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CABRAMET

A phase 2 study of cabozantinib in metastatic renal cell carcinoma (mRCC) with brain metastases

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Coordinating Centre	Direction de la Recherche Clinique et de l'Innovation (DRCI) – CLB
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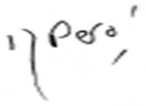
PROTOCOL APPROVALS

French Competent Authority: ANSM	Approval Date: 16/04/2019 Reference: MEDAECNAT-2019-03-00008
French Ethic Committee: Comité de Protection des Personnes Ile de France X	Approval Date: 13/05/2019 Reference: 33-2019
ICMJE-approved registry: Clinicaltrial.gov	Registration Date: 27/05/2019 Reference: NCT03967522

SIGNATURE OF PROTOCOL

The signatories agree to the content of the CABRAMET clinical study protocol as presented, to comply with the National regulations and ICH Harmonized Tripartite Guideline for Good Clinical Practice for conducting clinical trials and local regulations and to conduct the above study under these standards.

Title	A phase 2 study of cabozantinib in metastatic renal cell carcinoma (mRCC) with brain metastases
Protocol	Version 7.0 dated 06/01/2025
Coordinating investigator	Pr Sylvie NEGRIER, MD, PhD Date /Signature 06/01/2025 
Sponsor representative	David PEROL, MD, Head of Clinical Research Department Date /Signature 06/01/2025 

AMENDMENTS

Amendment number	Date	Protocol version number	Associated version		Summary of main and substantial changes
			Synopsis	ICF	
1	ANSM: - CPP: 06/02/2020	1.0	1.0	1.0	Investigators list update
2	ANSM: 03/11/2020 CPP: 23/11/2020	2.0	2.0	2.0	- Modification of I4 inclusion and E1 non-inclusion criteria - GDPR update - Investigators list update
3	ANSM: 22/03/2022 CPP: 21/04/2022	3.0	3.0	3.0	- Modification of the study design - Modification of the number of centres - Investigators list update
4	ANSM: 16/11/2022 CPP: 13/12/2022	4.0	4.0	4.0	- Modification of study drug label - Modification of follow-up duration - Modification of I2 inclusion criteria - Modification of the secondary objectives (response rate on the extracranial disease) - Modification of the SAE reporting time - Investigators list update
5	ANSM: - CPP: 04/04/2023	5.0	5.0	5.0	- Modification of inclusions duration
6	ANSM: - CPP: 08/03/2024	6.0	6.0	6.0	- Modification of inclusions duration
7_MSA4# MS1 CTIS	ANSM: - CPP:	7.0	7.0	7.0	- Changes related to EU CTR migration

LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
ALT	Alanine aminotransferase
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
AR	Adverse Reaction
AST	Aspartate aminotransferase
BM	Brain Metastases
CA	Competent Authority
CI	Confidence Intervals
CLB	Centre Léon Bérard
CNIL	Commission Nationale de l'Informatique et des Libertés
CPP	Comité de Protection des Personnes
CRF	Case Report Form
CRT	Clinical Research Technician
DPO	Data Protection Officer
DRCI	Direction de la Recherche Clinique et de l'Innovation
DSUR	Development Safety Update Report
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOS	End of study
EVCTM	EudraVigilance Clinical Trial Module
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICI	Immune Checkpoint Inhibitor
IMC	Independent Monitoring Committee
IMP	Investigational Medicinal Product
IRC	Independent Review Committee
IWRS	Interactive Web Response System
LVEF	Left ventricular ejection fraction
mRCC	Metastatic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
mTOR	Mechanistic Target Of Rapamycin
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Event
OS	Overall Survival
PS	Performance Status
RCC	Renal Cell Carcinoma
SAE	Serious Adverse Event
SB	Serious Breaches
SAP	Statistical Analysis Plan
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAP	Thorax Abdomen and Pelvic
TKI	Tyrosine Kinase Inhibitor
TMG	Trial Management Group
VEGFR	Vascular Endothelial Growth Factor Receptor
WMA	World Medical Association

SYNOPSIS

STUDY TITLE	CABRAMET - A phase 2 study of cabozantinib in renal cell carcinoma (mRCC) with brain metastases
SPONSOR	Centre Léon Bérard – 28 rue Laennec – 69373 Lyon Cedex 08
COORDINATING INVESTIGATOR	Pr Sylvie NEGRIER
NUMBER OF PATIENTS	**At least 28 patients** 28 patients will be enrolled to warrant 25 patients evaluable for response
PLANNED NUMBER OF CENTERS	15-20 centers from the GETUG
STUDY OBJECTIVES	***Primary objective*** To evaluate the **non progression rate in brain metastases at 6 months**. The absence of progression in brain will be evaluated according to RANO-BM criteria and validated by a independant review committee. ***Secondary objectives*** • Safety of cabozantinib, especially in terms of neurological tolerance (NCI-CTCAE), • Best response in brain metastases (RANO-BM criteria), • Response rate on the extra-cranial disease at 3 and 6 months (RECIST v1.1), • Progression-free survival (PFS), measured from the date of treatment beginning to the date of first documented disease progression or death from any cause, • Overall survival (OS), measured from the date of treatment beginning to the date of death from any cause), • Overall response rate at 6 months. ***Ancillary studies*** Biomarkers (serum and plasma samples). MET expression in available tumor.
EXPERIMENTAL PLAN	Open-label, single-arm, multicenter prospective interventional phase II trial
INDICATION	Metastatic renal cell carcinoma with non locally pre-treated brain metastases, in first line treatment or after one or two prior treatments.
STUDY POPULATION	***Inclusion Criteria*** **I1.** Age ≥ 18 years. **I2.** Histologically proven mRCC, in first line treatment or after one or two prior treatments. **I3.** Brain metastases not requiring corticosteroids at dose > 40 mg/day. **I4.** At least 1 locally untreated brain lesion ≥8 mm in longest diameter or >5 mm if > 1 lesion. **I5.** Not previously treated by cabozantinib. **I6.** Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 1. **I7.** Life expectancy ≥ 3 months **I8.** Adequate organ function as defined by the following criteria. - Total serum bilirubin ≤ 2 x ULN (Gilbert's disease exempted) - Serum transaminases and alkaline phosphatases ≤ 2.5 x ULN, or in case of liver or bone metastasis ≤ 5 x ULN - Serum creatinine ≤ 2 x ULN OR creatinine clearance ≥ 50 ml/min - Absolute neutrophil count (ANC) ≥ 1 500/mm^3 - Platelets ≥ 100 000/mm^3 (100 G/l) - Hemoglobin ≥ 9.0 g/dl. **I9.** Covered by a medical/health insurance. **I10.** Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures. **I11.** Signed and dated IRB/ICE approved informed consent form. **I12.** Accepting to use effective contraception (barrier contraceptives) during study treatment and within at least 4 months after final dose of study therapy. Oral contraceptives are not acceptable.

	Exclusion Criteria **E1.** Any local previous treatment of current brain metastases. [Stereotactic radiotherapy or cyberknife on some of the brain metastases is allowed if performed on brain met < 2 cm and at more than 2 weeks before inclusion.] **E2.** Any anti-coagulation therapy (except preventive treatment at low dose). **E3.** Contra-indication for MRI (i.e. pace-maker). **E4.** Uncontrolled seizures. **E5.** Any symptoms of intracranial hypertension. **E6.** Any of the following within 12 months prior to treatment initiation: severe/unstable angina, myocardial infarction, coronary artery bypass graft, symptomatic congestive heart failure, ischemic or hemorrhagic stroke including transient ischemic attack. **E7.** Uncontrolled hypertension defined as systolic blood pressure >150 mmHg or diastolic pressure >90 mmHg, despite optimal medical treatment. **E8.** Ongoing cardiac dysrhythmia of grade $\geq$ 2, atrial fibrillation of any grade, QTc interval > 0.43. **E9.** Pregnant or breast-feeding woman (mandatory negative serum or urinary pregnancy test at study entry for all women of childbearing potential). **E10.** Any acute or chronic medical or psychiatric condition or laboratory abnormality that would make the patient unsuited to study participation. **E11.** Any second malignancy within the last 3 years with the exception of basal cell carcinoma, in situ cervical cancer and pT1/a bladder cancer with no evidence of recurrent disease for 12 months. **E12.** Patients receiving strong inhibitor or inducer of CYP3A4 especially some anti-epileptic drugs. **E13.** Psychological, familial, sociological, geographical conditions that would limit compliance with study protocol requirements. **E14.** Participation to another clinical trial that might interfere with the evaluation of the main criterion. **E15.** Known hypersensitivity to the active substance or to any of the excipients. **E16.** Patient requiring tutorship or curatorship.
Study treatment	***Description*** Cabozantinib is formulated for oral administration as a yellow film-coated tablet. 3 dosage strengths are available: 20 mg (round), 40 mg (triangle shaped) and 60 mg (oval). Dosing compliance will be monitored at each clinic visit: patient will be asked to bring back the study packages at each clinic visit. ***Route of administration*:** By oral route The prescribed oral daily dose of cabozantinib is to be taken whole with a full glass of water. Cabozantinib should not be taken with food: cabozantinib must be taken 1 hour before a meal or 2 hours after. If a dose is missed for any reason, the missed dose should not be taken if there is less 12 hours before the next dose is due. The next prescribed dose should be taken at the usual time. ***Dose to be administered*:** 60 mg once daily per os (po). **Study treatment should be started within 7 days after the patient inclusion.** ***Storage:*** No special storage conditions, except for secure location. ***Cabozantinib dose adjustments*** Temporary or permanent discontinuation and/or dose reduction of cabozantinib therapy may be required for the management of some adverse reactions (see Table 1 below). When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. A patient who requires a dose interruption (regardless of the reason for the interruption) of more than 28 days (counting from the first day when a dose was missed) must discontinue the study treatment.

Table1: Recommended cabozantinib dose modifications for adverse reactions

Adverse reaction and severity (Grade NCI-CTCAE v5)	**Treatment modification**
Grade 1 et Grade 2 adverse reactions which are tolerable and easily managed.	Dose adjustment is usually not required. Consider adding supportive care as indicated.
Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care.	Interrupt treatment until the adverse reaction resolves to grade ≤ 1. Add supportive care as indicated. Consider re-initiating at a reduced dose.
Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities).	Interrupt treatment until the adverse reaction resolves to grade ≤ 1. Add supportive care as indicated. Consider re-initiating at a reduced dose.
Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities).	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to grade ≤ 1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue treatment.

End of cabozantinib treatment

Cabozantinib treatment may continue until one of the following criteria applies:

- Disease progression in brain according to RANO-BM criteria,
- Confirmed disease progression according to RECIST v1.1 in extracranial metastases,
- Unacceptable adverse event(s),
- Patient's willingness to stop the treatment,
- Pregnancy,
- Decision of the investigator to stop treatment (general or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator).
- Withdrawal of consent*.

*If a patient withdraws consent, no further evaluations should be performed and no attempt should be made to collect additional data.

