PROTOCOL SUMMARY

A) TRIAL IDENTIFICATION	
Sponsor – protocol code number: UC-GMP-2505	
Version (Number & date): 1.0 – 05 June 2025	
Trial title: Widening treatment options among adult patients with HER2-overexpressing or mutant solid cancers **Phase (for trials on medicinal products):** Phase II	
Trial title for lay people: Clinical trial evaluating the activity of zanidatamab for the treatment of patients with solid tumors with an alteration of the HER2 gene	
Abbreviated title: Erreur ! Source du renvoi introuvable.	
Coordinating investigator: Dr Barbara PISTILLI **Co- coordinating investigator:** Pr Jean-Philippe METGES	
Number of centres: 20 (France)	**Number of patients:** 105

B) SPONSOR IDENTIFICATION	
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C) TRIAL GENERAL INFORMATION
Indication: Adult Patients with HER2-IHC3+ selected solid cancers (endometrial, colorectal, head & neck or sarcoma) or HER2 mutant non-small cell lung cancer.

Rational:

1.1 Prevalence and Significance of HER2 alterations in solid tumors

HER2 pathway alterations, consisting of HER2 amplifications/overexpression or activating mutations, have been described across different solid malignancies (Table 1) [Connell, et al ESMO Open 2017; Omar et al., Pathogenesis 2015; Friedlaender et al., Nat Rev Clin Oncol,2022; Uzunparmak B, et al., Ann Oncol. 2023; Yan M, et al., Cancer Metastasis Rev. 2015].

HER2 (ERBB2) amplification and/or overexpression is widely present in several cancer locations (Table 1). Among the most commonly altered, 15-20% of breast and a similar proportion of gastroesophageal (GE) junction adenocarcinomas and gastric cancers are concerned, and are treated by several anti-HER2 strategies. Activating mutations of HER2 typically occur in the absence of gene amplification and have been described in 5-10% solid tumors (mainly bladder, gallbladder and cutaneous cancers). Mutations of ERBB2 have been found also in ~2% of lung cancers and breast cancers, with a higher prevalence in invasive lobular carcinomas harbouring CDH1 mutations [LeNoue-Newton et al, CCR 2022].

Table 1. HER2 overexpression/amplification/mutation across different tumor histologies

HER2 overexpression/amplification	HER2 mutations
• NSCLC (10-30%) • Breast cancer (15-20%) • Gastric/GEJ (15-20%) • Billiary cancer (5-20%) • Salivary cancer (5-20%) • Urothelial (10-45%) • CRC (2-11%) • Endometrial cancer (20-60%) • Ewing, Osteosarcoma (20-30%) • Acute Lymphoblastic Leukemia (30%)	• Bladder cancer (10-20%) • Uterine cervix/endometrial cancer (6%) • CRC (6%) • Gastric/GEJ (5%) • NSCLC (4%) • Breast cancer (4%)

Therefore, a wide range of tumor histologies relies on HER2-kinase hyperactivation via HER2 amplification/overexpression or mutations in the ERBB2 gene, which encodes for the HER2 protein. Likewise, HER2 amplification, ERBB2 somatic point mutations, most of which are located in HER2 extracellular domain or kinase domain, are associated to receptor hyperactivation and may serve as oncogenic drivers [Wang et al, Cancer Cell 2006; Bose et al, Cancer Disc 2013].

1.2 Efficacy of HER2 targeting therapies across tumors with HER2 amplification/mutation

Prior preclinical and clinical data have shown a heterogenous activity of HER2 directed agents in several tumor types bearing HER2 amplifications or mutations. Indeed, a differential sensitivity to monoclonal antibodies such as trastuzumab and pertuzumab, and tyrosine-kinase inhibitors (TKIs) such as lapatinib and neratinib has been observed across different tumor types with HER2 alterations. For example, efficacy of neratinib (a panHER kinase inhibitor) widely varied according to tumor histology, with responses observed in patients with breast, cervical, non-small cell lung, biliary and salivary gland cancers and no activity observed in bladder and colorectal cancer,

