CLINICAL STUDY PROTOCOL

BONSAI (ca**B**ozantinib in c**O**llecti**N**g duct**S** renal cell c**A**rc**I**noma)

Protocol Number:	**BONSAI**
Indication:	Advanced or Metastatic Collecting ducts renal cell carcinoma
Phase:	II
Sponsor	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy Gruppo Cooperativo Meet-Uro (codice progressivo studio: 02) Meet-Uro ITALIAN NETWORK FOR RESEARCH IN UROLOGIC ONCOLOGY
Therapeutic Area:	Medical Oncology
EudraCT number:	2017-003103-22

Protocol History	
Original	Version 1.1, date 23/11/2017

Investigator and Study Center:

Doctor Giuseppe Procopio
Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori
Via G. Venezian 1
20133 Milano, Italy
Telephone: +39-02-23904450

This is an investigator-initiated study. The principal investigator Dr. Giuseppe Procopio (who may also sometimes be referred to as the sponsor-investigator) is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

TITLE:	**Cabozantinib in Collecting Duct Renal Cell Carcinoma (BONSAI study)**
PRINCIPAL SITE:	s.c. Oncologia Medica 1-SS.Oncologia Genitourinaria- Fondazione IRCCS Istituto Nazionale dei Tumori Via G. Venezian n. 1, 20133 Milano – Italy
NUMBER OF CENTERS:	1
CLINICAL PHASE:	Phase II trial
INDICATION:	Metastatic Collecting Duct Renal Cell Carcinoma
RATIONALE:	Collecting duct carcinoma (CDC) accounts for 1-3% of all renal cell carcinomas (RCC), and it is characterized by an aggressive course and extremely poor prognosis. Treatments that are commonly effective in other forms of RCC are much less effective in CDC. Despite the fact that published reports suggest some level of activity of VEGF-targeted agents, overall their clinical impact is poor. In particular, we previously reported on 13 cases of advanced CDC patients treated with first-line targeted agents, including sorafenib, temsirolimus and sunitinib. Ten patients developed early disease progression, while only 3 patients showed long-lasting disease control with sorafenib and temsirolimus [*Procopio G et al., Anticancer Res 2014*]. For these reasons, paradigmatically new, effective treatment options are urgently needed for this highly aggressive form of RCC. Among the therapies under study, immunotherapy is emerging as a possible effective one, also based on the histological similarities between CDC and urothelial carcinomas. In particular, the recently demonstrations of superior antitumor efficacy of immune checkpoint inhibitors on standard chemotherapy in urothelial carcinomas may anticipate a similar efficacy in CDC [*Powles T et al., Nature 2014*]. However, apart from the histological similarities between the two types of tumors, the rationale behind the use of immune checkpoint inhibitors in CDCs is lacking [*Pecuchet N et al., Annal Oncol 2013; Procopio G et al., Clin Exp Nephrol. 2012*]. As compared to other RCC subtypes, whose genetics have been extensively analyzed and crucial proliferative and metabolic pathways have been identified, no studies have been performed so far to investigate genome-wide genetic and metabolic driving alterations in this disease. Studies performed in the last few years did not lead to the identification of prognostic/predictive biomarkers, with the exception of the gene c-erbB-2 amplification, which is found in about 50% of patients and correlates with poorer prognosis [*Selli C et al., J Urol 1997*]. Identifying the biological pathways that are responsible for cancer cell proliferation, apoptosis evasion, and resistance/sensitivity to specific cytotoxic and/or molecular-targeted therapies, is crucial to individualize the treatment and optimize clinical results.

	Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodeling, drug resistance, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2. The safety and efficacy of cabozantinib were evaluated in a randomized, open-label, multicenter Phase 3 study (namely the METEOR study) [*Choueiri TK et al., N Engl J Med 2015*]. A statistically significant improvement in progression-free survival (PFS) was demonstrated for cabozantinib compared to everolimus. A planned interim analysis of overall survival (OS) was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (HR=0.68 [0.51, 0.90], p=0.006). In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for patients randomized to cabozantinib as compared with everolimus (median of 21.4 months vs. 16.5 months; HR=0.66 [0.53, 0.83], p=0.0003) [*Choueiri TK et al., Lancet Oncol 2016*]. In a recent phase 2 trial, cabozantinib has also produced an advantage, in terms of objective response rate (ORR) and PFS, over sunitinib in the first-line treatment of RCC patients with poor-intermediate risk according to IMDCC criteria (CABOSUN trial) [*Choueiri TK et al., J Clin Oncol 2017*]. On the basis of preliminary, promising data, and due to its high-spectrum biological activity against multiple, and non-redundant, oncogenic pathways, cabozantinib may be superior to other angiogenesis inhibitors, especially in the treatment of rarer histologies of RCC, such as CDCs, which are commonly associated with a worse prognosis. In addition, cabozantinib, as most antiangiogenics [*Vanneman and Dranoff, Nature Rev Cancer 2016]*, may promote changes in the immunological features of CDC and associated immune microenvironment, favoring the onset of a more effective immunosurveillance or improving sensitivity to immunotherapeutic strategies including immune checkpoint inhibitors. Hypothesis: • due to the possible high mutational burden of CDC, the multi-kinase inhibitor Cabozantinib might be active to block multiple intracellular signal transduction pathways and achieve good response rates; • clinical responses may translate into significant improvements in PFS and, hopefully, of OS; • correlation between objective responses and the mutational status of crucial oncogenes and tumor suppressor genes may reveal novel predictive biomarkers; • cabozantinib may improve the immunogenicity of CDC or

	decrease the immunosuppressive properties either by acting directing on tumor pathways or interfering with immune responses.
OBJECTIVES:	The primary objective of this study is: • To evaluate activity of Cabozantinib in terms of ORR according to the RECIST 1.1 criteria. The secondary objectives of this study are: • to evaluate PFS and OS; • to evaluate tolerability of Cabozantinib.
EXPLORATORY ENDPOINTS	The exploratory objectives of this study are: • to identify the somatic mutation profiles in CDC on disease associated targets by NGS; • to identify transcript fusions of selected genes by performing a RNA sequencing; • to monitor the immunological properties of tumor cells and the state of circulating immune cells, to assess the modulating activity of cabozantinib on local and systemic tumor immunity.
TRIAL DESIGN:	This is a single-arm, phase II trial.
NUMBER OF PATIENTS:	23
PATIENT POPULATION:	Patients with histological diagnosis of CDC with untreated locally advanced or metastatic disease.
INCLUSION CRITERIA:	1. Written Informed Consent Form 2. Unresectable, advanced or metastatic collecting ducts carcinoma untreated with any systemic agent for advanced disease 3. Measurable disease as defined by RECIST v1.1 criteria 4. Age ≥18 years 5. ECOG Performance Status 0-1 6. Any of the following laboratory test findings: - Hemoglobin > 9 g/dL (5.6 mmol/L) - WBC > 2,000/mm3 - Neutrophils > 1,500/mm3 - Platelets > 100,000/mm3 - AST or ALT < 3 x ULN (< 5 x ULN if liver metastases are present) - Total Bilirubin < 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL) - Serum creatinine < 1.5 x upper limit of normal (ULN) or

	creatinine clearance ≥ 40 mL/min (measured or calculated by Cockroft-Gault formula) - Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis - PT-INR/PTT ≤ 1.5 x upper limit of normal [Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.] For patients on warfarin, close monitoring of at least weekly evaluations will be performed, until INR is stable based on a measurement at pre-dose, as defined by the local standard of care. 7. Availability of a representative FFPE tumor specimen collected within 24 months of starting first-line cabozantinib that enables the definitive diagnosis of CDC (the archival specimen must contain adequate viable tumor tissue to enable candidate biomarkers status; the specimen may consist of a tissue block or at least 15 unstained serial sections; for core needle biopsy specimens, at least two cores should be available for evaluation) 8. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the study and for 4 months after the last dose of study treatment 9. Female subjects of childbearing potential must not be pregnant at screening
EXCLUSION CRITERIA:	1. Previous therapy for advanced disease; any medical adjuvant treatment must have been stopped at least six months before entry into the study 2. History of any one or more of the following cardiovascular conditions within the past 6 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, symptomatic peripheral vascular disease, Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) 3. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]. 4. History of cerebrovascular accidents, including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible 5. Major surgery or trauma within 28 days before to study entry; the

	presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major surgery). 6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. 7. Evidence of active bleeding or bleeding diathesis and/or clinically-significant GI bleeding within 6 months before the first dose of study treatment; 3 months for pulmonary hemorrhage and patients with tumor invading or encasing any major blood vessels. 8. Patients with GI disorders associated with a high risk of perforation or fistula formation. 9. Subjects with clinically relevant ongoing complications from prior radiation therapy. 10. Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with subject's safety, provision of informed consent, or compliance to study procedures. 11. Previous or ongoing treatment (except for adjuvant therapies) with any of the following anti-cancer therapies: chemotherapy, immunotherapy, target therapies, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of Cabozantinib 12. Inability to swallow tablets or capsules. 13. Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
DURATION OF STUDY:	The treatment will be continued until disease progression or unacceptable toxicity.
TREATMENT ADMINISTRATION	Cabozantinib will be administered orally at a dose of 60 mg/day.
SAMPLE SIZE, ANALYSIS METHODS:	This is a single-arm phase II trial enrolling patients with histological diagnosis of CDC with untreated locally advanced or metastatic disease. The Simon's two-stage optimal design will be applied. In order to reject an ORR equal to 15% with a one-sided alpha error of 10% and to detect an ORR equal to 35% with a power of 80% 9 patients will be enrolled in the first stage. If at least 2 responses will be observed in the first stage other 14 patients will be enrolled in the second stage. If at least 6 responses will be collected after the second stage the interesting activity of Cabozantinib will be proved.

INDEX

FLOW CHART

		Treatment period				
	Baseline -28 to 0 day	At each cycle	Every 3 cycles	End of Treatment	Follow up	Survival
Informed Consent	X					
Demography	X					
Inclusion/Exclusion criteria	X					
Diagnosis	X					
Prior therapy	X					
History/Progress Notes	X			X		
Physical Exam (including weight)	X	X		X	X	
Vitals signs[a]	X	X		X	X	
Performance Status ECOG/Karnofsky	X	X		X	X	
Treatment Toxicity		X		X		
CBC, chemistries, LFTs	X	X		X		
Pregnancy test[b]	X	X		X		
Thyroid function test	X	X		X		
Coagulation test	X			X		
Biomarker analysis[c]	X	(X)		X		
Urinalysis[d]	X		X			
ECG	X		X			
ECHO or MUGA	X					
Drug accountability/dispensing		X				
Prior/concomitant medications	X	X				
Adverse Events		X		X		
CT scan /MRI[e]	X		X			
Bone scan[f]	(X)		(X)			
Anti-neoplastic therapies since discontinuation of study drug				X	X	X
Survival data					X	X

[a]Vital sign: Weight, height, blood preassure, HR, temperature

[b]Pregnancy test: only for female subjects of childbearing potential. It will performed at baseline, at each cycles and at the end of treatment .

[d]Urinalysis (dipstick): (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase,Nitrite, pH, Protein, Specific Gravity, Urobilinogen). Proteinuria 24 hours is requested if protein are positive at dipstick..

[c]Biomarker analysis: identification of somatic mutation profiles in CDC of selected gene panels and assessment of the mutational load by performing a clinical exome analysis (only at baseline); identification of transcript fusions of selected genes by performing a RNA sequencing evaluation (only at baseline); evaluation of the circulating immune cell profile as a potential predictive biomarker of clinical response at baseline, at cycle 1 day 28 , after cycle3 and at the end of treatment or progression disease.

[e]CT scan /MRI: A chest/abdominal/pelvic CT scan or MRI will be performed at baseline and every 3 cycles (time window for the scans is +/- 7 days). The same imaging modalities are to be used as were used at baseline. CT or MRI of the head must be conducted to rule out brain metastasis (at screening).

[f]Bone scan: is not mandatory at baseline, but should be obtained if bone metastases are suspected or documented. If bone metastases at baseline are confirmed, patients will repeat bone scan every 3 cycles.

LIST OF ABBREVIATIONS

(Update with additional abbreviations/remove un-used abbreviations as necessary.)

Abbreviation	Definition
°C	degrees Celsius
µM	micromolar
AE	adverse event
ANC	absolute neutrophil count
cm	centimeter
CR	complete response
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ht	height
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
kg	kilogram
m^2	square meters
mg	milligram
min	minute
mL	milliliter
mm^3	cubic millimeters
mmol	millimole
MTD	maximum tolerated dose
NCI	National Cancer Institute
ng	nanogram
nM	nanomole
PFS	progression free survival
PR	partial response
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
w/w	weight-to-weight ratio
WHO	world health organization
wt	weight

INTRODUCTION AND STUDY RATIONALE

1.1 Study rationale

Collecting duct carcinoma (CDC) accounts for 1-3% of all renal cell carcinomas (RCC), and it is characterized by an aggressive course and extremely poor prognosis. Treatments that are commonly effective in other forms of RCC are much less effective in CDC.

Despite the fact that published reports suggest some level of activity of VEGF-targeted agents, overall their clinical impact is poor. In particular, we previously reported on 13 cases of advanced CDC patients treated with first-line targeted agents, including sorafenib, temsirolimus and sunitinib. Ten patients developed early disease progression, while only 3 patients showed long-lasting disease control with sorafenib and temsirolimus.

For these reasons, paradigmatically new, effective treatment options are urgently needed for this highly aggressive form of RCC. Among the therapies under study, immunotherapy is emerging as a possible effective one, also based on the histological similarities between CDC and urothelial carcinomas. In particular, the recently demonstrations of superior antitumor efficacy of immune checkpoint inhibitors on standard chemotherapy in urothelial carcinomas may anticipate a similar efficacy in CDC. For example, a clinically significant tumor response to nivolumab has been reported in a case of CDC. However, apart from the histological similarities between the two types of tumors, the rationale behind the use of immune checkpoint inhibitors in CDCs is lacking.

As compared to other RCC subtypes, whose genetics have been extensively analyzed and crucial proliferative and metabolic pathways have been identified, no studies have been performed so far to investigate genome-wide genetic and metabolic driving alterations in this disease. Studies performed in the last few years did not lead to the identification of prognostic/predictive biomarkers, with the exception of the gene c-erbB-2 amplification, which is found in about 50% of patients and correlates with poorer prognosis.

As demonstrated in recent years in several types of human malignancies, such as colorectal and lung cancer, identifying the biological pathways that are responsible for cancer cell proliferation, apoptosis evasion, and resistance/sensitivity to specific cytotoxic and/or molecular-targeted therapies, is crucial to individualize the treatment and optimize clinical results.

Cabozantinib (CABOMETYX®) is an inhibitor of multiple kinases, including VEGFR 2, MET and AXL, which has been recently approved for the treatment of advanced RCC previously treated with angiogenesis inhibitor.

In a randomized, phase 3 trial comparing cabozantinib with everolimus (namely the METEOR study), cabozantinib demonstrated notable activity and clinically meaningful superiority in terms of ORR, PFS and OS as compared to everolimus. In a recent phase 2 trial, cabozantinib has also produced an advantage, in terms of ORR and PFS, over sunitinib in the first-line treatment of RCC patients with poor-intermediate risk according to IMDCC criteria (CABOSUN trial).

On the basis of preliminary, promising data, and due to its high-spectrum biological activity against multiple, and non-redundant, oncogenic pathways, cabozantinib may be superior to other angiogenesis inhibitors, especially in the treatment of rarer histologies of RCC, such as CDCs, which are commonly associated with a worse prognosis.