Prohibited concomitant therapy

Any investigational agent, within 28 days prior to cabozantinib start, and any other cancer treatments other than cabozantinib are prohibited.
Strong cytochrome P450 (CYP3A4/5) inhibitors should be used with caution, as it results in an increase in cabozantinib plasma exposure. Strong CYP3A4/5 inducers should be avoided, as it results in a decrease in cabozantinib plasma exposure.
P-glycoprotein substrate and MRP2 inhibitors should be approached with caution.
The use of steroids must be limited to the treatment of acute reactions and not be required for more than a week.

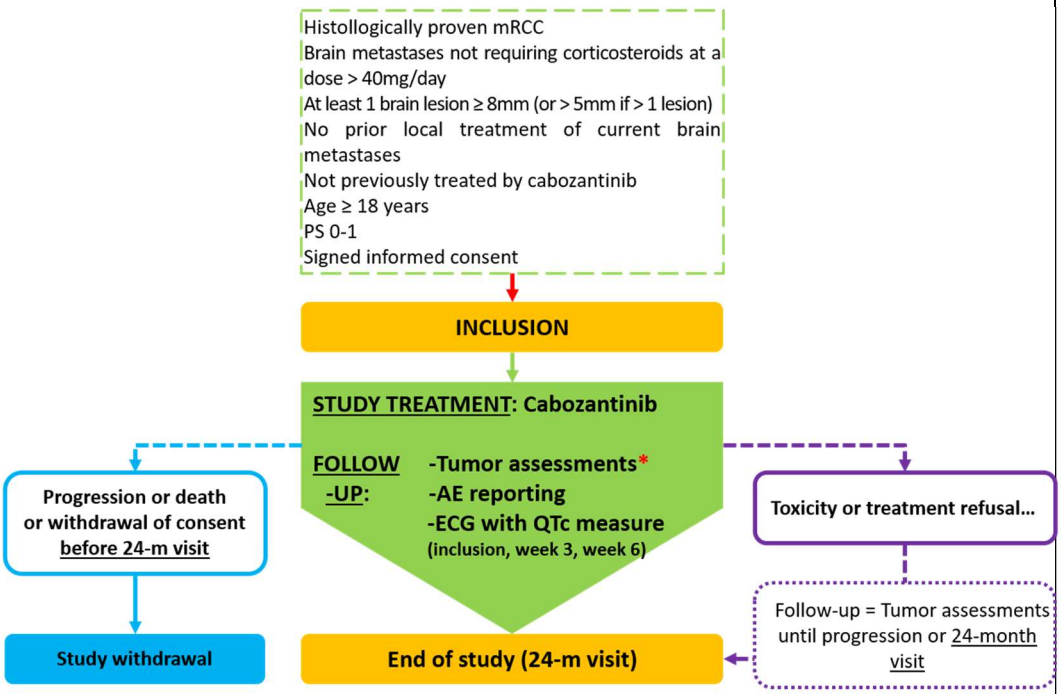
Permitted concomitant therapy

Supportive treatment as medically indicated for the patient's well-being may be prescribed at the investigator's discretion. Every medication or treatment prescribed to the patient during the trial must be recorded in the CRF.

Study assessments

Clinical assessments

- Complete medical history.
- Full physical examination: vital signs (i.e. systolic and diastolic blood pressure, pulse, temperature), weight, height and PS, any symptoms.
- 12-lead ECG recorded after a 10-minute rest in supine position, with QTc measure according to Bazett formula.
- Left ventricular ejection fraction (LVEF), if clinically indicated.
- Reporting of AEs according to NCI-CTC AE version 5.0.
- Tumor assessment (TAP CT-scan (or MRI) and brain MRI). Antitumor activity will be assessed using RECIST 1.1 criteria and according to RANO-BM criteria for brain metastases assessment.

	Biological assessments • Hematology: complete blood count (CBC) with platelets and differential counts, hemoglobin, and hematocrit. • Biochemistry: Electrolytes (sodium, potassium, chlore, calcium, corrected calcium, magnesium, phosphorus [Na, K, Cl, Ca, Mg, P]), protides, albumin, glucose, creatinin, calculated creatinine clearance [Cockcroft and MDRD formulas], uric acid, liver function tests (AST, ALT, alkaline phosphatase, GGT, LDH), total bilirubin, TSH, T4. • Urinary dipstick test. If ≥ 2+: perform 24h-protein urinalysis. ***Serum and plasma collection***: 20 ml at inclusion. ***Tumor collection***: Tumor tissue (MET expression…). ➡ See FLOW-CHART
Study scheme	 * using RECIST 1.1 criteria for extra cerebral metastases and RANO-BM criteria for brain metastases
Study procedures	***Inclusion*** After identification of a potentially eligible patient, the investigator should check the patient's eligibility status. The investigator will then inform the patient of the study design and will provide him/her with an information notice and a consent form. After being made aware of the study and adequate (24 hours minimum) time to consider his/her participation, the patient or designee must give his/her consent in writing by personally dating and signing the consent form, which will also be dated and signed by the investigator (original archived by the investigator, with one copy returned to the patient). An inclusion form will be filled up and signed by the investigator. Then the investigator/clinical studies department will proceed to the inclusion of the patient on the on-line inclusion platform. *Refer to Investigator Master File for the inclusion procedure.* ***Serum, plasma and tumor (archival FFPE block) collection*** At baseline only. *Refer to Lab Manual for the Blood sampling, storage and shipment procedures.* ***Follow-up*** (See FLOW-CHART): **Patients will be followed** (except in the case of consent's withdrawal) **for 24 months from the inclusion or until progression or death, whichever occurs first.** Adverse event(s) will be followed until resolution or stabilization. Patients' survival status will also be recorded once a year until final analysis. ***Radiological central review*** For all patients, brain MRI at baseline, 1.5, 3 and 6 months will have to be sent as soon as possible to the coordinating centre. An independent committee will review them and validate the absence of progression at 6 months .

Study calendar	Duration of inclusion:	54 months
	Duration of patient follow-up:	Maximum 24 months after inclusion (or until progression or death whichever occurs first)

1. CONTEXT AND RATIONALE

1.1. RENAL CELL CARCINOMA (RCC)

1.1.1. Epidemiology and diagnosis

Kidney cancer represents about 5% (115 000 patients per year in Europe) of all new cancer diagnoses. The most common form of kidney cancer, the renal cell carcinoma (RCC), arises from renal tubule epithelium. RCC subtypes include clear cell (ccRCC), the most common histological subtype (75-80% of cases). Then, among the non-clear cell RCC subtypes (20-25%), the most prevalent form is the papillary types I or II (10%), the chromophobe tumors (5% of cases) and other miscellaneous rare subtypes (<5%) (1, 2).
RCC is a male predominant disease with an average of onset around 60 years old. The TNM score is the most important factor in predicting prognosis of RCC as well as the histologic score throughout the ISUP grade which recently replaced the historic Fuhrman grade (3).

Initial treatment is commonly a nephrectomy (either partial or complete removal of the affected kidney) but around 20-25% of patients undergoing nephrectomy will eventually develop metastases.
The five-year survival rate of metastatic RCC (mRCC) is around 12%. Frequent sites of metastasis include the lungs (45%), bone (30%), lymph nodes (22%), liver (20%), brain is not so common (9%). Sites of metastases may carry distinct implications for prognosis. While patients with bone, liver and brain metastasis may carry an inferior prognosis relative to the overall population of mRCC patients, patients with pancreatic metastases may have a longer survival (4).
Based on the 6 validated and widely used Heng prognostic factors (5, 6) (Karnofsky performance status < 80%, time from initial RCC diagnosis to start of therapy < 1 year, low serum haemoglobin, elevated corrected serum calcium, platelets and neutrophils), patients with mRCC can be separated into three groups:

- Favourable prognostic group: with no risk factor and a median survival at 30 months,
- Intermediate prognostic group: with one or two risk factors and a median survival at 14 months,
- Poor prognostic group: with three or more risk factors and a median survival at 6 months.

Remarkable advances have been done in the knowledge of RCC molecular biology. For example, an analysis done by The Cancer Genome Atlas (TCGA) project shows that over 400 ccRCC, up to 90% of sporadic ccRCCs are related to an abnormal function of the VHL gene either through mutations or post transcriptional changes (7). Dysregulation of VHL gene promotes angiogenesis, cell growth and glycolysis through activation of VEGF (vascular endothelial growth factor), TGF (transforming growth factor alpha and beta) and platelet derived growth factor (PDGF) (8). Based on these findings, angiogenesis, which is essential for tumors growth and metastasis, is a key target for the treatment of mRCC. Angiogenic therapeutic strategies include inhibition of the VEGF receptor by tyrosine kinase inhibitors (TKI) or blockade of the ligand itself by monoclonal antibodies. Furthermore, some genes involved in chromatin modulation (like SETD2, KDM5C, PBRM1 and BAP1) appeared frequently mutated. It has also be found than tumors more aggressive had an up-regulation of genes involved in fatty acid synthesis and glycolysis and down regulation of genes involved in Krebs cycle and almost a third of cases had mutations in the PI3K/AKT/mTOR signaling pathway (9, 10).

Although VEGFR has been implicated as the key driver of tumor progression in RCC, there is emerging evidence that other transmembrane receptors may potentially drive metastasis, including MET and AXL (11).

Thus, the landscape of therapy for mRCC has evolved dramatically over the past decade. Indeed, since 2006, eleven agents directed against angiogenesis effectors, mTOR complex and programmed death-1 (PD-1) were

approved for the treatment of advanced RCC. The VEGF inhibitors indicated in mRCC are bevacizumab, sunitinib, pazopanib, axitinib, sorafenib, while inhibitors of mTOR are everolimus and temsirolimus. The most recent approvals (2016-2018) granted for mRCC concern 3 VEGFR TKIs with tivozanib, lenvatinib and cabozantinib, but also immune checkpoint inhibitors: nivolumab, an antibody directed against PD-1 and the combination of nivolumab with Ipilimumab an antibody directed to the CTLA4 receptor (2). These therapies have overall improved median survival estimates to approximately 2.5-3 years with a reduced risk of death from 13% to 36% for the immunotherapy combination (12).

However, despite these significant achievements, virtually all patients experience the progression of their disease after a variable period of control under treatment; this escape phenomenon is due to the development of resistance mechanisms that are finally responsible for patients' death. Improving treatments for these diseases is needed.

1.1.2. Standard of care

For patient with localized disease with no evidence of distant metastasis, local treatment by resection remains the gold standard, with an appropriate follow-up scheme depending on patient's risk level. No adjuvant therapies have been approved today in Europe (13, 14).

Regarding treatment of metastatic RCC, landscape has changed greatly over the past 15 years with era of targeted therapy. European guidelines (ESMO 2018 guidelines) recommend first line treatment with sunitinib, pazopanib, tivozanib or bevacizumab (plus IFNa) for patients with ccRCC in the favorable prognosis group prognosis. Patients of intermediate or poor prognosis group should receive the combination of nivolumab with ipilimumab when available or could also receive sunitinib, pazopanib, bevacizumab, cabozantinib or temsirolimus for patients of the poor risk group [Escudier in press]. For patients who experienced disease progression during (or who are intolerant to) treatment with a first-line TKI anti-VEGFR, subsequent treatments with the highest level of evidence include nivolumab, cabozantinib, depending on the previous treatment or axitinib that remains an option with a lower level of evidence. After failure of immune checkpoint inhibitors, VEGFR TKI can be offered. Sequential treatment with targeted agents is recommended although the optimal sequence has not been determined yet. Molecular markers and especially the expression of the immune-suppressive receptor PDL1 failed to demonstrate any predictive value for treatment choice (15).

