PROTOCOL SUMMARY

A) TRIAL IDENTIFICATION

SPONSOR – PROTOCOL CODE NUMBER: UC-GMP-2305

VERSION (NR & DATE): 1.1, 05 September, 2024

TRIAL TITLE: **Phase II trial evaluating the efficacy of pemigatinib in patients with recurrent and/or metastatic solid tumor harboring a FGFR alteration**

TRIAL TITLE FOR LAY PEOPLE: Clinical trial evaluating the efficacy of pemigatinib for the treatment of patients with solid tumours with an alteration of the gene FGFR

ABBREVIATED TITLE: **AcSé pemigatinib**

COORDINATING INVESTIGATOR: **Christophe Le Tourneau**

CO-COORDINATING INVESTIGATOR: **Nicolas Isambert**

NUMBER OF PARTICIPATING CENTRES (ESTIMATE): 30	NUMBER OF PATIENTS: 40

B) SPONSOR IDENTIFICATION

NAME:	**UNICANCER** **101, rue de Tolbiac** **75654 Paris Cedex 13 (France)**
CONTACT PERSON:	CELINE MAHIER AIT OUKHATAR Project Manager R&D UNICANCER Phone: +33 (0)6 17 51 34 29 Email: c-mahier@unicancer.fr

C) TRIAL GENERAL INFORMATION

INDICATION:

C) TRIAL GENERAL INFORMATION

Any adult patient with recurrent or metastatic solid cancer harboring a FGFR1,2,3 fusion/rearrangement or activating mutation, outside of the approved indications for any selective FGFR inhibitor in France.

RATIONAL:

- The **prevalence of FGFR fusions** in all cancer patients is <1%, with a higher prevalence in patients with **cholangiocarcinoma** (3%) and **bladder** cancer (5%). The prevalence of **FGFR mutations** in all cancers is around 2%. Mutations are more frequently found in **urothelial cancer, endometrial cancer, and glioma**.
- An ORR of 35.5% and 42% have been reported in **cholangiocarcinoma** patients harbouring a **FGFR2-fusion** with pemigatinib and futibatinib, respectively.
- An ORR of 45% and 23% have been reported in **urothelial carcinoma** patients harboring a **FGFR3 alteration including fusions and mutations** with erdafitinib and pemigatinib, respectively.
- An ORR of 30% has been reported across 16 different histologies in patients with **advanced solid tumors** harboring a **FGFR fusion or mutation** with erdafitinib.
- In France, pemigatinib is available for cholangiocarcinoma patients harboring a FGFR2 fusion.
- We aim in our study to evaluate the efficacy of the drug pemigatinib in patients harbouring a FGFR fusion or mutation.
- The hypothesis is that FGFR fusion is a **driver event** across cancer types, as observed with NTRK, ALK, and ROS1 fusions.
- Given the extremely low prevalence of FGFR fusions/mutations, a **randomized** trial is not feasible.
- Given the limited ORR of FGFR inhibitors reported so far in cholangiocarcinoma and bladder cancer patients, we propose a single arm phase II clinical trial in which efficacy will be assessed by using each patient as his/her own control in order to capture efficacy beyond objective responses according to RECIST1.1.
- Synthetic control arms are not available given the absence of analogous clinicogenomic database.

TRIAL DESCRIPTION/DESIGN:

Multicenter, single-arm phase II trial using a A'Hern single-stage design evaluating the efficacy of pemigatinib monotherapy in patients with recurrent and/or metastatic solid tumor harboring a FGFR alteration.

PRIMARY OBJECTIVE:

To evaluate the efficacy of pemigatinib monotherapy on tumor growth kinetics and tumoral response in patients with recurrent and/or metastatic cancer harboring a FGFR alteration (fusion/rearrangement or activating mutation).

C) TRIAL GENERAL INFORMATION

SECONDARY OBJECTIVE(S):

- To evaluate the efficacy in terms of:
  - Overall response rate (ORR)
  - Clinical benefit rate (CBR)
  - Duration of response (DoR)
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)
  - Overall survival (OS)
- To assess the safety and tolerability of pemigatinib
- To evaluate the quality of life.

Exploratory objective :

- To study the relevance of efficacy monitoring using longitudinal ctDNA sampling.