Hypothesis:

- Due to the possible high mutational burden of CDC, the multi-kinase inhibitor Cabozantinib might prove active to block multiple intracellular signal transduction pathways and achieve good response rates.
- Clinical responses may translate into significant improvements in PFS and, hopefully, of OS.

- Correlation between objective responses and the mutational status of crucial oncogenes and tumor suppressor genes, may reveal novel predictive biomarkers in CDCs.
- Cabozantinib may improve the immunogenicity of CDC or decrease the immunosuppressive properties either by acting directing on tumor pathways or interfering with immune responses.

1.2 Drug background

The safety and efficacy of cabozantinib were evaluated in a randomized, open-label, multicenter Phase 3 study. Patients (N=658) with advanced RCC with a clear cell component who had previously received at least 1 prior VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) were randomized (1:1) to receive cabozantinib (N=330) or everolimus (N=328). Patients could have received other prior therapies, including cytokines, and antibodies targeting VEGF, the programmed death 1 (PD-1) receptor, or its ligands. Patients with treated brain metastases were allowed. Progression-free survival (PFS) was assessed by a blinded independent radiology review committee, and the primary analysis was conducted among the first 375 subjects randomized. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumor assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter.

The baseline demographic and disease characteristics were similar between the cabozantinib and everolimus arms. The majority of the patients were male (75%), with a median age of 62 years. Seventy-one percent (71%) received only one prior VEGFR TKI; 41% of patients received sunitinib as their only prior VEGFR TKI. According to the Memorial Sloan Kettering Cancer Center criteria for prognostic risk category, 46% were favorable (0 risk factors), 42% were intermediate (1 risk factor), and 13% were poor (2 or 3 risk factors). Fifty-four percent (54%) of patients had 3 or more organs with metastatic disease, including lung (63%), lymph nodes (62%), liver (29%), and bone (22%). The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving cabozantinib and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

A statistically significant improvement in PFS was demonstrated for cabozantinib compared to everolimus (Figure 1 and Table 1). A planned interim analysis of OS was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (HR=0.68 [0.51, 0.90], p=0.006). In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for patients randomized to cabozantinib as compared with everolimus (median of 21.4 months vs. 16.5 months; HR=0.66 [0.53, 0.83], p=0.0003; Figure 2).

Exploratory analyses of PFS and OS in the ITT population have also shown consistent results in favour of cabozantinib compared to everolimus across different subgroups according to age (<65 vs. ≥65, sex, MSKCC risk group (favourable, intermediate, poor), ECOG status (0 vs. 1), time from diagnosis to randomisation (<1 year vs. ≥1 year), tumour MET status (high vs. low vs. unknown), bone metastases (absence vs. presence), visceral metastases (absence vs. presence), visceral and bone metastases (absence vs. presence), number of prior VEGFR-TKIs (1 vs. ≥2), duration of first VEGFR-TKI (≤6 months vs. >6 months).

Objective response rate findings are summarized in Table 2.

Figure 1: Kaplan Meier curve for progression-free survival by independent radiology review committee (first 375 randomized)

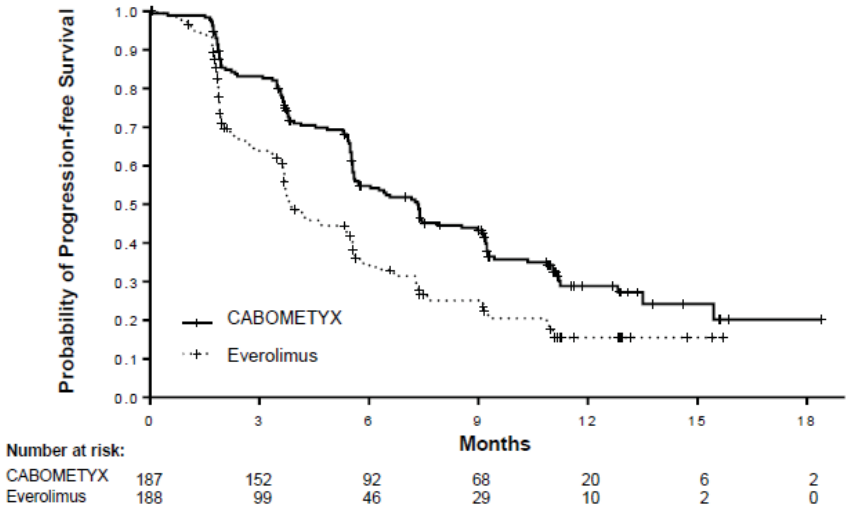

Table 1: Summary of PFS findings by independent radiology review committee

	Primary PFS analysis Population		Intent-To-Treat Population	
Endpoint	**CABOMETYX**	**Everolimus**	**CABOMETYX**	**Everolimus**
	N = 187	N = 188	N = 330	N = 328
Median PFS (95% CI), months	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)	7.4 (6.6, 9.1)	3.9 (3.7, 5.1)
HR (95% CI), p-value[1]	0.58 (0.45, 0.74), p<0.0001		0.51 (0.41, 0.62), p<0.0001	

[1] stratified log-rank test

Figure 2: Kaplan-Meier curve of overall survival

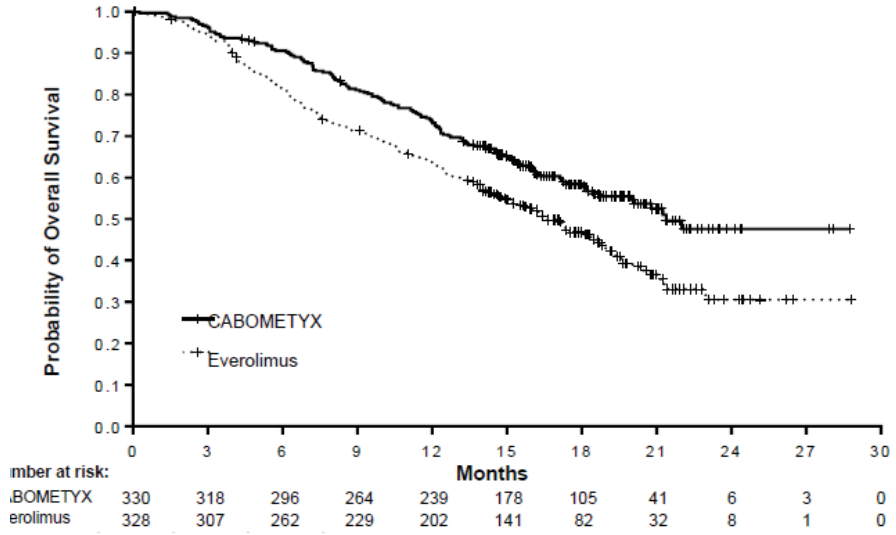

Table 2: Summary of ORR findings per independent radiology committee review (IRC) and investigator review

	Primary Analysis ORR Intent-To-Treat Population (IRC)		ORR per Investigator Review Intent-To-Treat Population	
Endpoint	**CABOMETYX**	**Everolimus**	**CABOMETYX**	**Everolimus**
	N = 330	N = 328	N = 330	N = 328
ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)	24% (19%, 29%)	4% (2%, 7%)
p-value[1]	p<0.0001		p< 0.0001	
Partial Response	17%	3%	24%	4%
Median time to First Response, months (95% CI)	1.91 (1.6, 11.0)	2.14 (1.9, 9.2)	1.91 (1.3, 9.8)	3.50 (1.8, 5.6)
Stable Disease as Best Response	65%	62%	63%	63%
Progressive Disease as Best Response	12%	27%	9%	27%

[1] chi-squared test

1.3 Safety Pharmacology, Toxicology and Drug Metabolism

1.3.1 Absorption

Following oral administration of cabozantinib, peak cabozantinib plasma concentrations are reached at 2 to 3 hours post-dose. Plasma-concentration time profiles show a second absorption peak approximately 24 hours after administration, which suggests that cabozantinib may undergo enterohepatic recirculation.

Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in an approximately a 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state is achieved by approximately Day 15.