1.2. BRAIN METASTASES (BM)

Brain metastases are less frequent than other metastatic sites in RCC patients but are associated with a dismal prognostic with an overall mean survival of less than one year (16). In addition, a higher number of brain metastasis is associated with poorer outcome despite local specific treatments (17). Indeed in a retrospective cohort of patients with mRCC treated for brain metastasis between 1975 and 1993 at Institut Gustave Roussy, Villejuif, France, the median survival time after a diagnosis of brain metastasis was 7 months (18) and in a more contemporary series of patients treated at the University of California, Los Angeles, between 1989 and 2006, the median overall survival time after a diagnosis of brain metastasis was 10.7 months, with survival rates of 48% at 1 year, 30% at 2 years, and 12% at 5 years (19). With the revolution of targeted therapy, according to the IMDC (2005-2011), the median survival time after first-line treatment with targeted therapy was 14.4 months for patients with brain metastasis *versus* 19.0 months for those with no brain metastasis in a probably selected population (17).

Local therapy is effective for brain metastasis and consists in surgical resection (standard for solitary brain metastasis) or stereotactic radiosurgery (SRS). Whole-brain radiotherapy (WBRT) used for widespread brain metastasis has a much more limited efficacy (20).

Cytotoxic systemic therapies are not used to treat brain metastasis in patients with cancer, given that the brain is thought be a sanctuary site protected by the more or less impermeable blood-brain barrier. Indeed, preclinical

studies show incomplete penetration with agents such as sunitinib and sorafenib (21). The prospective study, a phase 2 trial of sunitinib in patients with untreated brain metastasis (NCT00814021), has investigated the efficacy of VEGFR TKIs in RCC patients with brain metastases. Among 16 evaluable patients, the CNS objective response rate was 0%, and 5 patients (31%) had a CNS stable disease (22). A recent retrospective series in 711 patients did not evidenced a benefit from targeted therapies but acknowledged the benefit brought by locally focused treatment (SBRT) (16). Immunotherapy with nivolumab seems to have a limited activity mainly restricted to small (<1cm) metastases in the large phase 2 Nivoren trial [Flippot in revision].

The molecular characterization of brain metastases in patients with mRCC brought interesting results demonstrating the heterogeneity of MET and programmed death ligand 1 (PD-L1) expression that differ between primary tumors and metastatic biopsies .The discordance rates of PD-L1 and MET expression between the primary tumor and the brain metastases were respectively 40% and 67% (23), and MET gene alterations or MET receptor surexpression appear more frequent in brain metastases than in other RCC tumor sites.
Preclinical studies showed that cabozantinib does achieve CNS penetration in whole brain lysates of non-tumor bearing mice. Cabozantinib was reported to induce tumor response in metastatic non-small cell lung cancer with brain metastases, as well as in glioblastoma (24, 25). The interest of cabozantinib in brain RCC metastases is encouraged by 3 recent cases reports of significant responses of BM including a complete response of BM in one case (26, 27).
Thus, cabozantinib may represent an interesting approach for patients with brain metastasis.

1.3. CABOZANTINIB (CABOMETYX™)

Cabozantinib is a small molecule inhibitor of tyrosine kinases that are thought to be involved in tumor growth, tumor angiogenesis, tumor cell survival, tumor invasion and/or metastasis, and drug resistance. Main targets of cabozantinib include MET (hepatocyte growth factor receptor protein) and VEGFR (vascular endothelial growth factor receptors -1, -2 and -3). It has been shown that higher expression of MET is associated with a worse outcome in both clear cell and non-clear cell RCC (28). In addition, tyrosine kinases as AXL (GAS6, anexelekto), RET (Rearranged during transfection), FLT3 (Fms-like tyrosine kinase-3), KIT (mast/stem cell factor receptor), ROS1, MER, TYRO3, TRKB (Tropomyosin receptor kinase B) and TIE-2 (angiopoietins receptor) are also inhibited by cabozantinib. Similar to other TKIs, cabozantinib is a reversible, ATP-competitive inhibitor.

Early reports on the activity of cabozantinib in preclinical studies demonstrated inhibition of MET and VEGFR2 activation. For instance in xenograft murine models, cabozantinib inhibited VEGFR-2 and MET phosphorylation, disrupted tumor vasculature, induced tumour cell apoptosis and did not promote metastasis (29). Oral administration of cabozantinib inhibited MET phosphorylation in H441 lung tumor xenografts which harbor constitutively phosphorylated MET. In separate experiments in naïve mice, cabozantinib treatment inhibited phosphorylation of MET by HGF in liver tissue and phosphorylation of VEGFR2 by VEGF in lung tissue. According to RCC knowledges, it seems to emerge that cabozantinib may be the most efficient TKI for mRCC.

The clinical development of cabozantinib initially focused in patients who had already progressed to previous treatment. Thus, the METEOR phase III clinical trial (NCT01865747) randomized RCC patients refractory to antiangiogenics into two arms: cabozantinib at a dose of 60 mg daily and everolimus at a dose of 10 mg daily. The final analysis of survival shows a median OS of 21.4 months (95% CI 18.7- not estimable) with cabozantinib and 16.5 months (95% CI 14.7-18.8) with everolimus (HR 0.66 [95% CI 0.53-0.83]; p=0.00026). PFS is also improved HR 0.51 [95% CI 0.41–0.62]; p<0.0001, with a median PFS of 7.4 months (95% CI 6.6-9.1) in the cabozantinib group *versus* 3.9 months (95% CI 3.7-5.1) in the everolimus group. ORR was also better in the experimental arm, 17% (95% CI 13–22) with cabozantinib *versus* 3% (95% CI 2–6) with everolimus; p<0.0001, per independent radiology review among all randomized patients (30, 31). Cabozantinib has thus demonstrated significant activity in metastatic clear cell RCC after failure of one or 2 tyrosine kinase inhibitors (TKIs). Based on these METEOR trial results, cabozantinib is now approved in the second line setting in Europe (European Medicines Agency (EMA) approval in July 2016) (30-32).

Some efficacy was also demonstrated in patients in first line treatment when compared to sunitinib. Indeed, the CABOSUN randomized phase II trial (NCT01835128) conducted in patients with intermediate or poor prognosis mRCC showed, that cabozantinib was associated with a higher PFS than that obtained with sunitinib: 8.6 months (95% CI 6.8-14.0) and 5.3 months (95% CI 3.0-8.2) respectively (HR 0.48 [95% CI 0.31-0.74]. Cabozantinib was superior in terms of ORR: 20% (95%CI 12-30.8) *versus* 9% (95%CI 3.7-17.6) for sunitinib per independent radiology review (33, 34). For MET-positive patients (n = 62), median PFS was 13.8 months (95% CI 5.7—22.1) with cabozantinib and 3.0 months (95% CI 2.5—5.4) with sunitinib (HR 0.32 [95% CI 0.16—0.63]). For MET-negative patients (n = 69), median PFS was 6.9 months (95% CI 14.6) with cabozantinib and 6.1 months (95% CI 3.6—9.6) with sunitinib (HR 0.67 [95% CI 0.37—1.23]).
These latest clinical trials highlight the clinical activity of cabozantinib in advanced RCC, especially in patients whose tumor has MET alterations (35).

1.4. STUDY JUSTIFICATION

There is an urgent need to find more active treatments for mRCC patients with BM who have a poor outcome.
The accrual knowledges on molecular biology of mRCC and their metastases, recent success of cabozantinib in different types of cancer including mRCC and the molecular specificity of cabozantinib as multitarget inhibitor including VEGF and MET receptors suggest that cabozantinib could be a good option. However, its efficacy in brain metastases from RCC requires further evaluation.
On this basis, we propose to conduct an open-label exploratory single arm, multicenter prospective phase II trial to assess the efficacy of cabozantinib on brain metastases in mRCC patients.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. STUDY OBJECTIVES

The primary objective is to evaluate **the non progression rate in brain metastases at 6 months**.
The absence of progression in brain will be evaluated according to the specific RANO-BM criteria (Appendix 1) [7] and validated by a independant review committee.

The secondary objectives are:

- to evaluate the safety of cabozantinib, especially in terms of neurological tolerance,
- to estimate the best response in brain metastases, and the duration of response,
- to evaluate the response rate on the extracranial disease at 3 and 6 months,
- to evaluate the progression-free survival (PFS),
- to evaluate the overall survival (OS),
- to evaluate the overall response rate à 6 months (6m-ORR).

Ancillary studies**:**
Biomarkers (serum and plasma samples at baseline): The relationship between serum markers and efficacy data will be investigated using logistic regression models or Cox proportional hazard models (when evaluating impact on survival). MET expression and MET sequencing will be performed on available tumor tissues.

2.2. STUDY ENDPOINTS

Primary endpoint: **Progression-free rate in brain metastases at 6 months (6m-PFR)**.
Tumor assessment in brain will be performed by central review according to the RANO-BM criteria.

Secondary endpoints:

- Incidence of adverse events (AEs) assessed using the National Cancer Institute – Common Terminology Criteria for Adverse Event (NCI-CTCAE) v5 grading scale, specific registration of neurological event during study duration,
- Best response (complete response or partial response or stable disease or progressive disease) in brain metastases, evaluated according to RANO-BM criteria,
- Response on the extracranial disease, evaluated according to RECIST v1.1 criteria,
- PFS, measured from the date of inclusion to the date of first documented disease progression or death from any cause. Patients without event will be censored at the time of the last clinical evaluation,
- OS, measured from the date of inclusion to the date of death from any cause,
- 6m-ORR, defined as the proportion of patients with complete or partial response at 6 months.

3. EXPERIMENTAL PLAN

3.1. STUDY DESIGN

This is a multicenter, open-label, exploratory, single-arm, prospective phase II study to assess the efficacy and safety profile of cabozantinib in patients with BM from mRCC.

3.2. STUDY DURATION

The inclusions are planned during 54 months.
Patients will be followed (except in the case of consent's withdrawal) **for 24 months from the inclusion or until progression or death, whichever occurs first.**
Adverse event(s) will be followed until resolution or stabilization.
Patients' survival status will also be recorded once a year until final analysis.
*If a patient withdraws consent, no further evaluations should be performed and no attempt should be made to collect additional data.