INCLUSION CRITERIA:

To be eligible, patients must meet all of the following criteria:

1. Histologically or cytologically confirmed solid tumor
2. Patient with locally reccurent unresectable and/or advanced or metastatic disease harbouring a FGFR1,2,3 fusion/rearrangement or mutation (appendix 8 of the protocol)
3. Age ≥ 18 years
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
5. Patient for whom there is no appropriate therapeutic alternative and for whom a FGFR inhibitor is indicated by the institution or the regional multidisciplinary consultation meeting and who may derive a benefit, according to the physician assessment
6. Estimated life expectancy >3 months
7. Mesurable disease according to RECIST1.1, whatever the disease location. Tumor lesions located in a previously irradiated area, or in an area subjected to other loco-regional therapy, are considered measureable if progression has been clearly demonstrated in the lesion.
8. Availability of 2 pre-treatment tumor evaluations performed with an interval of at least 4 weeks and no more than 3 months between the examinations (CT or MRI, but same technics for both) and without any cancer treatment during this period
9. Patient with a minimal trend at 0.1 mm/day increase in tumor growth kinetics between pre-treatment and baseline scan, as assessed by the investigator
10. Adequate hematologic function: ANC > 1.5 x 10^9 /L; platelets > 75 x 10^9 /L; haemoglobin > 9.0 g/dL. Transfusion is allowed with a 2-week washout period before treatment initiation
11. Adequate hepatic function: ALT and AST < 2,5 x ULN (≤ 5 x ULN for liver metastasis); total bilirubin < 1.5 x ULN (< 2.5 x ULN if Gilbert's syndrome or liver metastasis); ALP < 3 x ULN
12. Adequate renal function: serum creatinine clearance > 30 mL/minute based on Cockroft-Gault formula
13. Value of serum phosphate ≤ ULN and value of serum calcium within institutional normal range (or serum albumin-corrected calcium within normal range when serum albumin is outside of the normal range)
14. Potassium levels within institutional normal range; supplementation can be used to correct potassium level during the screening.
15. Men, and women of childbearing potential (WOCBP) must agree to use adequate contraception for the duration of trial participation and for at least one week after the last dose of pemigatinib. Men must also agree to not donate sperm and women must agree to not donate oocytes during the specified period
16. Women of childbearing potential must have a negative serum pregnancy test performed within 14 days before treatment initiation
17. Patient is affiliated to a social security system

C) TRIAL GENERAL INFORMATION

18. Patient must have signed a written informed consent form prior to any trial specific procedures. When the patient is physically unable to give their written consent, a trusted person of their choice, independent from the investigator or the sponsor, can confirm in signing the patient's consent.

EXCLUSION CRITERIA:

The presence of any of the following will exclude a patient from enrolment:

1. Hematologic malignancies
2. Known hypersensitivity or severe reaction to pemigatinib or excipients of pemigatinib (refer to the Investigator Brochure)
3. Patient with a disease and a FGFR alteration covered by a marketed indication for any selective FGFR inhibitor (e.g cholangiocarcinoma with FGFR2-fusion or a FGFR mutation are not eligible, while FGFR1 or 3 fusion are eligible)
4. Patient who received prior selective FGFR inhibitor
5. Patient who can be included in a recruiting study assessing FGFR inhibitor (including pemigatinib)
6. Current evidence of clinically significant corneal or retinal disorder as confirmed by ophthalmologic examination
7. Other current malignancy, with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin. Cancer survivors, who have undergone potentially curative therapy for a prior malignancy, have no evidence of that disease for 5 years or more and are deemed at negligible risk for recurrence, are eligible for the trial
8. History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues such as skin, kidney tendon, or vessels due to injury, disease, or aging in the absence of systemic mineral imbalance)
9. Significant gastrointestinal disorder(s) that could interfere with absorption, metabolism, or excretion of pemigatinib
10. Inability to swallow and retain oral medication
11. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug/treatment administration, New York Heart Association Class III or IV congestive heart failure, and uncontrolled arrhythmia (participants with pacemaker or with atrial fibrillation and well-controlled heart rate are allowed)
12. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTcF interval > 480 ms is excluded.
13. Evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (defined as elevated transaminases or cirrhosis); chronic HBV/HCV infection with no cirrhosis and no elevated transaminases is allowed
14. Known HIV infection except if undetectable viral load