A high-fat meal moderately increased Cmax and AUC values (41% and 57%, respectively) relative to fasted conditions in healthy volunteers administered a single 140 mg oral cabozantinib dose. There is no information on the precise food-effect when taken 1 hour after administration of cabozantinib.

Bioequivalence could not be demonstrated between the cabozantinib capsule and tablet formulations following a single 140 mg dose in healthy subjects. A 19% increase in the Cmax of the tablet formulation (CABOMETYX) compared to the capsule formulation (COMETRIQ) was observed. A less than 10% difference in the AUC was observed between cabozantinib tablet (CABOMETYX) and capsule (COMETRIQ) formulations.

1.3.2 Distribution

Cabozantinib is highly protein bound *in vitro* in human plasma (≥ 99.7%). Based on the population-pharmacokinetic (PK) model, the volume of distribution (Vz) is approximately 319 L (SE: ± 2.7%). Protein binding was not altered in subjects with mild or moderately impaired renal or hepatic function.

1.3.3 Biotransformation

Cabozantinib was metabolized *in vivo*. Four metabolites were present in plasma at exposures (AUC) greater than 10% of parent: XL184-N-oxide, XL184 amide cleavage product, XL184 monohydroxy sulfate, and 6-desmethyl amide cleavage product sulfate. Two non-conjugated metabolites (XL184-N-oxide and XL184 amide cleavage product), which possess <1% of the on-target kinase inhibition potency of parent cabozantinib, each represent <10% of total drug-related plasma exposure.

Cabozantinib is a substrate for CYP3A4 metabolism *in vitro*, as a neutralizing antibody to CYP3A4 inhibited formation of metabolite XL184 N-oxide by >80% in a NADPH-catalyzed human liver microsomal (HLM) incubation; in contrast, neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. A neutralizing antibody to CYP2C9 showed a minimal effect on cabozantinib metabolite formation (ie, a <20% reduction).

1.3.4 Elimination

In a population PK analysis of cabozantinib using data collected from 318 patients with RCC and 63 normal healthy volunteers following oral administration of doses of 60 mg, 40 mg, and 20 mg, the plasma terminal half-life of cabozantinib is approximately 99 hours. Mean clearance (CL/F) at steady-state was estimated to be 2.2 L/hr. Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy volunteers, approximately 81% of the total administered radioactivity was recovered with 54% in faeces and 27% in urine.

1.3.5 Pharmacokinetics in special patient populations

Renal impairment

Results from a study in patients with renal impairment indicate that the ratios of geometric LS mean for plasma cabozantinib, Cmax and AUC0-inf were 19% and 30% higher, for subjects with mild renal impairment (90% CI for Cmax 91.60% to 155.51%; AUC0-inf 98.79% to 171.26%) and 2% and 6-7% higher (90% CI for Cmax 78.64% to 133.52%; AUC0-inf 79.61% to 140.11%), for subjects with moderate renal impairment compared to subjects with normal renal function. Patients with severe renal impairment have not been studied.

Hepatic impairment

Results from a study in patients with hepatic impairment indicate that exposure (AUC0-inf) increased by 81% and 63% in subjects with mild and moderate hepatic impairment, respectively (90% CI for AUC0-inf:

121.44% to 270.34% for mild and 107.37% to 246.67% for moderate). Patients with severe hepatic impairment have not been studied.

Race

A population PK analysis did not identify clinically relevant differences in PK of cabozantinib based on race.

Detailed information regarding the nonclinical pharmacology and toxicology of cabozantinib may be found in the IB.

1.4 Summary of safety profile

The most common serious adverse reactions associated with cabozantinib are abdominal pain (3%), pleural effusion (3%), diarrhoea (2%), and nausea (2%). The most frequent adverse reactions of any grade (experienced by at least 25% of patients) included diarrhoea (74%), fatigue (56%), nausea (50%), decreased appetite (46%), palmar-plantar erythrodysaesthesia syndrome (PPES) (42%), hypertension (37%), vomiting (32%), weight decreased (31%), and constipation (25%).

Adverse reactions are listed in Table 3 according to MedDRA system organ class and frequency categories. Frequencies are based on all grades and defined as: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), guidelines.

Table 3: Adverse reactions reported with cabozantinib

MedDRA System Organ Class	Very Common	Common	Uncommon
Infections and infestations		abscess	
Blood and lymphatic disorders	anaemia		
Endocrine disorders	hypothyroidism		
Metabolism and nutrition disorders	decreased appetite, hypophosphataemia, hypoalbuminaemia, hypomagnesaemia, hyponatraemia, hypokalaemia, hyperkalaemia, hypocalcaemia, hyperbilirubinemia	dehydration	
Nervous system disorders	dysgeusia, headache, dizziness		convulsion
Ear and labyrinth disorders		tinnitus	
Vascular disorders	hypertension	pulmonary embolism	
Respiratory, thoracic, and mediastinal disorders	dysphonia, dyspnea, cough		
Gastrointestinal disorders	diarrhoea, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia	abdominal pain upper, gastrooesophageal reflux disease, haemorrhoids	anal fistula, pancreatitis
Hepatobiliary disorders			hepatitis

			cholestatic
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome, rash, dry skin	pruritus, alopecia	
Musculoskeletal and connective tissue disorders	pain in extremity, muscle spasms, arthralgia		osteonecrosis of the jaw
Renal and urinary disorders	proteinuria		
General disorders and administration site conditions	fatigue, mucosal inflammation, asthenia	peripheral oedema	
Investigations	weight decreased, serum ALT, AST, and ALP increased, creatinine increased, triglycerides increased, hyperglycaemia, hypoglycaemia, lymphopenia, neutropenia, thrombocytopenia, GGT increased, amylase increased, blood cholesterol increased, lipase increased		

STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- to evaluate activity of cabozantinib in terms of objective response rate (ORR) according to the RECIST 1:1 criteria.

2.2 Secondary Objectives

The secondary objectives of this study are:

- to evaluate progression free survival (PFS) and overall survival (OS);
- to evaluate tolerability of cabozantinib.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- to identify the somatic mutation profiles in CDC on disease associated targets by NGS;
- to identify transcript fusions of selected genes by performing a RNA sequencing;
- to monitor the immunological properties of tumor cells and the state of circulating immune cells, to assess the modulating activity of cabozantinib on local and systemic tumor immunity.

STUDY DESIGN

This is, single-arm, monocentric, phase II trial, enrolling patients with histological diagnosis of collecting duct carcinoma of the kidney with untreated locally advanced or metastatic disease who will be treated with cabozantinib.

This study will involve the collection of a pre-existing archival primary and metastatic FFPE tumour specimen, if there is material available, following written consent.

The study will also involve collection of a blood sample taken at the commencement of treatment, at the first cycle, after cycle 3 and at the end of treatment or progression of disease, to be used for research purposes as described below.

With the patient's written consent, clinicopathogical and demographic data will be retrospectively collected and clinical outcome data will be prospectively collected.

STUDY POPULATION

4.1 Selection of study population

Patients with histological diagnosis of CDC with untreated locally advanced or metastatic disease.

4.2 Number of patients

The total number of patients to be enrolled on this study is 23.

Enrollment is defined as the first day of cabozantinib treatment (i.e. Day 1 of Cycle 1).

