract plus oral presentation) found cabozantinib to be associated with significant ($p < 0.0001$) mean fold changes from baseline to day 29 in plasma soluble VEGFR-2 and KIT receptor levels compared with placebo [17]. Significant correlations between the extent of the mean fold changes in plasma soluble VEGFR-2 ($p = 0.0003$) and plasma soluble KIT ($p = 0.0032$) levels and plasma cabozantinib exposure on day 29 were observed [17]. Moreover, higher baseline levels of, but not fold change values in, both soluble VEGFR-2 ($p = 0.0112$) and soluble KIT (p-value not reported) levels are predictive of an improved PFS benefit with cabozantinib therapy [17].

3 Pharmacokinetic Properties

Cabozantinib exhibited dose-proportional elevations in maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) from time zero to the last quantifiable timepoint (AUC_{last}) values in the individual dosing cohorts of a phase I study in 85 patients with advanced solid tumours (primarily MTC [$n = 37$]) (see Sect. 2 for dosage and design details) [13]. There was no significant difference in cabozantinib exposure between patients with versus those without MTC [13].

The absolute bioavailability of oral cabozantinib has yet to be determined [18]. The pharmacokinetics of oral cabozantinib are presented in Table 1. Steady state was achieved after approximately 15 days of once-daily dosing with cabozantinib [6, 18, 19], with mean accumulation (based on AUC) following the administration of cabozantinib 140 mg/day for 19 days 4- to 5-fold that of a single dose [6, 19]. Following a single oral dose of cabozantinib 140 mg, AUC and C_{max} values were elevated by 57 and 41 % with a high-fat meal relative to fasting conditions in healthy volunteers [6, 19]. Therefore, cabozantinib should not be administered with food (see Sect. 7). Cabozantinib does not extensively bind to red blood cells [18].

Four metabolites are present in the plasma at >10 % higher exposures than the parent drug: XL1814 *N*-oxide, XL184 amide cleavage product, XL184 monohydroxy sulphate and 6-desmethyl amide cleavage product sulphate [6]. The 6-desmethyl amide cleavage product sulphate metabolite is the major circulating metabolite of cabozantinib [18]. Two non-conjugated metabolites (XL184-*N*-

Table 1 Pharmacokinetic parameters of oral cabozantinib [6, 13, 18, 19]

Parameter	
Median time to C_{max}	2–5 h
Oral volume of distribution[a]	~349 L
Plasma protein binding	≥99.7 %
Mean terminal elimination half-life[b]	91 h
Mean clearance at steady state[c]	4.2 L/h

CAB cabozantinib, C_{max} maximum plasma concentration, *pts* patients

[a] Population pharmacokinetic analysis; 289 pts with solid tumours receiving CAB 140 mg/day

[b] In pts with solid tumours

[c] In pts with solid tumours receiving CAB 175 mg/day

oxide and XL184 amide cleavage product), which possess less than 1 % of the on-target kinase inhibition potency of the parent drug, each represent <10 % of total drug-related plasma exposure [6].

Cabozantinib is eliminated via hepatic and renal routes [18]. Following the administration of a single dose of radiolabelled cabozantinib to healthy volunteers, approximately 54 and 27 % of the radioactive dose was recovered in the faeces and urine, respectively, within a 48-day collection period [6, 19]. Multiple metabolites are detected in both the faeces and urine [18].

3.1 Special Populations

Data are lacking concerning the effects of renal impairment on the pharmacokinetics of cabozantinib [6, 19]. However, results from a population pharmacokinetic analysis suggest that mild to moderate renal impairment (creatinine clearance ≥30 mL/min) has no clinically relevant effect on the clearance of cabozantinib [19]. Therefore, dosage adjustments are not required for this patient population in the USA [19]; in the EU, caution is recommended in patients with renal impairment [6]. Data are lacking in patients with severe renal impairment [6, 19]; the utilization of cabozantinib in this patient population is not recommended in the EU [6].