3.3. STUDY SCHEME

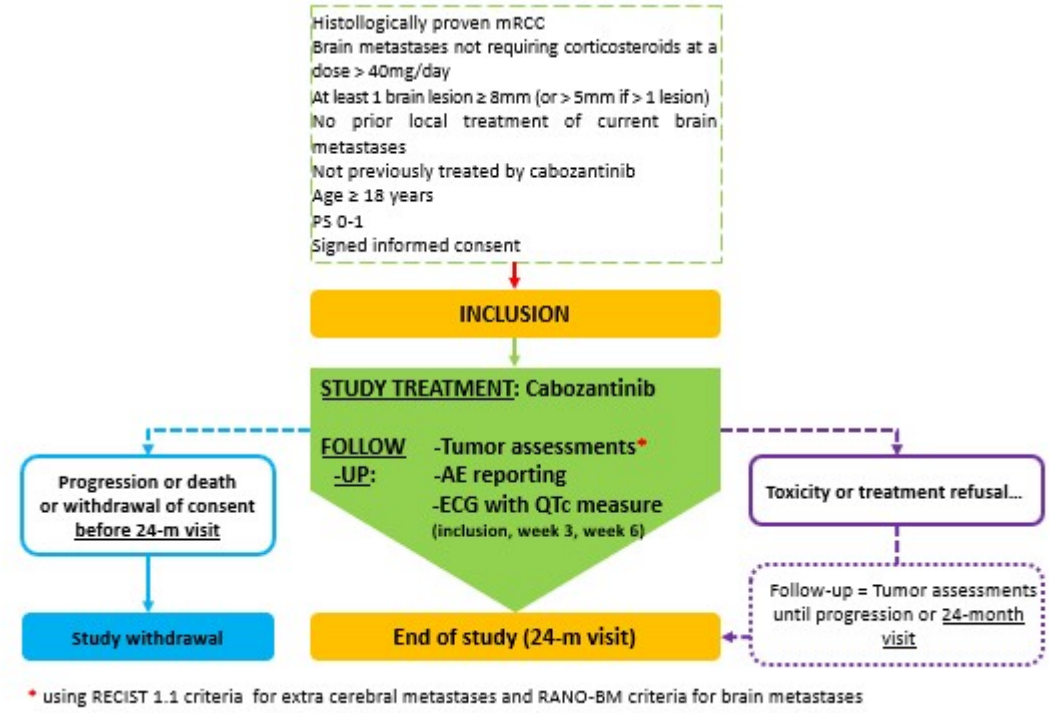


Figure 1: Study scheme

4. BENEFIT AND RISK ASSESSMENT

The benefit and risk assessment for the proposed study is based on the followings:

- Patients with RCC brain metastases have a poor prognosis with a much higher risk of premature death than patients without brain metastases.
- Today there is no standard of care out of local treatments that have some efficacy but do not prevent from the occurrence of new brain metastases.
- Cabozantinib is indicated for the treatment of mRCC and appears as an interesting therapeutic approach for patients with BM.
- The study dose (60 mg daily) is the current recommended dose.
- The risks related to study participation are the potential adverse reactions under cabozantinib. In all studies, the safety analyses showed that cabozantinib is well tolerated when its dosage is adapted accordingly. Potential risks associated to study participation will be cautiously followed-up with a specific monitoring plan.

- Study participation may generate potential benefits. The study treatment could be beneficial for patients via a delay of tumor progression and a prolonged survival.

All information from the study will contribute to improve the management of patients with BM of RCC.

Based on previous clinical experience, the proposed study design, the dose selection and the safety monitoring plan described in this protocol, the sponsor considers that the benefit-risk is favorable to proceed with the proposed clinical study.

5. STUDY POPULATION

The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken in consideration when deciding whether this protocol is suitable for a particular patient. Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study or regulatory acceptability.

5.1. INCLUSION CRITERIA

I1. Age ≥ 18 years.
I2. Histologically proven metastatic RCC, in first line treatment or after one or two prior treatments.
I3. Brain metastases not requiring corticosteroids at dose > 40 mg/day.
I4. At least 1 locally untreated brain lesion ≥ 8 mm in longest diameter or > 5 mm if > 1 lesion.
I5. Not previously treated by cabozantinib.
I6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 1.
I7. Life expectancy ≥ 3 months
I8. Adequate organ function as defined by the following criteria:
- Total serum bilirubin ≤ 2 x ULN (Gilbert's disease exempted)
- Serum transaminases and alkaline phosphatases ≤ 2.5 x ULN, or in case of liver or bone metastasis ≤ 5.0 x ULN
- Serum creatinine ≤ 2 x ULN OR creatinine clearance ≥ 50 ml/min
- Absolute neutrophil count (ANC) ≥ 1 500/mm^3
- Platelets ≥ 100 000/mm^3 (100 G/l)
- Hemoglobin ≥ 9.0 g/dl.

I9. Covered by a medical/health insurance.
I10. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
I11. Signed and dated IRB/ICE approved informed consent form.
I12. Accepting to use effective contraception (barrier contraceptives) during study treatment and within at least 4 months after final dose of study therapy. Oral contraceptives are not acceptable.

5.2. NON-INCLUSION CRITERIA

E1. Any local previous treatment of current brain metastases. [Stereotactic radiotherapy or cyberknife on some of the brain metastases is allowed if performed on brain met < 2 cm and at more than 2 weeks before inclusion.]
E2. Any anti-coagulation therapy (except preventive treatment at low dose).
E3. Contra-indication of Magnetic Resonance Imaging (MRI) (i.e.: pace-maker).
E4. Uncontrolled seizures.
E5. Any symptoms of intracranial hypertension.

E6. Any of the following within 12 months prior to treatment initiation: severe/unstable angina, myocardial infarction, coronary artery bypass graft, symptomatic congestive heart failure, ischemic or hemorrhagic stroke including transient ischemic attack.
E7. Uncontrolled hypertension defined as systolic blood pressure >150 mmHg or diastolic pressure >90 mmHg, despite optimal medical treatment.
E8. Ongoing cardiac dysrhythmia of grade ≥ 2, atrial fibrillation of any grade, QTc interval > 0.43.
E9. Pregnant or breast-feeding woman (mandatory negative serum or urinary pregnancy test at study entry for all women of childbearing potential).
E10. Any acute or chronic medical or psychiatric condition or laboratory abnormality that would make the patient unsuited to study participation.
E11. Any second malignancy within the last 3 years with the exception of basal cell carcinoma, in situ cervical cancer and pT1/a bladder cancer with no evidence of recurrent disease for 12 months.
E12. Patients receiving strong inhibitor or inducer of CYP3A4 especially some anti-epileptic drugs.
E13. Psychological, familial, sociological, geographical conditions that would limit compliance with study protocol requirements.
E14. Participation to another clinical trial that might interfere with the evaluation of the main criterion.
E15. Known hypersensitivity to the active substance or to any of the excipients of cabozantinib.
E16. Patient requiring tutorship or curatorship.

6. STUDY TREATMENTS

6.1. CABOZANTINIB

CABOZANTINIB	
Description	Cabozantinib is formulated for oral administration as a yellow film-coated tablet. 3 dosage strengths are available: 20 mg (round), 40 mg (triangle shaped) and 60 mg (oval). Dosing compliance will be monitored at each clinic visit: patient will be asked to bring back the study packages at each clinic visit.
Mode of action	MET, VEGFR and AXL inhibitor
Storage	No special storage conditions, except for secure location.
Method/Route of administration	By oral route The prescribed oral daily dose of cabozantinib is to be taken whole with a full glass of water. Cabozantinib should not be taken with food: patient should not eat anything for at least 2 hours before taking cabozantinib and for 1 hour after. If a dose is missed for any reason, the missed dose should not be taken if there is less than 12 hours before the next dose. The next prescribed dose should be taken at the usual time.
Dose to be administered	60 mg once daily per os (po). **Study treatment should be started within 7 days after the patient inclusion.**
Dispensation and destruction requirements	Cabozantinib shall be dispensed under the responsibility of the investigator and in accordance with the investigator's prescription. Maintenance of adequate records with information related to drug receipt, drug dispensing, drug return (by patient) and destruction will be performed under the responsibility of the centre principal investigator. These records must be available for inspection by the Sponsor representative (study monitor). Patients will be instructed to bring back all unused, partially or totally packs to each study visit. All returned or expired products should be kept until their destruction is authorized by the Sponsor.

<table>
<tr><td></td><td>No other use of cabozantinib study drug intended for use in this trial is authorized by the Sponsor. The investigational product should never be used outwards this clinical trial.

The investigator (or designee) will be responsible for the appropriate handling and disposition of residual study drug in partially used packs. Once returned to the investigator, tablets from partially used blisters/packs will not be re-dispensed to another subject.</td></tr>
<tr><td>Dose adjustment</td><td>Temporary or permanent discontinuation and/or dose reduction of cabozantinib therapy may be required for the management of some adverse reactions (see Table 1 below). When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.

A patient who requires a dose interruption (regardless of the reason for the interruption) of more than 28 days (counting from the first day when a dose was missed) must discontinue the study treatment.

Table1: Recommended cabozantinib dose modifications for adverse reactions
<table>
<tr><th>Adverse reaction and severity
(Grade NCI-CTCAE v5)</th><th>Treatment modification</th></tr>
<tr><td>Grade 1 et Grade 2 adverse reactions which are tolerable and easily managed</td><td>Dose adjustment is usually not required.
Consider adding supportive care as indicated.</td></tr>
<tr><td>Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care</td><td>Interrupt treatment until the adverse reaction resolves to grade ≤ 1.
Add supportive care as indicated.
Consider re-initiating at a reduced dose.</td></tr>
<tr><td>Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities)</td><td>Interrupt treatment until the adverse reaction resolves to grade ≤ 1.
Add supportive care as indicated.
Consider re-initiating at a reduced dose.</td></tr>
<tr><td>Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities)</td><td>Interrupt treatment.
Institute appropriate medical care.
If adverse reaction resolves to grade ≤ 1, re-initiate at a reduced dose.
If adverse reaction does not resolve, permanently discontinue treatment.</td></tr>
</table></td></tr>
<tr><td>Summary of the safety profile</td><td>The most common serious adverse drug reactions are fatigue, hypertension, diarrhea, palmar-plantar erythrodysaesthesia syndrome (PPES), pulmonary embolism, and hypomagnesaemia.

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) included diarrhea, hypertension, fatigue, AST increased, ALT increased, nausea, decreased appetite, PPES, dysgeusia, platelet count decreased, stomatitis, anemia, vomiting, weight decreased, dyspepsia, and constipation. Hypertension was observed more frequently in the treatment naïve RCC population (67%) compared to RCC patients following prior VEGF-targeted therapy (37%).

Events that generally have early onset include hypocalcaemia, hypokalemia, thrombocytopenia, hypertension, PPES, proteinuria, and gastrointestinal events (abdominal pain, mucosal inflammation, constipation, diarrhea, vomiting).</td></tr>
</table>

6.2. DURATION OF TREATMENT

Cabozantinib treatment may continue until one of the following criteria applies:

- Disease progression in brain according to RANO-BM criteria,
- Confirmed disease progression according to RECIST v1.1 in extracranial metastases,
- Unacceptable adverse event(s),
- Patient's willingness to stop the treatment,
- Pregnancy
- Withdrawal of consent*,
- Decision of the investigator to stop treatment (general or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator).

