PROTOCOL SUMMARY

SYNOPSIS

A) STUDY IDENTIFICATION	
SPONSOR – PROTOCOL CODE NUMBER: **UC-GIG-2104**	
STUDY TITLE: **TARGET**ED THERAPY DRUG **MONIT**ORING IN **DIG**ESTIVE ONCOLOGY	
VERSION (NUMBER & DATE): V1.1 22 MAY 2022	
STUDY TITLE FOR LAY PEOPLE: Dosing of active drug concentrations in plasma for patients treated for their digestive cancer, with the aim to determine the best optimal dose for each treatment in the future.	
ABBREVIATED TITLE: **TARGET MONITO DIG**	
COORDINATING INVESTIGATOR: Dr. David MALKA	
NUMBER OF CENTERS (PLANNED): 30	**NUMBER OF PATIENTS:** 330

B) SPONSOR IDENTIFICATION	
NAME:	**UNICANCER -** 101, rue de Tolbiac - 75654 Paris Cedex 13
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C) STUDY GENERAL INFORMATION
INDICATION:
Adult patients with advanced digestive cancer whose standard treatment plan with Multi-Kinase Inhibitor (MKI) is: • **Regorafenib** for GastroIntestinal Stromal Tumor (GIST), metastatic Colorectal Cancer (mCRC) and HepatoCellular Carcinoma (HCC), • **Everolimus** for gastroenteropancreatic NeuroEndocrine Tumor (gepNET), • **Sunitinib** for pancreatic NET (pNET) and GIST, • **Cabozantinib** for HCC, • **Encorafenib – cetuximab** combination for mCRC

STUDY DESCRIPTION:

National multicenter, open-label, prospective interventional phase IV study, involving the following cohorts:

1. **Regorafenib –** mCRC, GIST, HCC – 3 x 30 = 90 patients
2. **Everolimus –** gepNET – 60 patients
3. **Sunitinib –** pNET, GIST – 2 x 30 = 60 patients
4. **Cabozantinib** – HCC – 60 patients
5. **Encorafenib – cetuximab** - mCRC - 60 patients

PRIMARY OBJECTIVE:

To build a **Population PharmacoKinetics PK (PopPK) model** *(concentration versus time)* for standard MKI and Monoclonal Antibodies (MAb) treatments used in digestive oncology for patients with advanced digestive cancer, in order to **define the targeted plasma concentrations for each drug,** with a view to establish the **relationships between PK and PharmacoDynamics (PD;** *effect versus time*).

SECONDARY OBJECTIVES:

To elucidate the **relationships between PK and PD**, for each cohort, in term of:

- **Drug activity** (product efficacy):
  - Progression Free Survival [PFS],
  - Overall Survival [OS],
  - Objective Response Rate [ORR],
  - Disease Control Rate [DCR]
- **Drug toxicity occurrence related to standard treatment** (selected, Adverse Events (AE) of specific interest (AESI))

Exploratory objective (ancillary study for translational research):

To identify predictive biomarkers of efficacy and safety of the standard MKI and MAb studied in the present study in order to explore relationship between drug plasmatic exposure and tumor burden dynamics.

INCLUSION CRITERIA:

1. Patient aged 18 years or over
2. Advanced digestive cancer (histologically confirmed or confirmed by imaging for HCC) for which a ***standard*** treatment (*according to each drug SmPC and as per Standard of Care (SOC))* is planned with:
   - **Regorafenib** for GIST, mCRC and HCC,
   - **Everolimus** for gepNET,
   - **Sunitinib** for pNET or GIST,
   - **Cabozantinib** for HCC,
   - **Encorafenib – cetuximab** for mCRC
3. Life expectancy of greater than 3 months – at the discretion of the investigator
4. Measurable disease according to tumor evaluation criteria as per local practices (Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, etc.)
5. Patients must be affiliated to a Social Security System (or equivalent)
6. Patients must have signed a written informed consent form prior to any trial specific procedures. If the patients are physically unable to give their written consent, a trusted person of their choice, not related to the investigator or the sponsor, can confirm in writing the patient's consent.

NON-INCLUSION CRITERIA:

1. Other concomitant anticancer systemic treatment (chronic chemotherapy, antitumor hormone therapy or immunotherapy) than the one studied
2. Unresolved toxicity **higher than** National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 **Grade 1** attributed to any prior procedure *excluding alopecia and peripheral neuropathy*
3. Prior treatment with the same MKI molecule(s) planned to be given in the cohort. *If different MKI molecules (from the one(s) planned in the study) have been previously taken, **a wash out period of 2 weeks** before treatment should be observed.*
4. Other invasive malignancies either currently active or active in the last 3 years *(i.e. adequately treated in situ carcinoma of the cervix or basal/squamous cell carcinoma of the skin is allowed)*
5. Any condition that may jeopardize patient participation in the study as well asnon-contraception for male and female with child-bearing potential, pregnancy or breast feeding.
6. Patient unwilling or unable to comply with the medical follow-up required by the standard treatment taken (including PK sampling during treatment phase and vital status collection during follow-up phase) because of psychosocial, familial, social or geographical reasons
7. Participation in another clinical study with an **investigational** medicinal product during the last 30 days prior to inclusion and during the present study *(except if patient is included in the control arm, with placebo or with a product which have a marketed authorisation, used as per the SmPC for the given indication)*
8. Patient deprived of their liberty or under protective custody or guardianship.