4.3 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care;
- histologically confirmed diagnosis of collecting ducts renal cell carcinoma;
- age ≥18 years;
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1;
- unresectable, advanced or metastatic collecting ducts carcinoma untreated with any systemic agent for advanced disease;
- measurable disease as defined by RECIST v1.1 criteria;
- Any of the following laboratory test findings:
  - Hemoglobin > 9 g/dL (5.6 mmol/L)
  - WBC > 2,000/mm3
  - Neutrophils > 1,500/mm3
  - Platelets > 100,000/mm3
  - AST or ALT < 3 x ULN (< 5 x ULN if liver metastases are present)
  - Total Bilirubin < 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
  - Serum creatinine < 1.5 x upper limit of normal (ULN) or creatinine clearance ≥ 40 mL/min (measured or calculated by Cockroft-Gault formula)
  - Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis
  - PT-INR/PTT ≤ 1.5 x upper limit of normal [Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.] For patients on warfarin, close monitoring of at least weekly evaluations will be performed, until INR is stable based on a measurement at pre-dose, as defined by the local standard of care.
- Availability of a representative FFPE tumor specimen collected within 24 months of starting first-line cabozantinib that enables the definitive diagnosis of CDC (the archival specimen must contain adequate viable tumor tissue to enable candidate biomarkers status; the specimen may consist of a tissue block or at least 15 unstained serial sections; for core needle biopsy specimens, at least two cores should be available for evaluation).
- Female subject is either:
  - post-menopausal for at least one year before the screening visit, or
  - surgically sterilized, or
  - willing to use an acceptable method of birth control (ie, a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.

- Male subject, even if surgically sterilized (ie, status postvasectomy), agrees to use an acceptable method for contraception during the entire study treatment period through 4 months after the last dose of cabozantinib.
- Patients must be accessible for treatment and follow up as well as they must be willing and capable to comply with the requirements of the study.

4.4 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

- Previous therapy for advanced disease; any medical adjuvant treatment must have been stopped at least six months before entry into the study.
- History of any one or more of the following cardiovascular conditions within the past 6 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, symptomatic peripheral vascular disease, Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)
- Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].
- History of cerebrovascular accidents, including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible.
- Major surgery or trauma within 28 days before to study entry; the presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major surgery).
- Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization.
- Evidence of active bleeding or bleeding diathesis and/or clinically-significant GI bleeding within 6 months before the first dose of study treatment; 3 months for pulmonary hemorrhage and patients with tumor invading or encasing any major blood vessels.
- Patients with GI disorders associated with a high risk of perforation or fistula formation.
- Subjects with clinically relevant ongoing complications from prior radiation therapy.
- Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.
- Previous or ongoing treatment (except for adjuvant therapies) with any of the following anti-cancer therapies: chemotherapy, immunotherapy, target therapies, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of cabozantinib.
- Inability to swallow tablets or capsules.

Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

STUDY TREATMENTS

5.1 Preparation, Handling and Storage of Drugs

As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator.

5.2 Cabozantinib administration and Dosage Schedule

In this protocol cabozantinib will be administered at the recommended dose of 60 mg once daily.

Patients will receive study treatment until the evidence of disease progression or onset of unacceptable toxicity.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

The study drug (cabozantinib) will be provided by IPSEN and will be re-labeled at the pharmacy Fondazione IRCCS Istituto Nazionale dei Tumori.

5.3 Dose Modification and Delay

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective 14 June 2010.

These criteria are provided in the Study Manual and are available online at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

To manage excessive toxicity, reduction of the total cabozantinib dose can be done by reducing the daily dose administered and/or by interruption of the schedule treatment within a cycle.

When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Table 4).
If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose.

Table 4: Recommended CABOMETYX dose modifications for adverse reactions

Adverse reaction and severity	Treatment modification
Grade 1 and 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 non-relevant laboratory abnormalities)	Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose.

Grade 4 adverse reactions (except clinically non-relevant 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 CABOMETYX.

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4)

5.4 Excluded Concomitant Medications and Procedures

The initiation of any non-protocol specific anti tumour therapy or surgery is considered an indication of disease progression whereby study treatment should be terminated. Patients who require palliative radiotherapy or initiation of biphosphonates during therapy should be evaluated carefully for possible disease progression before starting these treatments.

Prior and Concomitant Therapy

All medication, which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator. All concomitant medications (including start/stop dates, dose frequency, route of administration and indication) must be recorded in the patient's source documentation, as well as in the appropriate pages of the CRF.

Cabozantinib is a CYP3A4 substrate. Concurrent administration of cabozantinib with the strong CYP3A4 inhibitor ketoconazole resulted in an increase in cabozantinib plasma exposure. Caution is required when administering cabozantinib with agents that are strong CYP3A4 inhibitors. Concurrent administration of cabozantinib with the strong CYP3A4 inducer rifampicin resulted in a decrease in cabozantinib plasma exposure. Therefore chronic administration of agents that are strong CYP3A4 inducers with cabozantinib should be avoided. Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Co-administration of proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers resulted in no clinically-significant effect on plasma cabozantinib exposure (AUC). No dose adjustment is indicated when gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) are co-administered with cabozantinib.

Cabozantinib was an inhibitor (IC50 = 7.0 μM), but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine) should be approached with caution.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The following medications and procedures are prohibited during the study:

- Anticancer chemotherapy or immunotherapy.
- Radiotherapy during study or within 3 weeks of start of study drug.
- Major surgery within 4 weeks of start of study.
- Autologous bone marrow transplant or stem cell rescue within 4 months of study.
- Use of biologic response modifiers, such as G-CSF, within 3 week of study entry. [G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity such as febrile

neutropenia when clinically indicated or at the discretion of the investigator, however they may not be substituted for a required dose reduction.] [Patients taking chronic erythropoietin are permitted provided no dose adjustment is undertaken within 2 months prior to the study or during the study].

- Investigational drug therapy outside of this trial during or within 4 weeks of study entry.
- Prior exposure to the study drug.
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
- Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study.
- Patients unable to swallow oral medications.
- Rifampicin.
- St. John's Worth (Hypericum perforatum).
- Use of Megestrol-acetate and medroxyprogesterone.
- Chronic treatment with corticosteroids (dose of >10 mg/day methylprednisolone equivalent) excluding inhaled steroids.

5.5 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Treatment with non-conventional therapies (e. g. herbs or acupuncture), and vitamin/mineral supplements is acceptable, provided that they do not interfere with the study endpoints, in the opinion of the Investigator.
- Patients may receive palliative and supportive care for any underlying illness.
- Patients receiving bisphosphonates as a prophylaxis for osteoporosis or treatment of bone metastases may continue while on treatment with cabozantinib.
- Continuous use of Erythropoietin is permitted.
- Best Supportive Care which may include analgesics, nutritional support, and other non-anti-neoplastics.

All other medical conditions should be treated at the discretion of the investigator in accordance with local community standards of medical care.

5.6 Treatment Compliance

All drug(s) will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers and total drug administered in milligrams.

5.7 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Intercurrent illness
- Occurrence of an unacceptable adverse event
- Patient request
- Protocol violations
- Non-compliance
- Administrative reasons

- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
- Progressive disease at any time

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

STUDY ASSESSMENT AND PROCEDURES

6.1 Recruitment

Patients with a histological diagnosis of CDC that are anticipated to be treated with cabozantinib will be approached for consideration for study entry whilst attending the oncology outpatient clinics at the Istituto Nazionale Tumori, or whilst an inpatient. Patients will be approached only once the appropriate official notification has been received by the chief investigator that the trial is open for recruitment.

6.2 Consent

Written informed consent will take place as a prerequisite for study entry. Consenting procedures will conform to GCP and local and national regulations. The patient will also consent to their GP being informed of their participation in the study.

6.3 Tissue specimen collection

As mandatory inclusion criteria, the tissue submitted will be used to assess exploratory biomarkers. The tissue submitted should be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen or 20 serial, freshly cut, unstained slides accompanied by an associated pathology report. Cytological samples are not acceptable.

Representative FFPE tissue samples will be collected from the primary tumour and/or any previous metastatic tissue specimens, so that further analysis may be performed on that/ those tissue sample(s) as appropriate. The samples will be initially received, processed and analysed at the Department of Pathology of Fondazione IRCCS Istituto Nazionale dei Tumori under the responsibility of Dr. Pruneri, for further analysis.

Tissue will be removed from a representative tumour block and tissue cores and sections will be subsequently be prepared for the purposes of DNA extraction and further testing as appropriate.