*If a patient withdraws consent, no further evaluations should be performed and no attempt should be made to collect additional data.

6.3. CONCOMITANT TREATMENT

All treatments being taken by the patient at the time of inclusion into the study and at any time during the study are regarded as concomitant treatments and the type and date of administration must be documented in his/her case report form (CRF).

Prohibited concomitant therapy

Any investigational agent, within 28 days prior to cabozantinib start, and any other cancer treatments other than cabozantinib are prohibited.

Strong cytochrome P450 (CYP3A4/5) inhibitors should be used with caution, as it results in an increase in cabozantinib plasma exposure. Strong CYP3A4/5 inducers should be avoided, as it results in a decrease in cabozantinib plasma exposure.

P-glycoprotein substrate and MRP2 inhibitors should be approached with caution.

The use of steroids must be limited to the treatment of acute reactions and not be required for more than a week.

Permitted concomitant therapy

Supportive treatment as medically indicated for the patient's well-being may be prescribed at the investigator's discretion.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed above.

Palliative radiotherapy is allowed during the course of the study except on the brain.

Please refer to the current version of cabozantinib summary of product characteristics (SPC) (see Appendix 2).

7. STUDY ASSESSMENTS

7.1. ASSESSMENT TO BE PERFORMED AT SCREENING

The investigator or designee staff will have to proceed to the following information/procedures during the screening visit:

- Inform the patient of the treatments, the objectives and the study design, answer to questions and sign with him/her the informed consent form (ICF). The investigator must not start any study related procedure before ICF is signed and dated by both patient and investigator.
- Perform the following standard exams:
  - Complete medical history, including complete diagnosis of mRCC, with histological confirmation and treatment history, prior and concomitant treatments.
  - Full physical examination: vital signs (i.e. systolic and diastolic blood pressure, pulse, temperature), weight, height and PS, any symptoms (according to NCI-CTC AE version 5.0).
  - 12-lead ECG recorded after a 10-minute rest in supine position, with QTc measure according to Bazett formula.
  - Left ventricular ejection fraction (LVEF), if clinically indicated.
  - Urinary dipstick test. If ≥ 2+: perform 24h-protein urinalysis.
  - Biological assessments: Hematology, biochemistry (including corrected total calcium and creatinine) and thyroid assessment – SEE FLOW-CHART.
  - Pregnancy test (if applicable).
  - Tumor assessments:
    - Brain Magnetic Resonance Imaging (MRI).
    - Thorax Abdomen and Pelvic (TAP) CT-scan or MRI.
- Check the eligibility criteria list.
- Serum and plasma collection: 20 ml.
- Sample of available tumor tissue.

7.2. ASSESSMENTS TO BE PERFORMED DURING STUDY PERIOD

Standard follow-up (see Flow-chart) will be performed with:

- Clinical examination: weight, ECOG PS (Appendix 3), vital signs (systolic and diastolic blood pressure, pulse).
- Concomitant treatments collection.
- Blood pressure monitoring. Blood pressure will be checked regularly during the study: 3 times a week during the first 12 weeks of cabozantinib treatment, weekly thereafter. A blood pressure monitor will be given to each patient.
- Reporting of AEs according to NCI-CTC AE version 5.0. Patient should be questioned at each scheduled visit concerning AE experienced since the last visit. The severity (as graded by the National Cancer Institute Common Terminology Criteria for AE (NCI-CTCAE) v5.0), date of onset, outcome and action taken on study treatment should be recorded for all AEs related to study treatments and in case of significant worsening of AEs related to the treatment of mRCC. Adverse event(s) will be followed until resolution or stabilization.
- Biological assessments: Hematology and biochemistry (including corrected total calcium and creatinine).
- Standard tumor assessment: TAP CT-scan (or MRI) and brain MRI. Antitumor activity will be assessed using RECIST 1.1 criteria and according to RANO-BM criteria for brain metastases assessment.

Patients will be followed at 3, 6, and 9 weeks, 3, 4.5 and 6 months and then every 3 months (± 2 weeks) during 24 months (except in the case of consent's withdrawal) **or until progression or death, whichever occurs first. Survival data will be collected for all patients once a year until final analysis.**

7.3. GLOBAL STUDY FLOW-CHART

Table 1: Global study flow-chart W: Week; M: Month

ASSESSMENT	BASELINE	W3	M1.5 W6	W9	M3 W12	M4.5 W18	M6 W24	EVERY 3 MONTHS (± 2 weeks) UNTIL END OF STUDY (EOS)[12]
Informed consent	X							
Clinical assessment								
Relevant medical history[1]	X							
Pregnancy test (if applicable)[2]	X[4]							
Physical examination (Performance Status ECOG, height[3], weight)	X[4]	X	X	X	X	X	X	X
Vital signs (pulse, systolic and diastolic blood pressure)	X[4]	X	X	X	X	X	X	X
Collection of toxicities[5] and SAE reporting	X[4]	X[11]						
Collection of concomitant treatments	X[4]	X	X	X	X	X	X	X
ECG with QTc measure (Bazett formula)	X[4]	X	X					
LVEF	X[6,9]							
Biological assessment								
Hematology[7]	X[4]	X	X	X	X	X	X	X
Biochemistry[8]	X[4]	X	X	X	X	X	X	X
Thyroid assessment (TSH, T4)	X[4]		X		X			X
Urinary dipstick test	X[4]		X		X	X	X	X
Tumor assessment								
TAP CT-scan or MRI + any other clinically indicated exams	X		X		X		X	X
Brain MRI	X[9]		X		X		X	X
Serum and plasma collection	X							
Tumor collection (MET expression)[10]	X							

1 Past relevant medical and surgical history, complete diagnosis of RCC and treatment history.
2 If urinary test is positive, a serum test should be performed.
3 At baseline only.
4 Within 1 week before inclusion ± 2 days.
5 According to NCI-CTCAE v5.
6 If clinically indicated.
7 Complete blood count (CBC) with platelets and differential counts, hemoglobin, and hematocrit.
8 Electrolytes (sodium, potassium, chlore, calcium, corrected calcium, magnesium, phosphate [Na, K, Cl, Ca, Mg, PO4]), albumin, glucose, creatinin, calculated creatinine clearance [Cockcroft and MDRD formulas], uric acid, liver function tests (AST, ALT, alkaline phosphatase, GGT, LDH), total bilirubin.
9 Within 2 weeks before inclusion ± 3 days.
10 Archival formalin-fixed and paraffin embedded (FFPE) block
11 Continuously during the study and until 28 days after the last cabozantinib intake.
12 EOS = 24 months or progression or death, whichever occurs first.

After the 24-month follow-up, survival data will be collected for all patients once a year until final analysis.

8. STUDY PROCEDURES

8.1. INCLUSION OF PATIENTS

After identification of a potentially eligible patient, the investigator (or staff designee) will check his/her eligibility status. The investigator will then inform the patient of the study design and provide him/her with an information notice and a consent form.
After being made aware of the study and adequate time (24 hours minimum) to consider his/her participation (see paragraph 13.2), the participant must give his/her consent in writing by personally dating and signing the consent form, which will also be dated and signed by the investigator (original archived by the investigator, with one copy returned to the patient).
An inclusion form will be filled up and then signed by the investigator. The investigator (or designee staff) will then proceed to the patient's inclusion on the on-line inclusion platform /Interactive Web Response System (IWRS), with confirmation of the patient's eligibility. A confirmation email will be sent automatically to the investigational staff and to the coordinating center.
Refer to Investigator Master File for the inclusion procedure.

8.2. SERUM AND PLASMA COLLECTION

Serum and plasma samples will be collected at inclusion. *Refer to Lab Manual for the sampling procedure.*

8.3. TUMOR COLLECTION

Available tumor tissue (archival FFPE block) will be collected. *Refer to Lab Manual for the shipment procedure*

8.4. TREATMENT DISCONTINUATION

The treatment with cabozantinib should be continued as per protocol whenever possible in accordance with the investigator's judgment and patient's consent. However, patients have the right to voluntary discontinue (i.e. permanently stop) study drug at any time for any reason. In addition, the investigator has the right to discontinue a patient from study treatment at any time.
Any discontinuation should be fully documented in the CRF with the date and reason.

A subject who discontinues study treatment prematurely for any reason (except for withdrawal of consent) will continue to be followed-up and to have assessments according to schedule listed in the study flow-chart.

If a patient withdraws consent, no further evaluations should be performed and no attempt should be made to collect additional data. This must be clearly documented in the patient's medical file.

8.5. PATIENT PREMATURE WITHDRAWAL

Will be considered as an early withdrawal of the study:
- Patient's progression or death, if occurring before 24 months;
- Patient's decision to withdraw from the study (withdrawal of consent)*.

An end of study form will then be completed.

Early treatment stop or treatment refusal will not be considered as study withdrawal. Patients will be followed as specified in paragraph 7.

* In case of withdrawal of consent, the effective date of patient's withdrawal of consent should be noted on the source data and no data and/or biospecimen collection could be performed after that date.

8.6. STUDY PREMATURE DISCONTINUATION

The Sponsor could stop the study at any time. Reasons for stopping the study may include, but are not limited to, the following:

- The incidence of severity of adverse events in this or other study indicate a potential health hazard to patients,
- Patients enrolment is unsatisfactory (low recruitment),
- If any information leads to doubt as to the benefit/risk ratio of the clinical trial.

In any case, the sponsor will notify the Investigator of its decision by written notice.

In all cases, the appropriate Ethics Committee(s) (EC) and Competent Authority (CA) should be informed according to applicable regulatory requirements.

In any event, the medical care of the patient is the responsibility of the investigator.

8.7. SITE DISCONTINUATION

The Sponsor has the possibility to replace a site at any time. Reasons for replacing a site may include, but are not limited to the following:

- Poor recruitment,
- Poor protocol adherence,
- Inaccurate or incomplete data recording,
- Noncompliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) or applicable laws and regulations.

In any case, the sponsor will notify the Investigator of its decision by written notice.

The investigator has also the right to stop the study at any time. He/she must notify (30 days' prior notice), the sponsor of his/her decision and give the reason in writing.

8.8. RADIOLOGICAL REVIEW

For all patients, brain MRI at baseline, 1.5, 3 and 6 months will have to be sent as soon as possible to the coordinating centre. An independent committee will review them and validate the absence of progression at 6 months.

9. SAFETY

ICH GCP requires that both investigators and sponsor follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section.

9.1. DEFINITIONS

The following standard definitions (Directive 2001/20/EC of the European Parliament) for adverse events will be used:

- **Adverse event (AE):** any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.
- **Adverse reaction (AR):** all untoward and unintended responses to an investigational medicinal product to any dose administered.
- **Serious adverse event (SAE):** any untoward medical occurrence or effect that at any dose:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation[1]of existing hospitalization
  - Results in persistent or significant disability/incapacity [2]
  - Is a congenital abnormality or birth defect
  - Is a significant medical event, (i.e. that may jeopardize the patient or may require intervention to prevent one of the serious outcomes mentioned previously).
- **Suspected unexpected serious adverse reaction (SUSAR):** An adverse reaction, not mentioned in or differing in terms of nature, intensity, frequency or clinical course from that listed in the latest version of cabozantinib SPC.
- **New safety issues**: Any new safety data that could lead to reevaluate the ratio between the benefits and risks of the research, or that could be sufficiently important to consider modifications of the research documents, the research management or, if need be, the drug utilization or to suspend, to interrupt or to modify the protocol of the research or of similar researches.