There are currently no data concerning the effects of hepatic impairment on the pharmacokinetics of cabozantinib [6, 19]. Therefore, in the EU, the utilization of cabozantinib is not recommended in patients with hepatic impairment [6], with the US prescribing information recommending that cabozantinib be avoided in patients with moderate or severe hepatic impairment [19].

Dosage adjustments are not required in elderly patients (aged ≥65 years) in the EU [6], with limited data currently preventing the determination of dosage adjustments in this patient population in the USA [19]. Limited data are also currently preventing the determination of dosage adjustments in patients with cardiac impairment in the EU [6].

The efficacy and tolerability of cabozantinib in children and adolescents aged <18 years have not been established [6, 19] as data are lacking [6].

4 Potential Drug Interactions

Cabozantinib is a substrate of cytochrome P450 (CYP) 3A4 and, to a lesser extent, CYP2C9 [6, 18, 19]. The coadministration of cabozantinib with rifampicin (rifampin) (a strong CYP3A4 inducer) reduced single-dose plasma cabozantinib AUC from time zero to infinity (AUC_{∞}) by 77 % and increased cabozantinib clearance by 4.3-fold in healthy volunteers [6, 19]. Therefore, the chronic utilization of strong CYP3A4 inducers should be avoided [6, 19], with the US prescribing information recommending an increase in the dosage of cabozantinib by 40 mg once daily, as tolerated, in those patients that require treatment with a strong CYP3A4 inducer [19]. The dose utilized prior to the initiation of the CYP3A4 inducer should be resumed 2–3 days following discontinuation of the strong CYP3A4 inducer [19]. Moreover, concurrent therapy with cabozantinib and ketoconazole (a strong CYP3A4 inhibitor) increased single-dose plasma cabozantinib AUC_{∞} by 38 % and reduced cabozantinib clearance by 29 % in healthy volunteers [6, 19]. Therefore, in the EU, caution is advised with the coadministration of cabozantinib and strong CYP3A4 inhibitors [6], with the US prescribing information recommending avoidance or a reduction in the dosage of cabozantinib by 40 mg once daily in those patients requiring treatment with a strong CYP3A4 inhibitor [19]. The dose utilized prior to the initiation of the CYP3A4 inhibitor should be resumed 2–3 days following discontinuation of the strong CYP3A4 inhibitor [19].

The solubility of cabozantinib is pH dependent, with a pH >3 resulting in a very low solubility [6, 18]. While the effect of proton pump inhibitors on the gastrointestinal absorption of cabozantinib has yet to be determined, coadministration may reduce the exposure of cabozantinib. Thus, concurrent therapy is not recommended in the EU [6].

Cabozantinib is an inhibitor (IC_{50} 7.0 μmol/L), but not a substrate, of P-glycoprotein (P-gp) transporter and, therefore, may have the potential to elevate the plasma concentrations of concurrently administered substrates of P-gp (e.g. digoxin) [6]. The EU summary of product characteristics (SPC) therefore advises caution with the coadministration of cabozantinib and a P-gp substrate [6].

5 Therapeutic Efficacy

Discussion in this section focuses on a double-blind, placebo-controlled, multinational, phase III study assessing the efficacy of oral cabozantinib in the treatment of adults with unresectable, locally advanced or metastatic MTC and radiographic evidence of disease progression at screening [16]. Limited supplementary data have been procured from an abstract plus oral presentation [20], the EU assessment report [18], the EU SPC [6] and the US FDA summary review [21].

Patients aged ≥18 years with an Eastern Cooperative Oncology Group performance status score of 0–2 and histologically confirmed, unresectable, locally advanced or metastatic MTC were eligible for enrolment [16]. Patients were required to have documented radiographic disease progression (assessed according to modified Response

Evaluation Criteria in Solid Tumors [mRECIST] criteria [22]) at screening compared with an image obtained within the previous 14 months [16]. The key exclusion criteria were prior systemic antitumour therapy within 4 weeks or significant cardiac, haematopoietic, hepatic or renal dysfunction. There were no limitations with regard to prior therapy, including exposure to other tyrosine kinase inhibitors [16].