regardless of type of HER2 mutation [Hyman et al, Nature 2018]. Similarly, a differential activity was observed according to tumor histology in patients with HER2-overexpressing tumors. For example, while the combination trastuzumab + pertuzumab and chemotherapy changed the natural history of HER2-positive metastatic breast cancer, it was associated to a modest improvement of survival outcomes in patients with HER2-positive metastastic gastric or GE cancers [Bang et al, Lancet 2010; Tabernero et al, Lancet Oncology 2018]. In the same way, the second-generation antibody drug conjugates (ADC), trastuzumab-emtansine (T-DM1) showed modest activity in HER2-positive gastric cancer and did not outperform taxol in patients with metastatic gastric cancer, while it showed meaningful activity in HER2-positive lung cancer, with higher benefit in HER2 3+ and HER2-mutated subtypes [Thuss-Patience et al, 2017; Jhaveri et al, Ann Oncol 2019; Chang et al, Clin Colorectal Cancer, 2022; Stinchcombe et al, JCO 2017; Li et al, Cancer Discovery 2020]. Third-generation HER2-targeting ADCs have demonstrated a greater efficacy across different HER2-expressing tumor types. T-DXd has proven significant activity in patients with HER2-positive and HER2-low-expressing advanced breast cancer, with a meaningful efficacy that has been confirmed in phase II and III trials, DESTINY BREAST01, DESTINY BREAST03 and DESTINY BREAST04 [Beck et al, 2017; Modi et al, 2020; Cortes et al, 2021; Modi et al, 2022]. Similarly, T-DXd significantly improved disease and survival outcomes among heavily pretreated patients with HER2-pos advanced gastric cancer [Shitara et al, NEJM 2020] and patients with HER2-mutant advanced NSCLC [Li et al, NEJM 2022].

1.3 Data on zanidatamab across different tumor types

Zanidatamab (ZW25, JZP598) is a novel humanized bispecific antibody (IgG1-like) directed against 2 non-overlapping HER2 epitopes: ECD4 and ECD2, which are also targeted by trastuzumab and pertuzumab, respectively. Preclinical data have shown greater activity as compared to trastuzumab and/or pertuzumab, as it relies on multiple mechanisms of action that include: improved receptor internalization and HER2 downregulation, inhibition of ligand-dependent and -independent cellular growth, activation of ADCC and uniquely, CDC [Weisser et al, Nat Commun. 2023]. The first-in-human phase I study (ZWI-ZW25-101, NCT02892123) demonstrated that zanidatamab is well tolerated and has promising single agent activity across patients with a wide range of HER2-expressing/amplified solid tumors (biliary tract cancer, colorectal cancer, breast and gastro-oesophageal cancers) that have progressed after standard of care therapies, including HER2-targeted agents such as trastuzumab, pertuzumab and T-DM1. The ORR was 37.0% (95% CI 27.0–48.7) and the most frequent treatment-related adverse events were diarrhoea (43%, all grade 1–2 except for one patient) and infusion reactions (34%, all grade 1–2). The selected zanidatamab dose for this study is the 2-tiered flat dosing regimen of 1800 and 2400 mg for participants with body weight < 70 and ≥ 70 kg, respectively. Zanidatamab will be administered Q3W, day 1 of each cycle.

Zanidatamab has also been evaluated in the HERIZON-BTC-01 global single-arm phase 2b study in patients with HER2-positive ABC that have progressed after treatment with a gemcitabine-containing regimen (Harding, 2023). 80 patients were included in cohort 1 (IHC 2+ or 3+; ISH +) and 7 in cohort 2 (IHC 0 or 1+), all treated with zanidatamab monotherapy (20 mg/kg Q2W). The primary objective was confirmed objective response rate (cORR). It was achieved in cohort 1 only. In this population refractory to a first line gemcitabine-based chemotherapy, the cORR was 41·3% [95% CI 30·4-52·8] in cohort 1. Responses were durable, with median DOR of 14.92 months (range, 1.5 to 20.6). Results for PFS (5,49 months (95% CI 3.65 – 7.29)) and OS (15,54 months (95% CI 10.38 – 18.46)) supported the primary endpoint and demonstrate persistence of the

zanidatamab treatment effect observed in Cohort 1. Zanidatamab exhibited a manageable and tolerable safety profile in participants with HER2 amplified BTC who had received at least 1 prior gemcitabine-containing regimen. Incidence of grade 3 AE was 63.2%. The most common TEAEs were diarrhea, infusion-related-reaction, and anemia that were generally manageable in the outpatient setting without zanidatamab dose reduction. Two patients (2.3%) discontinued zanidatamab due to an AE, and 3 (3.4%) had dose reduction due to an AE. There were 3 deaths due to TEAEs but none were considered by the investigator to be related to zanidatamab treatment. HER2 inhibitors have been associated with decreases in LVEF and pulmonary toxicity. These events were observed with zanidatamab treatment at an incidence of 5.7% for cardiac events, and 1.1% for pulmonary toxicity. Upon these data, FDA and EMA granted a marketed authorisation in this setting for IHC 3+ HER2 positive patients.

In HER2 positive endometrial cancer, zanidatamab failed to demonstrate a significant efficacy in a phase II study (Lumish et al., Gynecol Oncol. 2024). However, this result should be taken with caution in view of the limitations of the study: a low number of patients (n=16), different histologies and a heterogenous HER2 status.