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15. Other active chronic or current infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment within 2 weeks before enrollment (participants with asymptomatic chronic infections on prophylactic treatment are allowed)
16. Prior anticancer therapy, including radiotherapy, endocrine therapy, immunotherapy, chemotherapy or other investigational agents within the last 4 weeks (6 weeks for nitrosoureas and mitomycin C). A 1-week washout is permitted for palliative radiation to non-CNS disease. Patients must have recovered (≤ Grade 1) from AEs from previously administered therapies or local treatments before treatment initiation (excluding alopecia, anemia and decreased creatinine clearance)
17. Use of any potent CYP3A4 inhibitors or inducers or moderate CYP3A4 inducers within 14 days or five half-lives (whichever is shorter) before the first dose of study drug
18. Any condition which in the Investigator's opinion makes it undesirable for the subject to participate in the trial or which would jeopardize compliance with the protocol
19. Inability or unlikeliness of the participant to comply with the dose schedule or with the medical evaluations and follow-up required by the trial because of geographic, familial, social, or psychological reasons
20. Women who are pregnant or breastfeeding
21. History of hypovitaminosis D requiring supraphysiologic doses (eg, 50,000 UI/weekly) to replenish the deficiency.
22. Participation in another therapeutic trial within the 30 days prior to inclusion
23. Individuals deprived of liberty or placed under protective custody or guardianship.

PRIMARY ENDPOINT:

Proportion of patients experiencing an objective response or at least a 30% decrease in tumor growth kinetics at disease progression on study treatment as compared to the one calculated from the two pre-treatment tumor evaluations. The tumor kinetics variation is measured by the tumor growth ratio (TGr) defined as the ratio of the slope of tumor growth on treatment (between the nadir and disease progression) and the slope of tumor growth before treatment, as established in a previous work by Le Tourneau et al. (BJC 2012). The sum of the diameters of target lesions according to RECIST 1.1 will be calculated on each patient's imaging by the Blinded Independent Central Review (BICR).

SECONDARY ENDPOINT(S):

- ORR defined as the proportion of patients with a complete response (CR) or a partial response (PR) as best overall response during the study, based on RECIST1.1, as assessed by the BICR and by the physician.
- CBR defined as the proportion of patients with a complete response (CR) or a partial response (PR) or a stable disease (SD) lasting ≥ 24 weeks (6 months) as best overall response during the study, based on RECIST1.1, as assessed by the BICR and by the physician.

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- Duration of response (DoR) measured in responder patients from the time of first documented response (CR or PR) until the first documented disease progression (according to RECIST1.1) or death due to any cause, as assessed by the BICR and by the physician.
- PFS measured from the date of inclusion to the date of event defined as the first documented disease progression (according to RECIST1.1) or death from any cause, whichever occurs first as assessed by the BICR and by physicians. Patients with no event at the time of analysis will be censored at the date of last adequate tumor assessment.
- TTF defined as the time from the date of inclusion to the date of permanent study treatment discontinuation (any cause, including disease progression, treatment toxicity and death, withdrawal of consent). Patients without treatment failure at the time of the analysis will be censored at the date of last tumor assessment.
- OS measured from the date of inclusion to the date of death from any cause. Patients who are alive at the time of analysis (including lost to follow-up) will be censored at the date of last contact.
- Safety and tolerability, as assessed by the occurrence of TEAEs and treatment-related AEs according to NCI CTCAE v5.0.
- QoL (pre, 3- and 6-months post-treatment initiation, and EOT) EORTC QLQ-C30.

EXPLORATORY ENDPOINTS:

- Longitudinal assessment of FGFR alterations on ctDNA.

D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:

Drug name (INN)	Registered name	Pharmaceutical form	Administration route	Posology
pemigatinib	Pemazyre® *(information not present on bottles as clinical trial batches will be supplied)*	tablets	oral	13.5 mg QD 2 weeks on – 1 week off

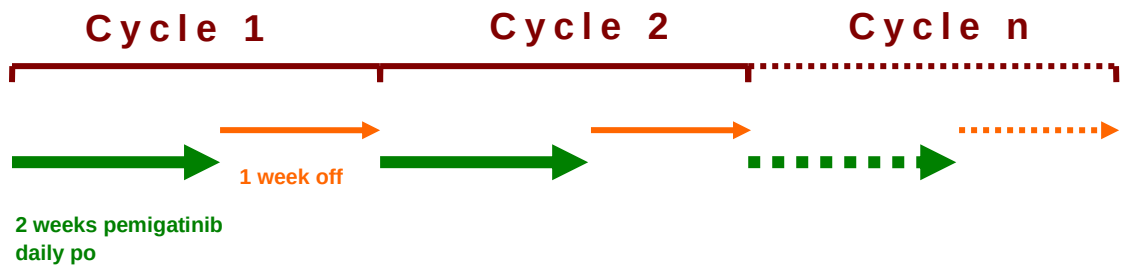
THERAPEUTIC REGIMENS:

Pemigatinib will be administered orally once daily for 2 weeks followed by a 1-week off (intermittent schedule 2/1).