Eligible patients were stratified by age (≤65 years vs. >65 years) and previous tyrosine kinase inhibitor therapy and randomized to receive cabozantinib 140 mg (freebase equivalent) or placebo once daily, with subsequent doses delayed and/or reduced (to a minimum of 60 mg/day) as required [16]. Therapy continued until disease progression (assessed according to mRECIST criteria) or unacceptable toxicity. At the data cut-off date of 15 June 2011, the arithmetic median durations of exposure to cabozantinib and placebo were 204 and 105 days. At this timepoint, 45 % (98 of 219 patients) of cabozantinib recipients and 14 % (15 of 111) of placebo recipients were still receiving the study medication (mean dosage 106 mg/day and 175 mg/day) [16].

At baseline, patient demographic and disease characteristics were well balanced between the cabozantinib and placebo groups [16]. Overall, 78 % of patients were aged ≤65 years; 86 % had sporadic disease, 78 % had not received prior tyrosine kinase inhibitor therapy and 48 % were RET mutation positive. The predominant RET mutation was M918T (74 % of 159 patients with documented mutations) [16].

PFS (see Table 2 for definition) [primary endpoint] was assessed at the prespecified primary analysis (data cut-off date of 6 April 2011) conducted after 139 events of disease progression (assessed by blinded independent radiological review according to mRECIST criteria) or death [16]. Key secondary endpoints included objective response (defined as the proportion of patients with measurable disease achieving a complete or partial response; assessed by blinded independent radiological review according to mRECIST criteria) [data cut-off date of 15 June 2011] and overall survival [16]. Overall survival was assessed at a prespecified interim analysis (data cut-off date of 15 June 2011) conducted after 96 deaths (of the prespecified total of 217 deaths) [16] and an unplanned interim analysis (data cut-off date of 15 June 2012) conducted at the request of the US FDA after 162 deaths [18, 21]. The study was unblinded after analysis of the primary PFS data and the prespecified interim overall survival data; placebo recipients were not permitted to crossover to cabozantinib [16]. At the data cut-off date of 15 June 2011, the median duration of follow-up was 13.9 months. Analyses were conducted in the intent-to-treat population (defined as all randomized patients). Patients who missed tumour assessments before the event or received subsequent anticancer therapy, or for whom no event was observed by the data cut-off date were censored at the last independent radiological review tumour assessment. Patients with no post-baseline tumour assessments who lived at least 26 weeks following randomization were censored at the date of randomization; those who died within 26 weeks of randomization were counted as events at the date of death [16].

5.1 Primary Endpoint Analyses

Therapy with oral cabozantinib significantly prolonged PFS relative to placebo at the primary analysis (data cut-off date of 6 April 2011) [hazard ratio (HR) 0.28 (95 % CI

Table 2 Efficacy of oral cabozantinib in adults with unresectable, locally advanced or metastatic medullary thyroid cancer. Results in the intent-to-treat population (data cut-off date 6 April 2011) of a multinational phase III study [16]

Analysis	Estimated median PFS[a] (mo)		Stratified HR (95 % CI)
	CAB ($n = 219$)	PL ($n = 111$)	
Primary (independent review)	11.2	4.0	0.28 (0.19–0.4)*
Sensitivity			
Deviation of tumour assessment (independent review)[b]	11.1	5.4	0.29 (0.20–0.42)**
Investigator review[c]	13.8	3.1	0.29 (0.21–0.42)**
Expanded disease progression definition (investigator review)[d]	11.2	3.0	0.32 (0.23–0.43)**

CAB cabozantinib, *HR* hazard ratio, *mRECIST* modified Response Evaluation Criteria in Solid Tumors, *PFS* progression-free survival, *PL* placebo, *rDP* radiographic disease progression

* $p < 0.001$, ** $p < 0.0001$ vs. PL

[a] The time from randomization to the documentation of disease progression (as per mRECIST [22]) or death

[b] Date of rDP determined by the scheduled tumour assessment rather than the date progression was recorded

[c] Disease progression events based on an investigator review of rDP

[d] Disease progression events included rDP, clinical deterioration and initiation of subsequent systemic antitumour therapy

0.19–0.4); $p < 0.001$] (Table 2) [16]. Consistent with the primary analysis, all prespecified sensitivity analyses demonstrated that the PFS benefit obtained with cabozantinib was generally robust to variations in event definitions (Table 2) [16].

