**Supplementary Information:**

Allowed Therapies:

* Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
* Granulocyte colony-stimulating factors are acceptable while the subject is enrolled in the study. However, these should not be administered prophylactically before initial treatment with study drug. Transfusions should be used in accordance with institutional guidelines.
* Hormone replacement and short-term systemic steroid treatment may be utilized as indicated by standard clinical practice while the subject is enrolled in the study.
* The protocol does not restrict the use of heparins at prophylactic doses. Therapeutic doses of heparins are allowed after registration if clinically indicated for supportive treatment and the benefit outweighs the risk per the investigator’s discretion. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Therapeutic doses of oral anticoagulants (eg, warfarin or warfarin-related agents, thrombin or FXa inhibitors, antiplatelet agents such as clopidogrel) are not allowed after registration until study treatment is permanently discontinued.
* Subjects with active HBV should be on appropriate antiviral therapy.

Prohibited or Restricted Therapies:

* Any investigational agent or investigational medical device
* Any drug or herbal product used specifically for the treatment of HCC
* Therapeutic doses of oral anticoagulants (eg, warfarin or warfarin-related agents, thrombin or fxa inhibitors, antiplatelet agents such as clopidogrel)
* Interferon treatment
* Liver-directed local anti-cancer therapy (eg, transarterial tumor embolization or chemoembolization, radiofrequency or microwave ablation, percutaneous ethanol or acetic acid ablation, injection or infusion of drug eluting or radiation-emitting beads, cryoablation, radiation therapy [including stereotactic radiotherapy], or surgery) or systemic antitumor therapies are not permitted on study treatment. If a subject requires additional systemic anticancer treatment or liver-directed local anti-cancer therapy, study treatment must be discontinued. Palliative external radiation to bone metastasis or skin/subcutaneous metastasis, is allowed but discouraged unless medically unavoidable. Subjects who have such intervention may be considered inevaluable for certain efficacy endpoints.
* Erythropoietic-stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin.
* The chronic co-administration of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.
* Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.
* Coadministration of strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Biological specimens (Plans for collection, laboratory evaluation, and storage of specimens):

1. **Tumor biopsies:**

* **WES of tumor**: WES of tumor DNA and germline DNA will be performed in OICR with already established protocol using next generation DNA sequencing. Data generated will be analyzed using established bioinformatics pipelines to study somatic mutations and derive potential mutational signatures. These results should be available within 8 weeks of baseline fresh tumor biopsy. Germline mutations detected in study subjects will be reported to the co-investigator (treating physician) to facilitate clinical confirmation of mutation(s). Participants with pathogenic germline mutations identified through the study who have consented to be informed of genetic information will be approached by the study genetic counselor (Canadian and American board certified) for a research results disclosure session. In this session, the participant will receive genetic counseling about the research finding and need for confirmation testing. The session will also summarize gene specific risks and inheritance pattern. The study genetic counselor will offer confirmation testing of the research finding through a clinically accredited laboratory. Once clinical confirmation results are available, these will be disclosed to the participant and their treating physician by the genetic counselor in a clinical results disclosure session. The genetic counselor will summarize gene specific cancer risks, inheritance, surveillance for early detection and/or surgical interventions for prevention, and procedures for testing family members.
* **RNA sequencing of tumor:** Whole transcriptome sequencing of tumor RNA will be performed using next generation sequencing in OICR with established protocols. RNAseq data will be used to perform exploratory analysis. Planned analyses include evaluation of differences in gene expression levels between responders and non-responders to study treatment. Further exploratory analyses will include interrogation of inflammatory signatures. In patients consenting for a second optional biopsy, immune signatures will be compared pre and post treatment.
* **Methylation profiling:** Tumor methylation profiling will be correlated with that seen in cfDNA.
* **Tumor microbiome evaluation:** Tumour samples will undergo next-generation sequencing of 16S rRNA sequencing to identify and classify the bacteria present. Bacteria in the tumour samples will be compared with stool samples
* Tumour specimens will be snap frozen

1. Blood for biomarker studies:

* **CtDNA:** 2 X 10 ml STRECK tubes will be drawn on days 1, cycle 1 day 15+/- 2 days and cycle 3, day 1 (day 85) +/- 7days. A further sample will be collected at progression. Whole blood samples should be processed (double spun) within 4 hours of collection to separate cells from plasma. Cell free DNA will be analyzed for circulating tumour DNA quantitative analysis.
* **Germline analysis:** Blood draw at C1D1 will also be used to obtain a buffy coat for DNA extraction and germline analysis. Sample should be transferred to OICR and stored at -80oC for further processing.
* **PBMC:** PBMCs separated from 1 x 10 mL peripheral blood specimens in EDTA and undergo characterization and classification using flow cytometry at UHN
* Handling: Whole blood will be collected in STRECK tubes for ctDNA and methylation analysis and heparin tubes for PMBC.

1. **Microbiome analysis:**

* Collection: Stool samples will be collected using rectal swab (Puritan 6" Foam Swab w/Nylon) and will be stored at 80 degrees until the shipment for the DNA extraction.
* Shipping: Samples for microbiome analyses will be sent in dry ice
* Stool will be analyzed using 16S rRNA sequencing to allow bacterial identification within the samples

Confidentiality:

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study. Any party with direct access will take all reasonable precautions within the constraints of applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and proprietary information. The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents as applicable. All study participant study materials collected shall be used solely in accordance with this protocol and any written agreements.

Retention of Patient Records and Study Files:

The ICH guidance document, Good Clinical Practice: Consolidated Guidelines (ICH Guidance Document E6) (1997) states that the investigator and sponsor shall retain study records relating to the study until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In the event of a trial discontinuation, sponsor records should also be kept for a minimum of 2 years. Per Health Canada, all original records should be maintained for 25 years after the above requirements are satisfied and the final report has been issued. Records contained in the Clinical Trial Application should be maintained on file for at least 25 years. We will comply with these regulations. The Sponsor will notify sites when documents are to be destroyed.