Analysis on biomarkers is exploratory by nature and will be performed retrospectively after the main study analysis is completed. These assessments will be performed at the Department of "Genomica Funzionale e Bio-Informatica- Drast" under the responsibility of Dr.ssa Sensi.

Tissue received in excess to that required by this study will be returned to the histopathology department from where it was originally requested.

Tissue assessments will include the identification of somatic mutations in CDC and the assessment of the mutational load by focused exome analysis, as well as the identification of transcript fusions by RNA sequencing.

6.4 Blood specimen collection

Blood samples will be collected for exploratory research. In particular, 30 ml of research blood sample (EDTA or equivalent tube) will be collected at baseline, at first cycle, after cycle 3 and at the end of treatment or progression of disease. If the patients goes off the study for unacceptable toxicity or treatment refusal, blood sample can still be collected until PD in consenting patients.

Samples will be sent to the Laboratory of Clinical Pharmacology of the Sponsor (Fondazione IRCCS Istituto Nazionale dei Tumori) for collection.

Plasma and viable peripheral blood mononuclear cell (PBMC) will be isolated and stored frozen for subsequent analysis. PBMC will be studied for immune cell profile by multicolor cytofluorimetry (including frequency and activation state of antitumor and immunosuppressive cell subsets of both innate and adaptive

immunity), associated with gene-expression profiling and Cibersort analysis for assessing the activation state of the immune cell subsets.

Results will be crossed with clinical data in terms of response rate (RR), to detect any predictive value of blood immune cell profiling during treatment, with the aim of identifying early biomarkers of response, or immune cell profiles in CDC.

These analysis will be conducted at the Experimental Oncology and Molecular Medicine Department, Unit of Immunotherapy of Human Tumors of the Fondazione IRCCS Istituto Nazionale dei Tumori, under the responsibility of Dr.ssa Rivoltini.

6.5 Collection of clinicopathological and demographic data

Initial data will be collected on a study-specific CRF to summarise information regarding the individual patient's case. This will enable correlation of clinicopathological and demographic data with data from the biological studies performed. The CRF will include information on: age, date of diagnosis, site of disease, stage at presentation, sites and diagnosis of metastatic disease, histological features at presentation, treatment, response to treatment, date of progressive disease, date of death, specific features of past medical history and family history.

6.6 Screening procedures

Pre-treatment evaluation will only be performed after the subject has agreed to participate and has signed and dated the ICF. No treatment or trial-related procedures will be initiated before the signed consent has been obtained. Imaging may be done before obtaining informed consent if done routinely. Subjects will not be required to undergo additional scanning if suitable images taken within 4 weeks of treatment period or randomization are available. Pre-treatment evaluations will be performed according to the eligibility criteria. If the subject is eligible for the study, the parameters at the screening visit showing subject health status, including blood values, will be recorded in the eCRF.

The following procedure and evaluations will be performed at screening (as per clinical practice):

- Sign informed consent: enrolment in the study is defined as the signing of the Informed Consent. The Informed Consent Document must be signed prior to any study related procedures that are performed.
- Subject registration and subject number assignment
- Review of inclusion and exclusion criteria and confirm eligibility
- Clinical Examination
- ECOG-PS
- Demographics
- Record disease history
- Record medical history
- Record AEs
- Record concomitant medications / therapy
- Record previously anti-cancer treatment (prior and current)
- Perform full physical examination
- Within 28 days prior to start of study drug radiological assessment should be performed. This radiological evaluation must include a CT or MRI of the chest, abdomen and pelvis and should meet the standard of care for imaging of lesions in the respective organ system(s). All additional suspected sites of disease should be imaged. CT or MRI of the head must be conducted to rule out brain metastasis.
- Appropriate radiological evaluation (bone scan etc.) should be obtained if bone metastases are suspected.

- 12-lead electrocardiogram (ECG)
- A multi-gated acquisition (MUGA) scan or a cardiac echocardiogram (ECHO) should be obtained. A MUGA scan or cardiac ECHO taken within 4 weeks prior to randomization is acceptable.
- Record vital signs: blood pressure, heart rate, respiratory rate, temperature, height (cm) and weight (kg).

The following evaluations will be performed within 7 days prior to treatment period:

- Vital Signs
- Red blood count (RBC): haemoglobin, hematocrit, platelet count, white blood cell count (WBC). WBC should include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts.
- Electrolyte panel: sodium, potassium, chloride and corrected calcium.
- Chemistry panel: Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT), bilirubin (total and direct), alkaline phosphatase, uric acid, total protein, albumin, calcium, lipase, amylase (amylase and lipase only at the screening), phosphate, Lactic Dehydrogenase (LDH), glucose, creatinine, Blood Urea Nitrogen (BUN).
- Thyroid function tests: FT3, FT4, TSH.
- Coagulation panel: Prothrombin Time (PT) or the International Ratio of PT (PT-INR), and Partial Thromboplastin Time (PTT) only the screening. (Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists. In addition, these patients must be monitored with weekly coagulation assessments throughout the study until stable INR has been established).
- Urine or serum pregnancy test for women of childbearing potential (must be negative).
- Urinalysis **(dipstick):** (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase,Nitrite, pH, Protein, Specific Gravity, Urobilinogen). Proteinuria 24 hours is requested if protein are positive at dipstick..

Any sign or symptom that begins, or is ongoing after enrolment (even if prior to start of study medication) must be documented on an Adverse Event page using the NCI CTCAE, Version 4.03 NCI CTCAE guidelines (Appendix 13.2). Any medical conditions must be recorded on the Medical History page.

6.7 Treatment period

The treatment period extends from the day of first treatment with cabozantinib to 4 weeks. The time between patient consent signed and first administration should be as brief as possible in accordance with the country-specific drug order lead time.

Assessments to be performed at cycle 1:

- Perform full physical examination
- ECOG-PS
- Vital sign
- Blood draw for hematology and chemistry evaluations (performed only if done within 7 days from day 1)
- Record AEs, SAEs
- Record concomitant medications/therapy
- Drug accountability/dispensing
- Biomarkers analysis (to be conducted on blood samples).

The following testing should be performed on the first day of each cycle (every 4 weeks) during the treatment period (+/- 7 days):

- Perform full physical examination

• ECOG-PS
• Vital sign
• Blood draw for hematology and chemistry evaluations (performed within 2 day from treatment)
• Electrolyte panel: sodium, potassium, chloride and corrected calcium.
• Urine or serum pregnancy test for women of childbearing potential (must be negative).
• Record AEs, SAEs
• Record concomitant medications/therapy
• Drug accountability/dispensing

Assessments to be performed every 3 cycles:

• A chest/abdominal/pelvic CT scan or MRI (time window for the scans is +/- 7 days). The same imaging modalities are to be used as were used at baseline. If a subject experiences radiological progression at CT scan can be discontinued. CT or MRI of the head must be conducted to rule out brain metastasis.
• Appropriate radiological evaluation (bone scan etc.) should be obtained if bone metastases are suspected.
• 12-lead electrocardiogram (ECG)
• Urinalysis **(dipstick):** (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase,Nitrite, pH, Protein, Specific Gravity, Urobilinogen). Proteinuria 24 hours is requested if protein are positive at dipstick..

End of treatment visit:

When a patient is to be taken off treatment, the following assessment should be done 30 days (+/- 7 days) after study treatment has stopped:

• Brief medical history and complete physical examination including review of all organ systems, examination of pertinent organ systems, vital signs Blood Pressure and weight.

• ECOG performance status.

• Laboratory Evaluations:

- Complete Blood Count (CBC)
- Electrolyte panel
- Chemistry panel

• Toxicity and adverse events documentation

• Concomitant medication

• Biomarkers analysis (to be conducted on blood samples)
• Urine or serum pregnancy test for women of childbearing potential (must be negative).

For patients who discontinue for reasons other than Disease Progression, tumor measurements and evaluation of tumor response of all measurable lesions should be performed according to RECIST criteria.