PFS outcomes significantly favoured cabozantinib over placebo across most prespecified subgroups (including patient age, the presence of bone metastases and previous tyrosine kinase inhibitor status) [16]. A significant PFS benefit with cabozantinib versus placebo was also observed across various ad hoc patient subgroups (including sporadic or hereditary MTC and a positive RET mutational status). In patients with a negative RET mutational status, the HR was 0.47, although the upper limit of the 95 % confidence interval crossed one [16]. Limited data from a post hoc analysis of patients with a positive RAS mutation status ($n = 16$) found cabozantinib significantly prolonged PFS relative to placebo (estimated median PFS 47 vs. 8 weeks; HR 0.15 [95 % CI 0.02–1.10]; $p = 0.0317$) [20]. Of note, compared with other mutational subgroups, patients with a negative RET mutational status and no evidence of a RAS mutation ($n = 33$) demonstrated a reduced PFS benefit (HR 0.87) and a lower objective response rate (18 %) [no further data reported] [6].

The estimated 3-, 6-, 9- and 12-month PFS rates were 86, 70, 59 and 47 %, respectively, in cabozantinib recipients and 57, 26, 14 and 7 %, respectively, in placebo recipients [18].

5.2 Secondary and Other Endpoint Analyses

Among patients with measurable disease at baseline, a significantly higher proportion of those receiving cabozantinib than placebo achieved an objective response (as their best overall response) [data cut-off date of 15 June 2011] (28 % [58/208] vs. 0 % [0/104]; $p < 0.001$); all objective responses were partial responses [16]. The median estimated duration of response in cabozantinib recipients was 14.6 months [6, 16]. The objective response rates in cabozantinib recipients with a positive or negative RET mutation status were 32 and 25 % [16]. Compared with placebo, therapy with cabozantinib resulted in disease stabilization in a significantly higher proportion of patients with measurable disease at baseline (14 % vs. 55 %; $p < 0.0001$); approximately 50 % of patients in each of the groups achieved stable disease (as their best overall response) [16, 18]. Disease stabilization was defined as the percentage of patients achieving a complete or partial response, or stable disease (as their best overall response) at or after the week 24 tumour assessment [16].

Among patients with measurable disease at baseline and at least one post-baseline assessment, 94 % (170 of 180 patients) of cabozantinib recipients and 27 % (24 of 89) of placebo recipients demonstrated a detectable reduction in target lesion size [16].

At the time of both the prespecified interim and unplanned interim analyses, the reduction in the risk of death associated with cabozantinib relative to placebo was not statistically significant (prespecified interim: HR 0.98 [95 % CI 0.63–1.52] [16]; unplanned interim: stratified HR 0.83 [95 % CI 0.60–1.14] [21]). At the time of the prespecified interim analysis (data cut-off date of 15 June 2011), the median overall survival duration was 21 months in the cabozantinib group, but could not be estimated in the placebo group; 30 and 27 % of cabozantinib and placebo recipients had died [16, 18]. At the time of the unplanned interim analysis (data cut-off date of 15 June 2012), the median overall survival duration following therapy with cabozantinib or placebo was 26.0 and 20.3 months; 47 and 53 % of cabozantinib and placebo recipients had died [6, 21]. A relationship between PFS prolongation and a significant improvement in overall survival for cabozantinib versus placebo (HR 0.53; $p = 0.0179$) has been observed in patients with a positive RET M918T mutation status [6]. Other RET and/or RAS patient subgroups have yet to undergo such an analysis [6].

Treatment discontinuations because of disease progression occurred in 26 % of cabozantinib recipients and 60 % of placebo recipients [16].

6 Tolerability

Discussion in this section focuses on tolerability data derived from the phase III study [16] discussed in Sect. 5. Adverse event severity was assessed utilizing the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. Analyses were conducted in the safety population (defined as all patients who received at least one dose of the study medication), comprising 214 patients receiving oral cabozantinib and 109 patients receiving placebo, after a median duration of follow-up of 13.9 months [16].