The starting dose will be 13.5 mg daily with provision for dose reduction based on tolerability.

D) INVESTIGATIONAL MEDICINAL PRODUCTS

TRIAL FLOWCHART:



STARTING LEVEL

Level 1: 13.5 mg

DOSE REDUCTION LEVELS

Level -1: 9 mg

Level -2: 4.5 mg

1 cycle = 3 weeks (2 weeks on treatment + 1 week off treatment)

Dose	Dose reduction levels	
	First	Second
13.5 mg taken orally once daily for 14 days on, followed by 7 days off treatment.	9 mg taken orally once daily for 14 days on, followed by 7 days off treatment.	4.5 mg taken orally once daily for 14 days on, followed by 7 days off treatment.

Treatment should be permanently discontinued if patient is unable to tolerate 4.5 mg pemigatinib once daily.

TREATMENT DURATION:

Until disease progression (RECIST1.1) assessed by the investigator, unacceptable toxicity, patient's decision, or investigator's decision.

DOSE ESCALATION (IF APPLICABLE): NA

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED / INCLUDED: 40

A success is defined as an objective response (CR or PR) or a TGr < 0.7. The TGr is defined as the ratio of the slope of tumor growth on treatment (between the nadir and progression), and the slope of tumor growth before treatment. .

Forty (40) patients will be required for the study by using a A'Hern single-stage phase II design, with the following hypotheses:

- A success rate of 30% would be the minimal efficacy bound of pemigatinib justifying to consider the use of pemigatinib in the proposed therapeutic indication, based on the published results from Le Tourneau et al. (BJC 2012). In this previous work, among 44 patients with solid tumors treated with molecularly targeted agents, 16 patients (36%) had a TGr < 0.7; when restricted to the 32 patients with no new lesion during the study treatment, 10 patients (31%) had a TGr < 0.7.
- With a null hypothesis of a maximal ineffective success rate of 10%, 90% power and a one-sided alpha risk of 5%, 33 recurrent and/or metastatic cancer harbouring a FGFR fusion patients are needed.

Assuming 20% of not eligible patients for the calculation of the TGr, we plan to include about 40 patients in the study.

STATISTICAL ANALYSIS:

PRIMARY ENDPOINT

Treatment response will be estimated based on a binary variable (« success »/ « failure ») defined as follows, and as assessed by the BICR:

- Patients with an objective response or a TGr<0.7 will be considered in “success”
- Non-responder patients with a TGr >=0.7 will be considered in “failure”
- Patients for whom new lesions are reported at the time of progression (whatever the value of TGr) will be considered in “failure”
- Patients with unavailable first on-treatment tumoral evaluation due to early treatment discontinuation for progression or toxicity or death will be considered in “failure”
- Patients who do not meet any of the conditions described above will be considered as non-evaluable

The proportion of patients in success for the primary endpoint will be described with the associated unilateral 95% CI. At the end of the study, at least 7 patients experiencing a success are required to accept that pemigatinib could be effective. This means that the unilateral 95% CI should contain 30%, with a lower bound over 10% to accept that pemigatinib could be effective.

SECONDARY ENDPOINTS

E) STATISTICAL ANALYSIS PLAN

PFS, TTF, OS and DoR will be estimated using the Kaplan-Meier method, and will be described in terms of medians along with the associated 2-sided 95% CIs for the estimates; rates at appropriate time frames will be provided with the associated 95% CI when relevant.

ORR and CBR will be described with the associated 95% CI.

Safety will be assessed through recording of adverse events using NCI-CTCAE toxicity classification,

Quality of life, using the EORTC QLQ-C30 will be analyzed descriptively and according to the scoring manual. Evolution as compared to baseline will be calculated by patient. Graphic representations will be used to facilitate the interpretation of QoL data.

DEMOGRAPHIC DATA

Continuous variables will be summarized using median, minimum, maximum, mean SD, upper and lower quartile and number of available observations. Qualitative variables will be summarized using: counts, percents, number of missing data

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES:

Sequential blood samples for ctDNA analyses (every 3 cycles).

Archived FFPE tumor sample collected prior to the study (from initial primary, relapsed, or metastatic lesion)

SAMPLE QUANTITIES:

Blood: 2x 10mL tubes sampling at baseline, at each tumor evaluation (every 3 cycles), and at EOT. Sampling frequency will be adapted for long responder patients.

Tumor: 1 to 2 blocks of archived FFPE tissue.