1.4 Role of liquid biopsy in the assessment of HER2 expression/amplifications/mutations

Over the past 10 years, the development of new technologies has allowed a rapid escalation in the use of liquid biopsy (CTCs and ctDNA) in clinical research. Several studies have demonstrated the prognostic role of CTCs and ctDNA in multiple tumor subtypes and a number of ongoing trials have been evaluating their impact on treatment choices. Indeed, the assessment of genomic alterations in ctDNA and in some cases on CTCs and of mRNA transcripts and protein on CTCs has the potential of providing more dynamic and comprehensive evaluation of the tumor heterogeneity. HER2 expression may be consistently assessed on CTCs, although some discrepancies have been observed between primary tumors and CTCs [Fehm et al, Br Cancer Res Treat 2010], likewise ctDNA sequencing has been used for detecting HER2 mutations [Shishido et al, NPJ 2022]. Detection of HER2 alterations on CTCs and ctDNA has therefore the potential of providing a tumor monitoring tool able to early detect treatment response/resistance.

1.6 Scope of the project

We propose here a tumor agnostic multi-cohort basket trial evaluating the antitumor activity of zanidatamab as single agent in multiple adult solid tumors selected on HER2 IHC3+ or mutations. Through this trial we will be able to determine the activity of zanidatamab on large number of tumor histologies, including rare tumors that would otherwise have no access to this compound.

Trial description/design:

Open-label, non-randomized, single arm, multicentre, multi-cohort basket phase II trial evaluating the antitumor activity of zanidatamab as single agent in adult patients with HER2-IHC3+ or HER2 mutant selected solid cancers.

Primary objective:

The main objective is to assess the antitumor activity of zanidatamab in each cohort, using the confirmed objective response rate (ORR). Response to treatment will be assessed by investigators.

Secondary objectives:

To determine, in each cohort, the antitumor activity in terms of:

- Confirmed Objective Response Rate assessed by the Blinded Independent Central Review (BICR)
- Duration of Response assessed by the physicians and by the BICR
- Progression Free Survival assessed by the physicians and by the BICR
- Clinical Benefit Rate assessed by the physicians and by the BICR
- Overall Survival

To evaluate in each cohort and in the overall study population:

- Safety and tolerability of zanidatamab single-agent as per NCI-CTC AE v 5.0

Exploratory objectives:

Exploratory objectives will aim at deciphering mechanisms of response and resistance through:

- Investigation of immune response and immune related markers
- ctDNA and CTC response and dynamics

Inclusion criteria:

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

1. Histologically or cytologically confirmed endometrial, colorectal, head & neck, non-small cell lung cancer (NSCLC), or sarcoma
2. Patient with progressive, unresectable and/or advanced or metastatic disease harboring a locally performed, centrally reviewed HER2-overexpressing (IHC 3+ exclusively) for endometrial, colorectal, head & neck cancers, or sarcoma or a HER2 activating mutation for NSCLC, determined on tissue (see Section 7.1.2 of the protocol)
3. Age ≥ 18 years at inclusion
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
5. Patient who progressed at least after 1 line of therapy, for whom there is no other standard therapeutic option available
6. Patient with a HER2 alteration covered by a standard marketed indication for any HER2 targeting therapy should be included after standard anti-HER2 strategy has been exhausted.
7. Estimated life expectancy >3 months
8. Measurable 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 measurable if progression has been clearly demonstrated in the lesion
9. Adequate bone marrow function: absolute neutrophil count (ANC) ≥1.5 × 10^9/L, platelet count ≥75 × 10^9/L, and haemoglobin ≥9 g/dL. Transfusion is allowed with a 2-week washout period before treatment initiation
10. Adequate liver function: total bilirubin level ≤1.5 × the upper limit of normal (ULN) range (total bilirubin ≤3.0 ULN when the patient has documented Gilbert syndrome or liver metastasis), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤2.5 × ULN (AST and ALT ≤5 ULN when documented tumor liver involvement)
11. Adequate cardiac function: left ventricular ejection fraction (LVEF) ≥ 50% at baseline as determined by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 14 days before inclusion
12. Normal prothrombin time (PT) >70% and partial thromboplastin time (PTT), except for patient who uses anticoagulants
13. Adequate renal function: estimated serum creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula
14. Man, and woman of childbearing potential must agree to use highly effective contraception for the duration of trial participation and as required after completing study treatment (refer to Table 6 in the protocol). Man must also agree to not donate sperm and women must agree to not donate oocytes during the specified period
15. Woman of childbearing potential must have a negative serum pregnancy test performed within 3 days before the date of treatment initiation
16. Availability of a suitable archived FFPE sample of primary or metastatic tumor tissue (archived FFPE is <2 years old (desirable), maximum 5 years (accepted), buffered formalin fixed only. Fine-needle aspiration (cytology samples) and biopsies from sites of bone metastases are not acceptable) or patient accepts an optional biopsy under study
17. Willing and able to comply with the protocol for the duration of the study including scheduled visits, treatment plan, laboratory tests, specimen sampling for research, and other study procedures