6.1 General Profile

The tolerability profile of oral cabozantinib in adults with unresectable, locally advanced or metastatic MTC and radiographic evidence of disease progression is typical for a small molecule targeting the VEGFR and other tyrosine kinase-mediated pathways [18]. In the phase III study, treatment-emergent adverse events were generally managed with supportive therapy, dose reductions and/or dose interruptions [16]. Dose reductions were required by 79 % of cabozantinib recipients and 9 % of placebo recipients [16]; overall, 41 % of cabozantinib recipients required at

least two dose reductions, with a median time to the first dose reduction of 43 days [6, 18]. Dose interruptions because of treatment-emergent adverse events were required by 65 and 17 % of patients receiving cabozantinib and placebo [16]; overall, the median time to the first dose interruption in cabozantinib recipients was 33 days [6]. Treatment discontinuations because of treatment-emergent adverse events occurred in 16 % of cabozantinib recipients and 8 % of placebo recipients [16]. Diarrhoea, fatigue, hypertension, hypocalcaemia, increased lipase levels, nausea, palmar-plantar erythrodysesthesia syndrome (PPES), pancreatitis, tracheal fistula formation and vomiting were the most frequent adverse reactions leading to treatment discontinuation [19]. Fatal adverse reactions occurred in 6 % of patients receiving cabozantinib and 5 % of patients receiving placebo [19].

Treatment-emergent adverse events were reported in 100 % of cabozantinib recipients and 95 % of placebo recipients, most of which were assessed as related to the study medication (99 and 74 %) [18]. The most frequently reported treatment-emergent adverse events (all grades) following therapy with cabozantinib or placebo were diarrhoea (63 vs. 33 % of patients), PPES (50 vs. 2 %), weight loss (48 vs. 10 %), reduced appetite (46 vs. 16 %), nausea (43 vs. 21 %) and fatigue (41 vs. 28 %) [16].

Grade 3 or 4 treatment-emergent adverse events were reported in 69 % of cabozantinib recipients and 33 % of placebo recipients [16]. The most frequently reported grade 3 or 4 adverse events and laboratory abnormalities observed following therapy with cabozantinib were diarrhoea (16 % of patients), lymphopenia (16 %), PPES (13 %), hypocalcaemia (12 %), fatigue (9 %) and hypertension (8 %) [16, 19], with the presence of diarrhoea, PPES and fatigue generally consistent with what has been observed in other studies with VEGF inhibitors, including other tyrosine kinase inhibitors [16]. Grade 3 or 4 treatment-related adverse events occurred in 64 and 19 % of patients receiving cabozantinib or placebo [18]. Grade 5 treatment-emergent adverse events occurring within 30 days of the last dose of study medication were reported in 17 (8 %) cabozantinib recipients and 8 (7 %) placebo recipients, with nine (three cases of fistula [one of whom also had concurrent pneumonia] and one case each of cardiopulmonary failure, haemorrhage, multi-organ failure/sepsis, respiratory failure, sudden death and unspecified death) and two (one case each of cardiopulmonary failure and deterioration in general physical health/pneumonia) patients experiencing events deemed related to therapy [16].

Serious treatment-emergent adverse events were reported in 42 and 23 % of patients receiving cabozantinib and placebo, with the most common (occurring at a $\geq$2 % higher incidence in cabozantinib versus placebo recipients) being hypocalcaemia (2.8 vs. 0 % of patients), mucosal inflammation (2.8 vs. 0 %), hypertension (2.3 vs. 0 %) and pulmonary embolism (2.3 vs. 0 %) [16]. According to the EU SPC, the most common serious adverse reactions associated with cabozantinib are pneumonia, mucosal inflammation, hypocalcaemia, dysphagia, dehydration, pulmonary embolism and hypertension [6]. Serious treatment-related adverse events occurred in 33 and 6 % of patients receiving cabozantinib or placebo in the phase III study [18]. Death occurred in 30 % of cabozantinib recipients and 28 % of placebo recipients, with over three-quarters (77 and 80 %) of the deaths in each treatment group attributable to disease progression [16]. One patient who did not receive the study medication also died [16].