6.8 Follow up

After study drug treatment ends, patients will be evaluated approximately every 3 months to determine follow-up. All patients who are discontinued from study drug for any reason other than disease progression will continue to have tumor assessments as per the schedule and until the patient has documented disease progression determined by the local radiologist and/or the investigator or until the initiation of new anticancer therapy.

6.9 Survival

Patients who discontinued therapy due to progression of disease should be performed the “survival” every 3 months in order to define if the patient is alive and the subsequent therapies.

RADIOLOGICAL TUMOR ASSESSMENT

Response and progression will be evaluated in this study using the updated international criteria proposed by RECIST (Response Evaluation Criteria in Solid Tumours) committee *(Eisenhauer EA et al., Eur J Cancer 2009)*. Changes in only the largest diameter (unidimensional measurement) of the tumour lesions are used in the RECIST criteria.

ADVERSE EVENTS AND SAFETY

8.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

8.2 Serious Adverse Event Definition

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

• Results in death.

• Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

• Requires inpatient hospitalization or prolongation of an existing hospitalization.

• Results in persistent or significant disability or incapacity (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

• Is a congenital anomaly/birth defect.

• Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), whether pathogenic or non-pathogenic, is considered an infectious agent.

• Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.3 Unlisted (Unexpected) Adverse Event

For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For a comparator product with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics.

8.4 Adverse Drug Reaction

Any adverse event which has at least a reasonable possibility to be related to the drug.

8.5 Serious Adverse Drug Reaction

Any serious adverse event which has at least a reasonable possibility to be related to the drug.

8.6 Serious Unexpected Suspected Adverse Reaction (SUSAR)

It means those events which:

• are Serious (regardless of the dosage) according to the definition contained in the preceding sub-paragraph;

• have a certain degree of probability of being harmful, as a reaction to the medicinal product under investigation, regardless of the dosage administered (in other words, may be qualified as an adverse reaction);

• are unexpected, that is to say, the nature and severity of the adverse reaction is not in agreement with the product information as recorded.

8.7 Attribution Definitions

8.7.1 Intensity (Severity) Reporting and Attribution

For both serious and non-serious adverse events, the Investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Intensity should be defined according to the following criteria:

• Grade 1 Mild: Awareness of sign or symptom, but easily tolerated

• Grade 2 Moderate: Discomfort enough to cause interference with normal daily activities

• Grade 3 Severe: Inability to perform normal daily activities

• Grade 4 Life Threatening: Immediate risk of death from the event as it occurred.

• Grade 5 Death: Results in death.

Intensity will be determined by using the last version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 4.03 NCI CTCAE) as a guideline, wherever possible; a copy can be downloaded at the website indicated hereafter (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Relationship to study drug administration will be determined as follows:

• Not related: an adverse event which is not related to the use of the drug.

• Unlikely/Doubtful: an adverse event for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

• Possible: an adverse event which might be due to the use of the drug. An alternative explanation, e.g. concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

• Probable: an adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

• Definite/Very Likely: an adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

8.8 Reporting procedure

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.9 All Adverse Events

All adverse events that occur between the first study-related procedure and 30 days after the last dose of study drug will be reported. All events that meet the definition of a serious adverse event will be reported as serious adverse event, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Investigator-Sponsor instructions.

All severe adverse events, considered related, must be followed until resolution of the event, or the event improves to an acceptable gravity degree related to the disease. The unresolved aforementioned events will be followed for a maximum of 6 months.

Serious adverse event reports will be submitted as described in the next Section.

8.10 Procedures for Reporting Serious Adverse Events (SAEs)

The Sponsor of the study will comply with serious adverse events reporting responsibilities as a provider in EudraVigilance.

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs will be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

All serious adverse events occurring during the clinical study will be reported to the Pharmacovigilance Unit of the study sponsor Institution (Fondazione IRCCS Istituto Nazionale dei Tumori) by the Investigator or a delegate member of investigational staff within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the Investigator-Sponsor or his delegate using the Serious Adverse Event Form, which must be signed by a delegated member of the investigational staff. The initial report of a serious adverse event may be reported by fax or by mail. Initial telephone report may be accepted, but it should be followed by a written report: a Serious Adverse Event Form must be completed by the investigational staff (delegated member) and transmitted to the Investigator-Sponsor within 1 calendar day.

Pharmacovigilance e-mail: **farmacovigilanza.studispontanei@istitutotumori.mi.it**.

The initial report should be followed by submission of more detailed adverse event information within 5 calendar days after the Investigator first became aware of the serious event. Reporting requirements for adverse events are summarized in the table below.

Investigator's Reporting requirements for adverse events:

Seriousness	**Reporting Time**	**Type of Report**
SERIOUS	Within 24 hours	Initial report on designated serious adverse event form
	Within 5 calendar days	Follow-up/Final report on designated serious adverse event form
NON-SERIOUS	Per case report form procedure	Appropriate section of case report form

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to EMA and to AIFA, to the Ethics Committees and all the Investigators according to Italian Decree 17 December 2004 and the European Directive 2001/20/EC which was transposed into the Italian clinical trial legislation (D. Lgs. n. 211/2003). A copy of SUSARs should be forwarded also to the holder of the study drugs administered to the patient.

8.11 Serious Unexpected Suspected Adverse Reaction

According to Italian law Serious Unexpected Suspected Adverse Reaction reports will be entered in the Clinical Trial Electronic Module of EudraVigilance database and copied to AIFA (http://eudravigilance.emea.europa.eu/human/index.asp).

All Serious Unexpected Suspected Adverse Reaction reports will be periodically (at least every 12 months) reported to investigators and IEC as a line listing accompanied by a brief report by the sponsor highlighting the main points of concern.

8.12 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

8.12.1 Pregnancy in Female Patients

Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug.

8.12.2 Pregnancy in Female partners of Male Patients

Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. Because oral contraceptives might possibly not be considered as “effective methods of contraception”, they should be used together with another method, such as a barrier method.

STATISTICAL PROCEDURES

9.1 Accrual and sample size

The total number of patients enrolled will be 23.

Trial expected duration (comprehensive of accrual, treatment and follow-up): 24 months (stage 1 + stage 2). This should be added to a planned duration of follow up of 6 months since the enrollment of the last patient (resulting in a maximum of 30 months).

9.2 Analysis population

The population will be analyzed according to Intention-To-Treat (ITT) and per protocol principle.

In the ITT principle, all patients included in the trial by signing the informed consent and assigned a study patient number will be considered for the analysis.

Using per protocol principle, patients who did not receive treatment for any causes, severely violated protocol inclusion/exclusion criteria or withdrawal informed consent will be excluded for the analysis.

9.3 Statistical analysis

This is a single-arm phase II trial enrolling patients with histological diagnosis of CDC with untreated locally advanced or metastatic disease.

The Simon's two-stage optimal design will be applied. In order to reject an ORR equal to 15% with a one-sided alpha error of 10% and to detect an ORR equal to 35% with a power of 80% 9 patients will be enrolled in the first stage. If at least 2 responses will be observed in the first stage other 14 patients will be enrolled in the second stage. If at least 6 responses will be collected after the second stage the interesting activity of cabozantinib will be proved.

9.4 Safety analysis

Patients not receiving at least one dose of study drug will be excluded from the analysis of safety.

Tables of adverse event incidence and individual incidence will be produced according to the primary system-organ class (SOC) and within the category defined in the CTCAE v 4.03.

The summaries will be overall (severity grades 1-5) and for grade ≥ 3 events. Multiple occurrences of the same event will be counted once at the maximum severity.

A complementary analysis of adverse events by severity of event and by relationship to trial treatment will also be performed.

The actions taken in terms of treatment discontinuation will be also reported.

A standard safety analysis with tables and shift tables for laboratory data will be provided. Vital signs, coded as clinically normal or abnormal, will be described. Similar summaries will be made for serious adverse events.

Description of dosage incidents, hospitalizations and premature withdrawals will be provided.

9.5 Statistical software

The statistical analyses will be carried out using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp).