The CTEP version 5.0 of the NCI-CTCAE will be used for AE reporting (Appendix 4).
The intensity of adverse events not listed in this classification will be assessed using the following descriptors:

- Mild (grade 1): does not affect the patient's usual daily activities,
- Moderate (grade 2): disturbs the patient's usual daily activities,
- Severe (grade 3): prevents the patient's usual daily activities,
- Life-Threatening (grade 4): requires critical care,
- Death (grade 5).

9.2. REPORTING OF ADVERSE EVENTS

General Guidelines for reporting of Clinical AE

AE, regardless of the seriousness or relationship to the investigational medicinal product (IMP), occurring from the signature of the ICF until the end of the study for the patient, are to be recorded on the corresponding CRF pages or screen (only the highest grade):

As far as possible, the adverse event should be described using medical terms: diagnosis or single syndrome should be reported instead of symptoms.

[1] Prolongation of hospitalization is defined as prolongation of at least 1 day.
[2] The terms disability and incapacity refer to any clinically significant physical or mental handicap, whether temporary or permanent, which affects the patient's physical activity or quality of life.

For all AE, the Investigator should specify:

1. ***Whether the event is serious or not***. The severity is related to the intensity whereas a serious AE is defined by the criteria described in Section 9.1. A severe AE should not be always considered as serious, and a serious AE may not be of severe intensity.
2. ***The date of onset and its duration (start and end dates)***. The Investigator should follow up the outcome of any AEs until the return to normal or consolidation of the patient's condition. Once resolved, the details should be recorded in the CRF: All adverse events still evolving at the end of the study are to be followed up by the investigator until their resolution or stabilization.
3. ***The intensity*** (using NCI CTCAE v.5.0 – Appendix 4), **only the worst grade of a specific event should be recorded.**
4. ***The action taken with respect to IMP*** (no action taken; IMP dosage adjusted/temporarily interrupted; IMP permanently discontinued due to this adverse event, concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization), corrective treatment/therapy given, additional investigations performed, outcome
5. ***The relationship between the IMP and the AE***, using the EVCTM (EudraVigilance Clinical Trial Module) criteria: related / not related.

NB: Signs and symptoms that are present prior to the first study drug administration are to be recorded on the medical history pages included in the CRF. They are to be recorded as adverse events as soon as one of the following changes occurs: increased intensity, relationship, action taken regarding study drug.

Case of routine laboratory measurements

A value outside the normal or reference range in a routine safety assessment, such as clinical laboratory, vital signs or ECG, may be considered as an adverse event. However, laboratory, as well as vital signs and ECG abnormalities are to be recorded into the CRF as AE only if they are considered medically relevant by the investigator: i.e. symptomatic, requiring corrective treatment, leading to IMP discontinuation/dose modification (reduction and/or delay), and/or fulfilling a seriousness criterion.

NB: If the findings contribute to a clinical diagnosis (such as hepatitis in case of increased liver enzymes) this diagnosis should be recorded as an adverse event.

9.3. REPORTING OF SERIOUS ADVERSE EVENTS

The investigator must report to the sponsor AND coordinating center, without delay after awareness, any serious adverse events (SAEs or new information), occurring during the course of the study, from the date the informed consent is signed until 28 days after the last IMP intake or until death, whichever occurs first).

SAEs occurring after these 28 days need to be reported only if a relationship to the study procedures is suspected by the investigator.

Exceptions to serious adverse events reporting

The following events **will not** be considered as SAE:

- Any event requiring short consultation in a hospital
- Hospitalization (1 night or more) or hospitalization prolongation for one of the following reasons:
  - Planned hospitalization for routine intervention,
  - Hospitalization or intervention requested by the protocol,
  - Hospitalization for explorations not related to a modification of the patient's health,
  - Hospitalization for comfort or for social reasons (for example: hospitalization of an elderly person due to dependence on his/her partner who was hospitalized),
  - Hospitalization not related to a patient health worsening and not related to the study objectives (for example: plastic surgery),
  - Hospitalization for progression of the cancer being investigated,

- Any death related to cancer progression occurring more than 28 days after study treatment completion.

Expected adverse events possibly related to study treatments

The evaluation of expectedness is based on knowledge of the adverse reaction on the reference document: the current reference document is the latest version of the cabozantinib's SPC.

SAE reporting procedure

In case of SAE, the investigator will have to:

1. Fill and sign a SAE Report Form,
2. Collect any additional anonymized document necessary for SAE assessment (such as hospitalization report, biological results),
3. Assess the seriousness and causality of the event with the IMP using the EVCTM criteria: related, not related,
4. Send the SAE report form without delay and additional anonymized documents by fax to:

Sponsor's vigilance (Anne Millaret, PharmD) - Fax: + 33 (0)9 81 40 42 80
AND
Coordinating Centre - Fax: + 33 (0)4 78 78 27 15

A complete description and medical diagnosis shall be provided.
In case of incomplete information, the investigator will have to provide follow-up information (outcome, more precise medical details, results of investigations, copy of discharge summary, etc.) as soon as possible, again using the SAE Report Form (follow-up) to the sponsor's vigilance and to the study monitors. When this information is passed on, care must be taken to continue to respect patient anonymity. The study monitor or sponsor's vigilance may contact, or visit the investigator, in order to obtain details of the event.

Please refer to Investigator Master File for the reporting form and procedure.

All SAE must be followed by the investigator until resolution or stabilization, and a final assessment sent to sponsor's vigilance as a SAE Report Form (SAE follow-up).
The Investigator is responsible for providing appropriate medical follow-up for patients until resolution or stabilization of the AE or until the patient's death. Sometimes this may mean that follow-up will extend beyond the patient's withdrawal from the trial.
The Investigator shall supply the sponsor with any additional requested information.

Original SAE form will be archived by the investigator in the appropriate Investigator Master File section. A copy of these reports is stored by the sponsor in the trial master file.

In sum up, SAE should be reported to the Sponsor according to the requirement defined in Table below:

Period	Requirement for reporting
From ICF signature to 28 days after the last IMP intake or until death, whichever occurs first	All SAEs, with the exceptions above-mentioned.
Long term follow-up	Only related SAEs

9.4. RESPONSIBILITIES OF THE SPONSOR

For all SAEs, the sponsor will evaluate the causal relationship to study treatments, study protocol, concomitant treatments and/or any associated diseases, and the expectedness of all SAEs.
The Sponsor will have to report all SUSARs to the European Medicines Agency (Eudravigilance (EMA and ANSM)within the requested period, i.e.

- **As soon as possible** and in any event no later than 7 days after awareness of the reaction by the sponsor for death and life-threatening SUSAR.
- **No later than** 15 days after awareness of the reaction by the sponsor for the others SUSARs.

The information's follow-up must be transmitted within a new delay of 8 days for death and life-threatening SUSARs and within a new delay of 15 days for the other SUSARs.

The sponsor will also have to inform the Competent Authority of any SAE and or any Safety Issues with the potential to modify the benefit/risk ratio of the present study.

The Sponsor will be responsible for reporting the Development Update Safety Report (annual report) to the Competent Authority and to the Ethics Committee.

The sponsor will be responsible to alert the Principal Investigator in case of identification of a new safety issue and will propose urgent security measures to be applied.

The sponsor will be responsible for reporting New Safety Issues and the urgent safety measures to be proposed without undue delay **and at the latest 7 days following the date on which the measures were taken** to National Competent Authorities and to Ethics Committees.

The sponsor will be responsible to notify the appropriate EC, CA and principal investigators of serious breaches (i.e. likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial), without undue delay and at the latest in the 7 days after awareness.

The Sponsor shall notify the Principal Investigators of any information which might affect the patient's safety.

10. STATISTICAL CONSIDERATIONS

10.1. SAMPLE SIZE DETERMINATION

The number of patients to be included was calculated using A'Hern single stage design for phase II trials with the following hypotheses, where π is the true probability of success.
The sample size calculation was based on a minimum success (cerebral **progression-free at 6 months**) rate considered of interest of p_1=70% and an uninteresting rate of p_0=45%. Assuming a type I error alpha of 5% and 80% power, 25 evaluable patients are needed to reject the null hypothesis H_0: $\pi < p_0$ *versus* the alternative hypothesis H_1: $\pi \geq p_1$ in an unilateral situation.
At the time of the analysis, a minimum of 16 successes will be needed to indicate that the treatment is effective. Based on the assumption that 10% of the patients may be non-evaluable, at least 28 patients will be included in the study.

10.2. ANALYSIS POPULATIONS

The following populations will be defined for the statistical analysis:

- The whole protocol population includes all included patients.
- The efficacy-evaluable population consists of all patients of the global population having received at least 3 weeks of cabozantinib treatment or discontinued cabozantinib treatment before 3 weeks for progression or toxicity (treatment failures) AND with no major protocol violation which could impact efficacy analyses.
- The safety population consists of all patients who received at least one dose of study drug.
- The per protocol (PP) population consists of a subset of the whole protocol population and includes all patients with no major protocol violation for inclusion and non-inclusion criteria and who are compliant with requirements of the study protocol.

All protocol deviations leading to exclusion from the whole protocol population to the PP population will be detailed in the analysis plan.
Baseline characteristics will be described on the whole protocol population, efficacy will be described on the efficacy-evaluable population, and safety data will be described on the safety-evaluable population.
Subgroup analysis will be performed (VEGF-naïve patients group and VEGF-experienced patients group).

10.3. STATISTICAL ANALYSIS

All data analyses will be performed using the SAS version 9.4 statistical software (SAS Institute, Cary, NC, USA, 2003). Any changes to the methodological details of the planned analyses will be documented in the statistical analysis plan (SAP).
Qualitative data will be described using frequency and percentage distributions. The number of missing data will be given, but will not be considered for the calculation of proportions.
Quantitative data will be described using the number of observations, mean, standard deviation, median, minimum and maximum values.

The primary efficacy endpoint is the progression-free rate in brain at 6 months based on assessments by the review committee. It will be reported with its unilateral 95% confidence interval (CI).
The progression-free rate at 6 months based on assessments by the investigators will also be reported.

PFS and OS will be estimated using the Kaplan-Meier method, and will be described in terms of medians along with the associated 2-sided 95% CIs for the estimates.
For PFS, patients with no event (progression or death) at the time of analysis will be censored at the date of last adequate tumor assessment.
For OS, patients who are alive at the time of analysis will be censored at the date of last contact.
The assessment of safety will be based mainly on the frequency of adverse events coded using the common toxicity criteria (NCI-CTC v5.0) grade. Descriptive statistics will be provided for characterizing and assessing patient tolerance to treatment. Adverse events will be coded according to the MedDRA®.