Cabozantinib does not appear to be associated with clinically relevant Fridericia-corrected QT (QTcF) interval prolongation (i.e. QTcF prolongation of >500 ms) [16, 18]. A mean elevation from baseline in the QTcF interval at day 29 (at which time cabozantinib steady state concentrations had been reached) of 10–15 ms was observed following the administration of therapeutic dosages of cabozantinib [6, 18, 19]. Few cabozantinib recipients experienced grade 1 (three patients) or 2 (one patient) QT interval prolongation; this was not associated with a change in cardiac wave form morphology or new rhythms [6, 18]. No clinically relevant changes in PR and QRS intervals were observed [18]. Moreover, no other cardiac arrhythmias, including Torsade de pointes, have been observed [18].

The most frequently reported grade 3 or 4 chemistry abnormalities in cabozantinib recipients occurring at a higher incidence than in placebo recipients were increased alanine aminotransferase (6 vs. 2 %) and hypocalcaemia (12 vs. 3 %) [16]. The most frequently reported grade 3 or 4 haematological abnormality in cabozantinib recipients occurring at a higher incidence than in placebo recipients was lymphopenia (16 vs. 11 %) [16]. Above normal thyroid-stimulating hormone (TSH) levels were observed following therapy initiation in 57 % of cabozantinib recipients and 19 % of placebo recipients (no further data reported) [16]. The majority (92 and 89 %) of cabozantinib recipients had undergone a thyroidectomy or were receiving thyroid hormone replacement therapy prior to the first dose of the study medication [19]. No study medication-induced severe liver injury was observed [16].

6.2 Adverse Events Associated with Vascular Endothelial Growth Factor Pathway Inhibition

Adverse events associated with VEGF inhibitor therapy typically result from the suppression of cellular signalling pathways key to the regulation and maintenance of the

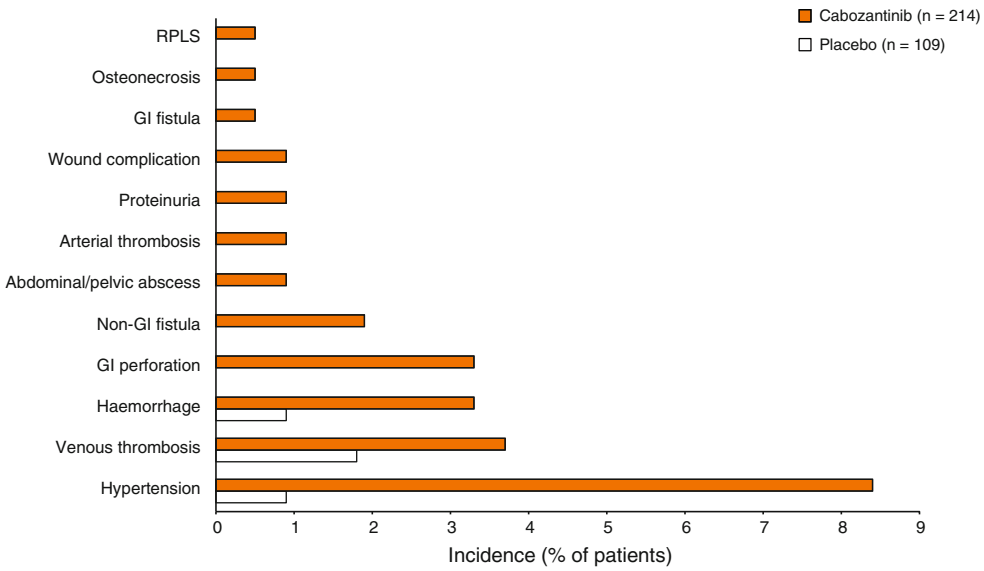

Fig. 2 Incidence of adverse events (grades ≥3) associated with the inhibition of the vascular endothelial growth factor pathway in a multinational phase III study in adults with unresectable, locally advanced or metastatic medullary thyroid cancer [16]. Analyses were conducted at the data cut-off date of 15 June 2011 (median follow-up of 13.9 months). *GI* gastrointestinal, *RPLS* reversible posterior leucoencephalopathy syndrome