DATA MANAGEMENT

10.1 CRF

Participant data will be collected using protocol-specific case report forms (CRFs) developed from GU Unit The CRF will include information on: age, date of diagnosis, site of disease, stage at presentation, sites and diagnosis of metastatic disease, histological features at presentation, treatment, response to treatment, date of progressive disease, date of death, specific features of past medical history and family history.

Data will be collected and maintained according to ICH-GCP standards.

ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

11.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Section 9.1). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator

11.3 Patient Information and Informed Consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.
It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Data Center. This must be done in accordance with the national and local regulatory requirements.
For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

11.4 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator by the terminating party.
Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study materials will be stored for 10 years at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan.

11.5 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

REFERENCES

1. Abbas M, Steffens S, Bellut M, Eggers H, Großhennig A, Becker JU, Wegener G, Schrader AJ, Grünwald V, Ivanyi P. Intratumoral expression of programmed death ligand 1 (PD-L1) in patients with clear cell renal cell carcinoma (ccRCC). Med Oncol. 2016 Jul;33(7):80. doi: 10.1007/s12032-016-0794-0.
2. Choueiri TK, Fay AP, Gray KP, Callea M, Ho TH, Albiges L, et al. PD-L1 expression in non-clear cell renal cell carcinoma. Ann Oncol. 2014. doi:10.1093/annonc/mdu445.
3. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, Hammers H, Hutson TE, Lee JL, Peltola K, Roth BJ, Bjarnason GA, Géczi L, Keam B, Maroto P, Heng DY, Schmidinger M, Kantoff PW, Borgman-Hagey A, Hessel C, Scheffold C, Schwab GM, Tannir NM, Motzer RJ; METEOR Investigators. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1814-23. doi: 10.1056/NEJMoa1510016. Epub 2015 Sep 25.
4. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, Hammers HJ, Donskov F, Roth BJ, Peltola K, Lee JL, Heng DY,Schmidinger M, Agarwal N, Sternberg CN, McDermott DF, Aftab DT, Hessel C, Scheffold C, Schwab G, Hutson TE, Pal S, Motzer RJ;METEOR investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomized, open-label, phase 3 trial. Lancet Oncol. 2016 Jul;17(7):917-27. doi: 10.1016/S1470-2045(16)30107-3. Epub 2016 Jun 5.
5. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, Feldman DR, Olencki T, Picus J, Small EJ, Dakhil S, George DJ, Morris MJ. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. J Clin Oncol. 2017 Feb 20;35(6):591-597. doi: 10.1200/JCO.2016.70.7398. Epub 2016 Nov 14.
6. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.
7. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol. 2012 Mar 22;12(4):253-68. doi: 10.1038/nri3175.
8. Geissler K, Fornara P, Lautenschläger C, Holzhausen HJ, Seliger B, Riemann D. Immune signature of tumor infiltrating immune cells in renal cancer. Oncoimmunology. 2015 Feb 3;4(1):e985082. eCollection 2015 Jan.
9. Iacovelli R, Nole F, Verri E, Renne G, Paglino C, Santoni M, et al. Prognostic role of PD-L1 expression in renal cell carcinoma. A systematic review and meta-analysis. Target Oncol. 2015. doi:10.1007/s11523-015-0392-7.
10. Leite KR, Reis ST, Junior JP, Zerati M, Gomes Dde O, Camara-Lopes LH, et al. PD-L1 expression in renal cell carcinoma clear cell type is related to unfavorable prognosis. Diagn Pathol. 2015;10:189. doi:10.1186/s13000-015-0414-x.
11. Oudard S, Banu E, Vieillefond A, Fournier L, Priou F, Medioni J, Banu A, Duclos B, Rolland F, Escudier B, Arakelyan N, Culine S; GETUG (Groupe d'Etudes des Tumeurs Uro-Génitales). Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Génitales) study. J Urol. 2007 May;177(5):1698-702.
12. Pécuchet N, Bigot F, Gachet J, Massard C, Albiges L, Teghom C, Allory Y, Méjean A, Escudier B, Oudard S. Triple combination of bevacizumab, gemcitabine and platinum salt in metastatic collecting duct carcinoma. Ann Oncol. 2013 Dec;24(12):2963-7. doi: 10.1093/annonc/mdt423. Epub 2013 Nov 4.
13. Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, Bellmunt J, Burris HA, Petrylak DP, Teng SL, Shen X, Boyd Z, Hegde PS, Chen DS,Vogelzang NJ. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014 Nov 27;515(7528):558-62. doi: 10.1038/nature13904.
14. Procopio G, Testa I, Iacovelli R, Grassi P, Verzoni E, Garanzini E, Colecchia M, Torelli T, De Braud

F. Treatment of collecting duct carcinoma: current status and future perspectives. Anticancer Res. 2014 Feb;34(2):1027-30.
15. Procopio G, Verzoni E, Iacovelli R, Colecchia M, Torelli T, Mariani L. Is there a role for targeted terapie in the collecting ducts of Bellini carcinoma? Clin Exp Nephrol. 2012 Jun;16(3):464-7. doi: 10.1007/s10157-012-0589-3. Epub 2012 Jan 26.
16. Selli C, Amorosi A, Vona G, Sestini R, Travaglini F, Bartoletti R, Orlando C. Retrospective evaluation of c-erbB-2 oncogene amplification using competitive PCR in collecting duct carcinoma of the kidney. J Urol. 1997 Jul;158(1):245-7.
17. Shin SJ, Jeon YK, Kim PJ, Cho YM, Koh J, Chung DH, et al. Clinicopathologic analysis of PD-L1 and PD-L2 expression in renal cell carcinoma: association with oncogenic proteins status. Ann Surg Oncol. 2016;23(2):694–702. doi:10.1245/s10434-015-4903-7.
18. Taube JM, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res. 2014;20(19):5064–74. doi:10.1158/1078-0432.CCR-13-3271.
19. Walter S, Weinschenk T, Stenzl A, Zdrojowy R, Pluzanska A, Szczylik C, Staehler M, Brugger W, Dietrich PY, Mendrzyk R, Hilf N, Schoor O, Fritsche J, Mahr A, Maurer D, Vass V, Trautwein C, Lewandrowski P, Flohr C, Pohla H, Stanczak JJ, Bronte V, Mandruzzato S, Biedermann T, Pawelec G, Derhovanessian E,Yamagishi H, Miki T, Hongo F, Takaha N, Hirakawa K, Tanaka H, Stevanovic S, Frisch J, Mayer-Mokler A, Kirner A, Rammensee HG, Reinhardt C, Singh-Jasuja H. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. Nat Med. 2012 Aug;18(8):1254-61. doi: 10.1038/nm.2883. Epub 2012 Jul 29.

APPENDICES

Declaration of Helsinki

World Medical Association Declaration of Helsinki:
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review

committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be

stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

1.1 Common Terminology Criteria for Adverse Events 4.03

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

1.2 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.

IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

1.3 Eastern Cooperative Oncology Group Scale for Performance Status (ECOG)

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

NOTE THAT:

ECOG 0 corresponds to Karnofsky performance status of 100-90

ECOG 1 corresponds to Karnofsky performance status of 80-70

ECOG 2 corresponds to Karnofsky performance status of 60-50

ECOG 3 corresponds to Karnfosky performance status of 40-30

ECOG 4 corresponds to Karnofsky performance status of 20-10

ECOG 5 corresponds to Karnofsky performance status of 0

1.4 Target and Non-Target Lesion Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
CR	CR	No	CR	>4 wk. confirmation
CR	Non-CR/Non-PD	No	PR	
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once > 4 wk. from baseline
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*". Every effort should be made to document the objective progression even after discontinuation of treatment.

Response criteria

Target Lesions:

Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.

Stable Disease (SD): steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Progressive Disease (PD): at least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Appearance of new lesions will also constitute progressive disease. In exceptional circumstances unequivocal progression of a non-measured lesion may be accepted as evidence of disease progression.

Non-Target Lesions:

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.