PRIMARY ENDPOINT:

The primary endpoint is to determine **drug plasmatic exposure** ($C_{ss,trough}$) through the PopPK model. Concentrations will be measured at the following time points:

- ~1 month after the first treatment administration,
- ~2 months after the first treatment administration,
- in case of progression,
- in case of selected toxicity: **AESI**, defined as any AE related to the study treatment **AND:**
  - grade 3 or 4 according to NCI CTC AE version 5.0 **OR**
  - leading to treatment modification (dose reduction or treatment interruption) **OR**
  - categorized as SAE **OR**
  - considered clinically significant by the investigator

SECONDARY ENDPOINTS:

In order to elucidate the **relationships between PK and PD**, for each cohort, the endpoints below will be assessed:

- **Drug activity:**
  - PFS - assessed according to RECIST v1.1, *defined as the time between inclusion and the first event of progression or death whatever the cause. Patients alive without disease progression at last follow-up will be censored at the date of last follow-up.*
  - OS, *defined as the time between inclusion and death whatever the cause. Alive patients are censored at the date of last follow-up.*
  - ORR - according to RECIST v1.1, *defined as percentage of patients with a best response during treatment being either Complete Response [CR] or Partial Response [PR].*
  - DCR - according to RECIST v1.1, *defined as percentage of patients with a best response during treatment that is not Disease Progression [DP]: either CR, PR, or Stable Disease [SD].*
- **Selected, drug-specific, toxicity:** AESI according to NCI-CTCAE V5.0.

EXPLORATORY ENDPOINTS (ANCILLARY STUDIES FOR TRANSLATIONAL RESEARCH)

To identify predictive biomarkers of efficacy and safety of the study treatments in order to explore relationships between drug plasmatic exposure and tumor burden dynamics, by analyses of patient blood samples collected at baseline, at steady state and at disease progression.

D) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE INCLUDED: 330 patients are required to be included in 3 years: 90 patients in cohort 1 and 60 patients each in cohorts 2, 3, 4, and 5, taking into account the attrition rate expected in this study.

Based on Kang et al.17, a minimum of 42 patients per cohort are needed to establish a PopPK model and perform PK-PD relationships based on exploratory study. The number of patients is calculated considering a difference of 50% in clearance, an inter-individual variability (IIV) of 80%, an intra-individual variability (IOV) of 30% and a power of 70%. Analyses will be performed using a non-linear mixed-effects model for each drug/cohort to estimate the requested relationships.

STATISTICAL ANALYSIS:

Descriptive analyses will be performed using mean and standard deviation or median and range for continuous covariates, frequency and percentage for categorical variables.

Baseline characteristics will be compared using the Student t test or the Wilcoxon test for continuous variables, and chi 2 or Fisher exact test for categorical variables.

The primary endpoint, determining drug plasmatic exposure ($C_{ss,\ trough}$), will be assessed through PopPK models (i.e., non-linear mixed effect models). The aim of a population PK model is, firstly, to define the PK of

a drug, secondly to evaluate the impact of covariates on PK parameters and thirdly to predict the PK of patients according to their covariates.

Different PK models (i.e. monocompartimental, bicompartimental…) with different absorption models (zero order, first order, transit compartment, lag-time…) and error model will be tested and compared using the objective function (OF) of the models.

We will also check if all parameters (random and mixed effects) are well estimated (<30-35 % for fixed effects and <50% for random effects) and the goodness of fits (GOF) of the plots.

Different covariates selection approaches using ΔOF (i.e., forward selection and backward elimination) will be compared. Once the final model defined, an internal validation of the model will be performed though bootstraps and visual predictive checks.

Concerning the secondary endpoints, ORR, DCR, incidence rates of adverse events and serious adverse events will be described in terms of number of observation and frequency.

To assess the impact of drug plasmatic exposure trough steady state concentration ($C_{ss,trough}$) on OS and PFS, for each cohort, Hazard Ratios (HRs) with 95% confidence interval (95%CI) will be estimated though Cox proportional hazard models; or, using thresholds described in the literature, Css and Ctrough will be discretized and comparison of survival distribution between groups will then be performed using the Log-rank test.

E) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES: Whole blood samples (Ethylene-Diamine-Tetra-Acetic Acid (EDTA)).
SAMPLE QUANTITIES: 1 tube (5 mL) per time point (3 time points):

1. At baseline (during screening phase i.e. within 28 days before starting treatment)
2. ~1 month after the first treatment administration (at the same time of PK1 sampling)
3. At disease progression (at the same time of PK_{prog} smapling)

F) STUDY DURATIONS

INCLUSION PERIOD: 3 years

TREATMENT PERIOD: Standard treatment should continue **as long as benefit is observed**, unless patient's refusal, investigator's decision or unacceptable toxicity.