The relationship between biomarkers and efficacy data will be investigated using logistic regression models (when evaluating impact on tumor response) or Cox proportional hazard models (when evaluating impact on PFS).

11. DATA COLLECTION & MANAGEMENT

The study will be coordinated by the coordinating center of Léon Bérard Cancer Centre in France (Direction de la Recherche Clinique et de l'Innovation (DRCI) of Centre Léon Bérard).

11.1. SITE SET-UP

All sites will be required to sign appropriate contracts with the Sponsor prior to participation. All members of the site research team will also be required to sign a Site Signature and Delegation Log which lists the range of duties that have been delegated to them for the trial. This should be counter-signed by the Principal Investigator and returned to the Sponsor.
Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data, and record keeping.
Sites will be provided with an Investigator Master File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Sponsor must be informed immediately of any change in the site research team.

11.2. DATA ENTRY AND DATA MANAGEMENT

All the data concerning the patients will be recorded online by investigators and authorized staff in the eCRF.
Data entry will be performed based on source documents and signed electronically by the principal investigator.
The investigator is responsible to ensure accuracy completeness and timeliness of the data reported in the eCRF.
The database will be submitted to a quality control. Queries will be generated automatically in the eCRF for missing, out of range and inconsistent data. It will be answered by the investigational site's staff in compliance with source data and saved in the eCRF.
All data base modifications will be explained (if necessary) and recorded in the audit trail. If the data are modified by another person than the investigator, the authorization of this person will be documented on the delegation form.
Adverse events codification will be performed according to MedDRA®.
A patient file will be validated once no more inconsistency is detected by the program.
The database will be locked after all queries are solved, and after data review and final validation. Computerized management of collected data will be performed by the coordinating Centre (DRCI – Centre Léon Bérard), in charge of the data management.

11.3. STUDY MONITORING

According to the ICH guidelines for GCP, the study monitor must check the CRF entries against the source documents. The sponsor will perform the study monitoring according to the monitoring plan summarized as follows:

- Site Initiation Visits will be performed by phone call when possible;
- Following a risk-based monitoring, all electronic CRF will be centrally analysed. Then, Source Data Verifications (SDV) will be performed on-site, tailored on central monitoring findings.
  Medical files will be fully reviewed by the monitor for all patients to identify any event related to the primary endpoint. In addition, a particular attention will be paid to consent procedures, selection criteria and safety concern.
  Anyway, each participating site will be visited yearly, provided that at least one new patient was included since the previous monitoring visit.
- Close-out visits will be conducted by phone call when possible.

A monitoring report will be written for each visit to document the progress of the clinical trial and give an account of all emergent problems.
The sponsor will help the investigators to conduct the study in compliance with the clinical trial protocol, Good Clinical Practices (GCP) and local law requirements.
In addition to the on-site monitoring visits, investigational sites will be contacted at regular intervals either by phone or by e-mail, by a representative of the coordinating centre (i.e. the study monitor) to review study progress, investigator's and patient's compliance with clinical trial protocol, and any emergent problems.
All personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information.

11.4. AUDIT AND INSPECTIONS

For the purpose of ensuring compliance with the clinical trial protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.
The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that auditors/inspectors are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.
The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.
The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

11.5. PROTOCOL DEVIATIONS AND SERIOUS BREACHES

11.5.1. Any deviation reporting

As per GCP and regulation in place, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

The investigator should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favorable opinion by the IRB/IEC. In case of protocol deviation (PD), the investigator, or person designated by the investigator, should inform, document and explain any protocol deviations from the approved protocol to the sponsor (during monitoring visits or through answers to note to file).

The sponsor is responsible for collecting and assessing PDs, developing and implementing appropriate CAPAs, as well as defining the impact of deviations on analyses. All important protocol deviations* will be registered by the sponsor into eCRF.

*Important Protocol Deviation (IPD): A PD that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD include major, critical and serious breach deviation.

11.5.2. Expedited reporting required for serious breach

Any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial will be considered as a "Serious Breach" (SB) regarding instructions given in the "Guideline for the notification of serious breaches of Regulation (EU No 536/2014 or the clinical trial protocol EMA/698382/2021)". The

investigator should have a process in place to ensure that the site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.

In case of a suspicion of a SB:

- The investigator, or person designated by the investigator, should promptly notify to sponsor of any (potential) serious breach of the protocol or regulations using the SB reporting form "Notification of Suspected Serious Breach" through e-mail to DRCIreglementaire@lyon.unicancer.fr.
- Sponsor will review all reported deviations to assess if there is the potential that it may constitute a serious breach. If additional information is required, sponsor will contact the investigator/institution and may also seek further advice from external clinicians and senior sponsor management to aid review.
- According to EU Clinical Trials Regulation 536/2014 applies, the sponsor is required to enter details of serious breaches into the EMA CTIS within 7 calendar days. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

12. STUDY COMMITTEES

12.1. TRIAL MANAGEMENT GROUP

A trial management group (TMG) will be established to oversee the conduct of the study and make any necessary recommendations as needed. It will be composed of:

- The coordinating investigator: Pr Sylvie NEGRIER, who will be the chairman of the TMG,
- The co-coordinating investigator: Dr Bernard ESCUDIER,
- The representatives of the sponsor (DRCI CLB),
- The principal investigator of the main centers.

It will follow-up the general organization and conduct of the trial. It will be therefore regularly informed of the inclusion rate and of any emergent problems, will decide of potential amendments and will propose the inclusion (or non-inclusion) of any participating center.
It will also review the activity and safety data (especially grade 3-4 neurological events) throughout the study. This committee will be in charge for the decision to continue the trial after the first part.

12.2. INDEPENDENT MONITORING COMMITTEE

No independent monitoring committee (IMC) will be constituted for this phase II trial, considering that risks are limited (standard treatments used according their marketing authorization and with known toxicities) and that the TMG will closely and regularly follow the clinical data and take the decision for study conduct and study amendments and, if required, study termination.

12.3. INDEPENDENT REVIEW COMMITTEE

An independent review committee (IRC) of radiologists will be responsible of reviewing and validating the brain tumor status at 6 months. Investigational sites will be asked to transfer pseudonymized imaging data according to the procedure described in the radiology manual.

13. ETHICAL AND REGULATORY ASPECTS

This clinical trial will be conducted in accordance with the World Medical Association (WMA) Declaration of Helsinki principles, laid down by the 18th WMA Assembly (Helsinki, 1964) and subsequent amendments, and the current ICH guidelines for GCP.
This Clinical Trial will be also conducted in compliance with French and European laws and regulations in force, as well as any applicable guidelines.
The trial will be registered on the European Medicine Agency (EMA) databases and on other sites, as appropriate, including American Food & Drug Administration clinical trial database (FDA - clinicaltrials.gov).

13.1. ETHICS COMMITTEE (EC) AND COMPETENT AUTHORITY (CA)

Prior to its implementation, this Clinical trial will receive the authorization from the Competent Authority in agreement with the Ethics Committee
During the Clinical Trial, any substantial modification (i.e. any change to any aspect of the clinical trial which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated) shall only be implemented if it has been approved, in accordance with the regulation in force, by the appropriate EC and/or Competent Authority depending on the modification.

13.2. INFORMED CONSENT

Prior to a patient's participation in the clinical trial, the investigator (or a medical doctor representing him/her, according to applicable regulatory requirements) shall fully inform the patient of all aspects of the clinical trial that are relevant to the patient's decision to participate as required by local laws and regulations in force. Such information shall be prepared in writing, be available to the patient and adequate time (24 hours minimum) shall be given for the patient to consider his/her decision to participate in the clinical trial.
Informed consent is documented by means of a written, dated and signed Informed Consent Form (ICF). The written ICF should be signed with name and date, personally filled-in by the patient and by the investigator after ensuring that the patient has understood the information.
A copy of the signed and dated written ICF will be provided to the patient.
The investigator must not start any study-related procedure before ICF is duly signed and dated by both, patient and investigator.
The ICF must be revised whenever there are substantial changes to the study protocol/procedures or when new information becomes available that may affect the willingness of the patient to participate. Patients must be re-consented to the most current version of the ICF during their participation in the study (see section 13.7). In case of withdrawal of consent, protocol dispositions will be followed as stated in section 8.4. *Patient premature withdrawal*.
This withdrawal has no impact on the already conducted activities as well as on previous collected data.

13.3. DATA PROTECTION

Personal data will be collected and processed in accordance with laws and regulations in force / Regulation (EC) No 2018/1725 and national data protection legislation implementing Regulation (EU) 2016/679 (General Data Protection Regulation), and repealing Directive 95/46/EC, respectively.
The Coordinating center (DRCI Centre Léon Bérard) committed to the Commission Nationale de l'Informatique et des Libertés (CNIL) to comply to the reference methodology 1 (Méthodologie de Référence MR-001): statement registered under #1994173 the 27/09/2016.
The personal data processing from this clinical trial falls within the scope of the MR-001.
Data protection will be also conducted in compliance with French and European laws and regulations in force, as well as any applicable guidelines.

Arrangements to comply with the applicable rules on the protection of personal data are implemented by the sponsor and coordinating center, including but not limited to:

- Personal data are collected and processed for the sole purpose of this clinical trial;
- Contracts signed between sites, investigators and sponsor include clauses on personal data protection;
- Patients will be identified by a code number and their initials excluding any directly identifying personal data. The matching list is kept on the site by the investigator;
- All the data concerning the patients will be recorded in the eCRF throughout the study. Data entry will be performed online by investigator(s) and authorized staff only. Access to the eCRF is protected with personal access codes;
- Access to the personal data, under sponsor's responsibility and within the legal frame, is restricted to the sponsor and persons acting on its behalf, investigators and their team as well as persons in charge of quality assurance and sponsor's study monitors under required conditions;
- The sponsor is responsible for the collected data processing. In agreement with the European regulations concerning data protection, the General Data Protection Regulation (GDPR), patient's data are carried out in research and public interest. Data will be transferred to French Authorities in conditions ensuring appropriate security, integrity and confidentiality. Personal data will not be transferred outside the European Union. If patientshave any question concerning their data protection, they can contact the investigator or the Data Protection Officer (DPO) at the following address: dpd@lyon.unicancer.fr. If a patient is not satisfied by the reply obtained, he/she can contact the Commission Nationale de l'Informatique et des Libertés (CNIL) using the following link: https://www.cnil.fr/
  In case a patient wants to withdraw from the study, the data collected prior to his/her withdrawal will be processed and will not be deleted. However, no further data will be collected in the database;
- In case a patient wants to withdraw from the study, the data collected prior to his/her withdrawal will be processed and will not be deleted. However, no further data will be collected in the database;
- If the patient retrieves his/her consent, the results obtained before the consent withdrawal will be kept in the database and analysed;
- Patients will be fully informed in the ICF on the study related personal data colleting and processing (nature, purpose, data recipients, use of already collected data in case of study exclusion or withdrawal of consent), their right of access, rectification, erasure, restriction of processing data and opposition. The investigator is the contact person on those matters
- Once the project completed, patients' data will be retained for a maximum of 2 years after the last scientific publication linked to the research project. Then, they will be archived for a maximum of 25 years.
- A specific consent for the future use of the data collected in the course of this study for research programs in the scientific field is also sought. Patients they will be informed that such consent can be rescinded and they can exercise their right to oppose at any time.