microvasculature [23]. Such adverse events occurred numerically more frequently in cabozantinib than placebo recipients participating in the phase III study (no statistical analysis reported), with hypertension (32.7 vs. 4.6 % of patients), haemorrhage (25.2 vs. 15.6 %), venous thrombosis (5.6 vs. 2.8 %), non-gastrointestinal fistula (3.7 vs. 0 %) and gastrointestinal perforation (3.3 vs. 0 %) the most frequently reported (all grades) [16]. Patient monitoring is recommended and dosage reductions, interruptions and/or treatment discontinuations may be required in patients who develop these adverse events (see Sect. 7).

Grade 3 or 4 adverse events associated with the inhibition of the VEGF pathway following therapy with cabozantinib or placebo are reported in Fig. 2 [16]. All of the gastrointestinal perforations and fistulas reported were serious, with one gastrointestinal fistula and two non-gastrointestinal fistulas resulting in death [19]. As reported in Sect. 6.1, all three cases of grade 5 fistula (one of whom also had concurrent pneumonia) and one of the cases of grade 5 haemorrhage occurring within 30 days of the last dose of cabozantinib were deemed related to therapy [16].

Of note, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (modified JNC criteria) [24] stage 1 or 2 hypertension was identified in 61 % of cabozantinib recipients and 30 % of placebo recipients [19]. No patient developed malignant hypertension (defined as diastolic blood pressure ≥120 mmHg according to modified JNC criteria) [19].

7 Dosage and Administration

The recommended dosage of oral cabozantinib is 140 mg once daily [6, 19]. Cabozantinib must be consumed on an empty stomach; no food should be consumed for at least 2 h before and at least 1 h after the administration of cabozantinib (see Sect. 3) [6, 19], with the US prescribing information recommending that foods (e.g. grapefruit) or nutritional supplements (e.g. St. John's wort [Hypericum]) known to induce or inhibit CYP activity be avoided during cabozantinib therapy [19]. Treatment should be initiated by a clinician experienced in the administration of anticancer therapies [6] and continued until disease progression or unacceptable toxicity [6, 19].

The EMA has advised clinicians that a potentially lower benefit may be observed in patients with a negative or unknown RET mutation status (see Sect. 5.1) and should be taken into account [6].

The US prescribing information carries a boxed warning regarding perforations and fistulas, and haemorrhage for patients treated with cabozantinib [19] (see Sect. 6.2). Patients should be monitored for the signs and symptoms of bleeding [19]; cabozantinib should not be administered to patients with severe haemorrhage [6, 19] or recent haemoptysis [6]. Therapy should be discontinued in patients who develop a visceral or gastrointestinal perforation, or a gastrointestinal or non-gastrointestinal fistula [6, 19]. Other events for which cabozantinib should be discontinued are persistent uncontrolled hypertension despite optimal medical management, malignant hypertension and hypertensive crisis; nephrotic syndrome; osteonecrosis of the jaw; reversible posterior leucoencephalopathy syndrome; serious arterial thromboembolic event (e.g. myocardial infarction) and/or wound healing complications requiring medical intervention [6, 19].

As the majority of adverse events (including hypocalcaemia, hypokalaemia, hypertension, gastrointestinal

events [e.g. abdominal or mouth pain, constipation, diarrhoea, mucosal inflammation and vomiting], PPES and thrombocytopenia) occur early in the treatment course and will likely require at least one dosage reduction (to 100 mg once daily, then to 60 mg once daily) and/or interruption, patients should be closely monitored during the first 8 weeks of therapy [6]. Of note, the occurrence of some serious adverse reactions (e.g. gastrointestinal fistula) may be dependent upon the cumulative dose and, thus, may present during a later stage of treatment [6].

Recommendations for the use of cabozantinib in special patient populations are summarized in Sect. 3.1. Local prescribing information should be consulted for detailed information, including contraindications, events for which dosage interruptions and/or reductions are recommended, drug interactions, precautions and use in special patient populations.