FOLLOW-UP: 1 year. An update will be performed after the Last Patient Last Visit (LPLV) occurrence in order to collect the **vital status** for all included patients.

PRIMARY ENDPOINT EVALUATION: Per cohort (as soon as the last PK sample required to build the popPK model will be analyzed).

OVERALL STUDY DURATION (INCLUDING FOLLOW-UP): 5 years

SCHEDULE OF VISITS AND ACTIVITIES (SOA)

PHASE	SCREENING	TREATMENT[3]						FOLLOW-UP (FUP)		
Visits TIMELINES	*(28 days before starting treatment)*	**Cycle 1** *(Day 1: before drug intake, unless otherwise specified[4])*	**Cycle 2** *(Day 1: before drug intake, unless otherwise specified[4])*	**Cycle 3 Day 1** *(+/-7 days) (before drug intake)*	**Every even cycles** (4, 6, 8…) except for NET and GIST: every 6 months (6, 12, 18…) **Day 1** *(before drug intake)*	**Every odd cycles** (5, 7, 9…) except for NET and GIST: every 6 months (9, 15, 21,…) **Day 1** *(before drug intake)*	**End of treatment (EOT)**	**Additional FUP visits until AE resolution,** if any	**1st FUP** *4-6 weeks after EOT*	**Further FUP up to 1 year after EOT** Every 2 months (+/-7 days) except for NET and GIST: every 3 months (+/-7 days)
Eligibility criteria	**X**									
Patient **signed informed consent form**	**X**									
Medical history (demography, etc.)	**X**									
Pregnancy test (urine/serum) and ECG	**X**									
Medical interview (compliance, concomitant medications, smoking status) + AE reporting	**X** *(except AE)*	**X**	**X**	**X**	**X**	**X**		**X**	**X** *(AE)*	
Complete physical examination: weight, BSA, ECOG PS, vital signs, **detailed** organ review	**X** *(+height)*			**X**		**X**	**X**	**X**		
Brief physical examination **:** weight**,** BSA**,** ECOG PS, vital signs, **quick** organ review		**X**	**X**		**X**				**X**	
Standard biological checkup [2]	**X** *within 7 days*		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
PK samples collection		**PK #1** *date[4]*	**PK #2** *date[4]*		**PK_{tox}** [5]	**PK_{tox}** [5]	**PK_{tox}** [5] **PK_{prog}** [6]			
Tumor assessments as per local practice	**X**			**X**		**X**	**X**			**X**
Survival status										**X**
Whole blood – biomarkers analysis	**X**	**X** *(same time than PK#1)*					**X** *(at progression)*			

1. Patient signed informed consent form will be registered in patient's medical record by the investigator
2. Standard Biological check-up includes CBC, ionogram, proteins (including albumin), creatinine, bilirubin (total & conjugated), ALAT and ASAT. The other parameters will be measured as per each drug's SmPC
3. Standard treatments (as per SOC):
   - Regorafenib:
     - Standard schedule: 160 mg p.o. taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is 1 treatment cycle.
     - Dose optimization (ReDOS schedule): cycle 1, weekly escalation from 80 to 120 to 160 mg/day according to patient's tolerance. Daily dose for subsequent cycles will be the maximal tolerated dose within cycle 1.
   - Everolimus for gepNET: 10 mg p.o. once daily.

- Sunitinib for pNET: 37, 5 mg p.o. once daily.
- Sunitinib for GIST: 50 mg p.o. once daily for 4 weeks followed by 2 weeks off. This 6-week period is 1 treatment cycle.
- Cabozantinib: 60 mg p.o. once daily.
- Encorafenib: 300 mg p.o. once daily + Cetuximab (I.V.) weekly: 400 mg/m² BSA first week only (loading dose), followed by 250 mg/m² BSA

4. **PK #1:** samples to be taken during a physical visit on site:
   - Regorafenib (standard schedule or ReDOS schedule at cycle 1): Cycle 1 Day 21 (-5/+2 days)
   - Sunitinib (GIST only; 4 weeks on, 2 weeks off schedule): Cycle 1 Day 28 (-5/+2 days)
   - Other drugs/indications (daily drug intake): Cycle 2 Day 1 (-5/+ 2 days)

   PK #2: samples to be taken during a physical visit on site:

   - Regorafenib (3 weeks on, 1 week off schedule): Cycle 2 Day 21 (-5/+2 days)
   - Sunitinib (GIST only; 4 weeks on, 2 weeks off schedule): Cycle 2 Day 28 (-5/+2 days)
   - Other drugs/indications (daily drug intake): Cycle 3 Day 1 (-5/+ 2 days)

5. **PKtox**: when an AESI occurs, samples to be taken within 48 hours of the AESI declaration, during a physical visit on site.
   PKprog: when disease progression (clinical or radiological) occurs, samples to be taken within 48 hours of the progression knowledge, during a physical visit on site.