G) TRIAL DURATIONS
INCLUSION PERIOD : 24 months
ESTIMATED TREATMENT PERIOD: 6 months
POST-TREATMENT FOLLOW-UP: 12 months
OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 42 months

H) SCHEDULE OF VISITS AND ACTIVITIES

Visit Day (Range)	Baseline	On-treatment phase				EOT 30d	Follow-Up	Note
		Cycle 1			Further cycles		Outcome	
	Days −28 to −1	Day 1 (before 1st drug intake)	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)		Every 3 months for at least 12 months from EOT	
Informed consent	X							
Inclusion/exclusion criteria	X							
Medical history								
Prior treatments, procedures, surgery for disease	X							
General and disease medical history	X							
Prior/concomitant medications	X	X	X	X	X	X		
Study treatment								
Administration of pemigatinib		D1 to D14			D1 to D14			
Recovery of used/empty bottles					X	X		
Safety assessments								
Eye examination : Slit-lamp, visual acuity, fundoscopy with digital imaging and optical coherence tomography (OCT)	X				X[1]	X		1- Once every 3 cycles starting at Cycle 3 (± 7 days) and as clinically indicated. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.
Physical examination/body weight/height	X[2]	X[3]	X	X	X	X		2-Height at baseline only. 3- If screening procedure performed within 3 days of C1D1, additional procedure not required.

Visit Day (Range)	Baseline	On-treatment phase				EOT 30d	Follow-Up	Note
		Cycle 1			Further cycles		Outcome	
	Days −28 to −1	Day 1 (before 1st drug intake)	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)		Every 3 months for at least 12 months from EOT	
Vital signs (blood pressure, pulse, respiratory rate, body temperature)	X	X[3]			X	X		3- If screening procedure performed within 3 days of C1D1, additional procedure not required.
AE assessments	X	X[3]	X	X	X	X		3- If screening procedure performed within 3 days of C1D1, additional procedure not required.
Single 12-lead ECG	X	X[3]			X	X		3- If screening procedure performed within 3 days of C1D1, additional procedure not required.
ECOG	X	X[3]			X	X		3- If screening procedure performed within 3 days of C1D1, additional procedure not required.
Efficacy assessments								
CT or MRI	X[4]				X[5]	X[6]	X[7]	4- 2 pre-treatment tumor evaluations performed with an interval of at least 4 weeks and no more than 3 months between the examinations (CT or MRI, but same technics for both). The second pre-treatment tumor assessment has to be done as close as possible to treatment initiation (no more than 7 days from treatment initiation). 5- Once every 3 cycles (9 weeks) starting at the end of Cycle 3 (± 3 days). 6- Perform at EOT if not done within 1 month prior to EOT. EOT due to clinical progression must be confirmed by a radiological assessement. 7- to be performed every 9 weeks (± 3 days) for patients who have discontinued treatment for other reasons than progression
QoL assessments	X				X[8]	X		8- at 3 and 6 months during treatment
Survival status							X[9]	9- Patients will be followed-up in the study for outcome status until the last patient in study had reached 12 months follow-upp from EOT.
Biological assessments (as described in the Table								

Visit Day (Range)	Baseline	On-treatment phase				EOT 30d	Follow-Up	Note
		Cycle 1			Further cycles		Outcome	
	Days −28 to −1	Day 1 (before 1st drug intake)	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)		Every 3 months for at least 12 months from EOT	
Required laboratory analytes)								
Blood chemistries	X	X[10]	X	X	X[11]	X		10- If screening analysis performed within 3 days of C1D1, additional analysis not required. 11- Hyperphosphatemia detected at Cycle 1 or later cycles requires testing of serum phosphate at Day 8 of further cycles
Hematology	X	X[10]			X	X		10- If screening analysis performed within 3 days of C1D1, additional analysis not required.
Coagulation	X	X[10]			X	X		10- If screening analysis performed within 3 days of C1D1, additional analysis not required.
Endocrine (PTH only)	X				X[11]	X		11- Every 3 cycles on Day 1 starting with Cycle 3.
HBV/HCV testing	X							
Urinalysis	X					X		
Serum/Urine pregnancy testing	D-14[12]	X[10]			X	X[12]		10- If screening analysis performed within 3 days of C1D1, additional analysis not required. 12- Serum testing
Translational research								
Plasma (for ctDNA) : 2x10 mL tubes	X				X[13]	X	X[7]	13- every 3 cycles (2 months) 7- to be performed every 9 weeks (± 3 days) for patients who have discontinued treatment for other reasons than progression
Archived FFPE tumor tissue	X							