8 Current Status of Cabozantinib in the Management of Medullary Thyroid Cancer

Oral cabozantinib is indicated for the treatment of adults with progressive, unresectable locally advanced (in the EU [6]) or metastatic (in the EU [6] and USA [19]) MTC. Approval of cabozantinib for these indications was primarily on the basis of a phase III study. Therapy with cabozantinib prolonged PFS to a significantly greater extent than placebo in adults with unresectable, locally advanced or metastatic MTC (primary analysis), reflecting a clinically relevant gain in median PFS of 7.2 months and a 72 % reduction in the risk of disease progression or death (Sect. 5.1). Such benefit was observed across multiple sensitivity and subgroup analyses (Sect. 5.1). Cabozantinib was also associated with significantly higher objective response and disease stabilization rates (Sect. 5.2). As expected, overall survival data were not mature by the cut-off dates, with only 96 (44 %) and 162 (75 %) of the prespecified total of 217 deaths required for the final analysis of overall survival having occurred. Prespecified interim and unplanned interim analyses did not demonstrate a significant overall survival benefit with cabozantinib compared with placebo (Sect. 5.2). Mature overall survival data are awaited with interest, particularly as limited data showed a significant relationship between PFS prolongation and an improvement in overall survival in cabozantinib recipients with a positive RET M918T.

The tolerability profile of cabozantinib is typical for a small molecule targeting the VEGFR and other tyrosine kinase-mediated pathways. In the phase III study, the most frequently reported grade 3 or 4 adverse events and laboratory abnormalities observed with cabozantinib therapy were diarrhoea, lymphopenia, PPES, hypocalcaemia and fatigue, with the presence of diarrhoea, PPES and fatigue generally consistent with what has been observed in other studies with VEGF inhibitors, including other tyrosine kinase inhibitors. Grade 3 or 4 adverse events (e.g. gastrointestinal perforation, haemorrhage, hypertension and venous thrombosis) associated with the inhibition of the VEGF pathway have been reported with cabozantinib, with perforations and fistulas, and haemorrhage prompting the US FDA to issue boxed warnings (Sect. 7). Patient monitoring is recommended and dosage reductions, delays and/or treatment discontinuations may be required in patients who develop these adverse events (see Sect. 7). The authors of the phase III study noted that the incidence of dose delays and reductions because of treatment-emergent adverse events was high (see Sect. 6) and that an evaluation of a lower starting dose of cabozantinib versus the approved dose of 140 mg in patients with progressive, metastatic MTC is planned [16]. Indeed, in order to clarify whether an efficacy similar to that achieved with cabozantinib 140 mg once daily can be obtained with a less toxic dosage regimen (see Sect. 6), a double-blind study will randomize patients with progressive, metastatic MTC to receive either the approved cabozantinib dosage of 140 mg once daily or a lower dosage (cabozantinib 60 mg once daily [18]) [25]. Data from this impending study will help to clarify the optimal posology of cabozantinib.

Cabozantinib is recommended by the US National Comprehensive Cancer Network (NCCN) [1] as a category 1 option for the treatment of recurrent or persistent (i.e. locoregional; asymptomatic or symptomatic, distant metastases; or disseminated symptomatic disease) MTC. At the time of publication of both the European Society for Medical Oncology [2] and the European Thyroid Association [5] guidelines, the role of cabozantinib was yet to be determined, although both guidelines mention the role of tyrosine kinase inhibitors in the treatment of MTC.

Although beyond the scope of this review, it is worth noting that cabozantinib, alone or in combination with other anticancer agents, is a current focus of interest in ongoing clinical studies in castration-resistant prostate cancer and in other indications (e.g. non-small-cell lung cancer and renal cell carcinoma). Results from these studies are awaited with interest.

Final overall survival data from the pivotal phase III study are awaited with interest. Current evidence suggests cabozantinib is a valuable treatment option for adults with progressive, unresectable locally advanced or metastatic MTC.

Data selection sources: Relevant medical literature (including published and unpublished data) on cabozantinib was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 7 July 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Cabozantinib
Study selection: Studies in patients with thyroid cancer who received cabozantinib. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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