13.4. BIOLOGICAL SAMPLES COLLECTION, STORAGE AND FUTURE USE

Biological samples from clinical trial subjects will be collected, stored and used in the future in compliance with the applicable rules, including but not limited to:

- Contracts signed between sites, investigators and sponsor include clauses on collection, storage and future use of biological samples from clinical trial subjects;
- Only qualified personnel will perform the collection in compliance with the protocol and specific study procedures detailed in the Biological samples book;
- Biological samples will be analyzed and stored in approved laboratories; traceability will be insured;
- Patients will be fully informed in the ICF on the study related biological samples collection (nature, purpose, recipients, use of already collected samples in case of study exclusion or withdrawal of consent) and a specific consent for the future use of those samples for research programs in the same field is also sought; they will be informed that such consent can be rescinded at any time.

13.5. RESPONSIBILITIES OF THE SPONSOR

The Sponsor (Centre Léon Bérard) takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial, including but not limited to:

- To publish the trial in the Clinical Trials Information System (CTIS) in the European Union – EMA and get an European drug regulatory authorities EU CT number;
- To subscribe an insurance for compensation for any damage suffered by a subject resulting from participation in the clinical trial which is appropriate to the nature and the extent of the risk;
- To submit the protocol to the appropriate EC and CA for approval/authorization before its implementation as well as if any substantial modification occurs throughout the study;
- To insure the suitability of individuals and sites involved in conducting the clinical trial;
- To provide to the investigator(s) all required information and documents to conduct properly the clinical trial;
- To insure that the clinical trial is conducted in compliance with the protocol and good clinical practice;
- To adequately monitor the conduct of the clinical trial in order to verify that the rights, safety and well-being of subjects are protected, that the reported data are reliable and robust, and that the conduct of the clinical trial is in compliance with the requirements of the regulation and laws in force;
- To insure arrangements for traceability, storage, return and destruction of investigational medicinal product(s), depending on the nature of the clinical trial;
- To notify EMA, CA and Principal Investigators for any SUSAR occurred, in and outside France, with the investigational product(s) or procedure(s) as well as to provide relevant additional information;
- To notify the appropriate EC, CA and Principal Investigators of serious breaches (i.e. likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial) as well as of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not SUSAR;
- To notify the appropriate EC, CA and Principal Investigators of urgent safety measures where an unexpected event is likely to seriously affect the benefit-risk balance;
- To communicate the annual security report (Development Safety Update Report [DSUR]) to theCA, appropriate EC and Principal Investigators;
- To keep a clinical trial master file at all times containing the essential documents relating to the clinical trial, relevant to sponsor's responsibility, and to archive its content during the minimum legal length after the end of the trial;
- To notify serious breaches the CA and the appropriate EC;

- To declare the start and end of the trial and communicate a summary of the results to the EMA, CA appropriate EC within requested time limits.

13.6. RESPONSIBILITIES OF THE INVESTIGATOR

Those Investigators participating in this trial, including National Coordinator and site's principal investigators, will receive compensation for their time but will receive no financial profit from their activities related to the trial.
The investigator is a qualified medical doctor who takes responsibility for the conduct of a clinical trial at a clinical trial site whereas the principal investigator is the responsible leader of a team of investigators.

The principal investigator shall:

- Demonstrate the suitability of the clinical trial site with the conduct of the study (facilities, recruitment potential, personnel qualification, availability…);
- Ensure compliance of the clinical trial at a clinical trial site with the protocol and requirements of the laws and regulations in force as well as any applicable guidelines, including GCP;
- Identify (if necessary) investigators to assist in the conduct of the clinical trial. Qualification of the investigators will be documented in a current curriculum vitae and other relevant documents;
- Assign tasks among the members of the team of investigators in a way which is not compromising the safety of subjects and the reliability and robustness of the data generated in the clinical trial at that clinical trial site. All investigators shall be appointed and listed in a timely manner;
  Under her/his responsibility, clinical research technicians provide administrative and logistic support to the study; assist in the auditing of source records and the documentation of eCRFs;
- Keep a clinical trial master file at all times containing the essential documents relating to the clinical trial, relevant to investigator's responsibility, and to archive its content during the minimum legal length after the end of the trial.

Responsibilities of the investigators include, but are not limited to:

- To ensure compliance with all procedures required by the clinical trial protocol, data collection and GCP;
- To collect subject's written express informed consent;
- To complete eCRF for each enrolled patient, to validate collected data in the eCRFs and if necessary to date, correct and sign DCF (Data Clarification Form);
- To store data and identification of enrolled patients in accordance with current legislation, for the minimal length after the end of the study;
- To record and document, when applicable, any AE or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol;
- To notify immediately any SAEs to Sponsor's PV and coordinating center (DRCI);
- To accept potential visits of control by monitors and inspectors mandated by the sponsor or the NCA.

13.7. PROTOCOL AMENDMENTS

Any modification of the protocol has to be agreed by the coordinating investigator and the sponsor in the form of a written amendment.
Any amendment which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial requires authorization/favorable opinion by CA and/or appropriate EC prior to its implementation unless there are overriding safety reasons.
In some instances, an amendment may require a change to the ICF. The investigator must receive an EC favorable opinion concerning the revised ICF prior to implementation of the change and patient's consent/signature should be collected again if applicable and as soon as possible.

13.8. CONFIDENTIALITY

All information disclosed or provided by Sponsor, or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the eCRFs, and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.
The submission of the Clinical Trial Protocol and other necessary documentation to the relevant Ethics Committees and/or National Competent Authorities is mandatory but their members have the same obligation of confidentiality.
The Investigator and their collaborators shall use the information solely for the purposes of this Clinical Trial, to the exclusion of any use for their own or for a third party's account.
Furthermore, the investigator and the sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study (See 13.3. *Data protection*).

13.9. PROPERTY RIGHTS

All information and documents provided by the sponsor, as well as all the results/data which arise directly or indirectly from the clinical trial are the sole and exclusive property of the sponsor. The investigator shall not mention any information in any application for a patent or for any other intellectual property rights.

13.10. INSURANCE

The sponsor has subscribed an insurance policy in compliance with local laws covering its responsibility for all the participants for any injury that might be caused by the clinical trial (Relyens Mutual Insurance18 rue Edouard Rochet 69372 LYON Cedex 08 – police 142883 - see the Investigator Master File). The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy.

14. REPORTING AND PUBLICATIONS

A clinical study report will be prepared under the responsibility of the sponsor. It will include the study objectives, the methodology, statistical analysis of primary and secondary endpoints as well as raw data listings, and the conclusions of the study. It will be submitted to the coordinating investigator for review and signature. The clinical study report will be prepared and will be available for health authorities within one year after the end of the study. Irrespective of the outcome of the clinical trial, the sponsor shall submit to EC, CA and EU database, within the same deadline, the summary of the results of the clinical trial containing regulatory required information in force at the time.
The manuscript of the publication will be prepared within the 6 months following the publication of the final clinical study report by the principal investigator, or upon agreement.
Investigators are informed that the sponsor reserves all rights to data generated from this study. Written approval from the sponsor must be obtained prior to any publication or presentation of data from this study.
The sponsor is not allowed to use investigator's name in any publication without a prior written consent. The investigator is not allowed to use sponsor's name in any publication without a prior written consent.
The coordinating investigator agrees to publish the results. No publication can be done without the coordinating investigator and the Sponsor approval; the funding source will be mentioned in the acknowledgments section.
The final decision for the publication of the study will be taken by the coordinating investigator and the sponsor.

Any publication or communication (oral or written) will be defined by mutual agreement between the investigators according to international guidelines (http://www.icmje.org/). All the authors who participated actively to the conception of the study, its development and writing of results will be cited, i.e.:

- The coordinating investigators and all principal investigators who have included and followed patients. The order of citation will be established according to the number of inclusion in the study.
- The contributors of the coordinating center team (DRCI-Sponsorship Unit) who participated in the drafting of the protocol, the statistical analysis of the study and the scientific papers writing.
- The Centre Léon Bérard will be cited as Sponsor of the study.
- Funding source(s) will be specified (IPSEN).

15. REFERENCES

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APPENDICES

APPENDIX 1 - RANO-BM criteria

APPENDIX 2 - Cabozantinib SPC

APPENDIX 3 - ECOG PERFORMANCE STATUS

APPENDIX 4 - NCI-CTC AE V.4.0

APPENDIX 1 – RANO-BM CRITERIA

For evaluation of parenchymal brain metastases

Measurable disease = contrast-enhancing lesion with:

- the longest diameter ≥ 10 mm in one dimension, visible on two or more axial slices that are at most 5 mm apart with 0-mm skip
- the diameter perpendicular to the longest diameter in the plane of measurement ≥ 5 mm

If MRI is performed with thicker slices, size of a measurable lesion at baseline should be two times the slice thickness. Cavities or cysts are considered non-measurable unless there is a nodular component measuring > 10 mm in longest diameter and > 5 mm in the perpendicular plane.

Non-Measurable disease

All other lesions, including lesions with longest dimension < 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, and leptomeningeal disease.

Tumor Response Evaluation

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five will be identified as target lesions. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD)

Evaluation of Target Lesions

- *Complete response (CR):* Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically
- *Partial response (PR):* At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
- *Progressive disease (PD):* At least a 20% increase in the sum LD of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
- *Stable disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the small sum LD while on study.

Non-target lesions

Non-target lesions should be assessed qualitatively at each of the timepoints specified in the protocol.

- *Complete response:* Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
- *Non-complete response or non-progressive disease:* Persistence of one or more non-target CNS lesion or lesions.
- *Progressive disease:* Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumour-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

Summary of the response criteria for CNS metastases proposed by RANO-BM

Criterion	CR	PR	SD	PD
Target lesions	None	≥ 30% decrease in sum LD relative to baseline!	< 30% decrease relative to baseline but < 20% increase in sum LD relative to nadir	≥ 20% increase in sum LD relative to nadir!
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s) †	None	None	None	Present
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable**
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any**

*Progression occurs when this criterion is met.

†A new lesion is one that not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression.

**Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

APPENDIX 2 – CABOZANTINIB SPC

The latest version of the summary of product characteristics of cabozantinib is available on the European Medicines Agency website.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=

In English
https://www.ema.europa.eu/documents/product-information/cabometyx-epar-product-information_en.pdf

In French
https://www.ema.europa.eu/documents/product-information/cabometyx-epar-product-information_fr.pdf

APPENDIX 3 – ECOG PERFORMANCE STATUS

Score	Activity
0	Asymptomatic (full active, able to carry on all predisease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5	Death

APPENDIX 4 - NCI-CTC AE V.5.0

Refer to NCI CTC AE v.5.0 online at the following NCI website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v50.

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.

Common Terminology Criteria for Adverse Events v5.0
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