18. Affiliated to a social security system
19. 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. Patient, in the judgment of the investigator, who should be included in another recruiting study assessing an anti-HER2 therapy (including zanidatamab)
2. Patient who received prior treatment with HER2-directed therapy unless marketed for the study cohort indication.
3. Other primary malignancies within 3 years 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 survivor, who has undergone potentially curative therapy for a prior malignancy, has no evidence of that disease for 4 years or more and is deemed at negligible risk for recurrence, is eligible for the trial
4. Any autoimmune, connective tissue or inflammatory disorder with pulmonary involvement not related to lung metastases (e.g. rheumatoid arthritis, Sjögren's syndrome, sarcoidosis)
5. Prior pneumonectomy
6. Patient with any condition or any evidence of severe or uncontrolled systemic diseases (e.g. active bleeding diatheses, active infection, or psychiatric illness) which in the investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required for eligibility
7. History of myocardial infarction or unstable angina within 6 months prior to enrolment, troponin levels consistent with myocardial infarction, or clinically significant cardiac disease, such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic congestive heart failure
8. Evidence of spinal cord compression or brain metastases, defined as being clinically active and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Patient with clinically inactive or treated brain metastases who are asymptomatic (i.e. without neurologic signs or symptoms and do not require treatment with corticosteroids or anticonvulsants) may be included in the study. Patient must have a stable neurologic status and no evidence of radiographic progression for at least 2 weeks prior to first zanidatamab dosing
9. Patient with evidence of any leptomeningeal disease. If leptomeningeal disease has been reported radiographically on baseline magnetic resonance imaging (MRI), but is not suspected clinically by the investigator, the subject must be free of neurological symptoms.
10. Acute or chronic uncontrolled pancreatitis or Child-Pugh Class C liver disease
11. Patient with unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to grade ≤1 or baseline, as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Patient with chronic Grade 2 toxicities may be enrolled at the discretion of the investigator after consultation and approval by the coordinating investigator.

12. Patient receiving chronic systemic corticosteroids dosed at >10 mg prednisone or equivalent anti-inflammatory activity or any form of immunosuppressive therapy within 2 weeks of first zanidatamab dosing unless otherwise approved by the coordinating investigator. Patient who requires use of bronchodilators, inhaled or topical or ocular steroids, or local steroid injections may be included in the study
13. Treatment with anthracyclines within 90 days before first dose of zanidatamab and/or total lifetime load exceeding 360 mg/m^2 doxorubicin or equivalent
14. A history of life-threatening hypersensitivity to monoclonal antibodies or recombinant proteins
15. Woman who is pregnant or breast-feeding
16. Participation in another therapeutic trial within the 30 days prior to entering the study. Participation in an observational trial would be acceptable
17. Patient unwilling or unable to comply with the medical follow-up required by the trial because of geographic, familial, social, or psychological reasons
18. Individual deprived of liberty or placed under protective custody or guardianship.

Primary endpoint:

Confirmed Objective Response Rate (ORR) for each cohort, based on best overall response, defined as the percentage of patients with a complete response (CR) or partial response (PR) during treatment or follow-up, assessed according to RECIST1.1, by investigator assessment and confirmed by a follow-up scan at ≥ 4 weeks from first response assessment.

Secondary endpoints:

- Confirmed ORR for each cohort, based on best overall response as adjudicated by the BICR, defined as the percentage of patients with a CR or PR during treatment or follow-up, assessed according to RECIST1.1 and confirmed by a follow-up scan at ≥ 4 weeks from first response assessment.
- Duration of Response (DoR) for each cohort will be evaluated in patients with either a CR or PR. DoR is defined as the time from the first assessment of a confirmed CR or PR until the date of the first occurrence of progressive disease (PD) according to RECIST1.1 or death from any cause (if death occurs within predefined period), whichever occurs first. At the time of analysis, a patient alive and without disease progression will be censored at the date of the last valid tumor assessment. DoR will be provided as assessed by investigators and as adjudicated by the BICR.
- Progression Free Survival (PFS) for each cohort is defined as the time from study registration until disease progression (per RECIST1.1) or death from any cause, whichever occurs first. At the time of analysis, a patient alive and without disease progression will be censored at the date of the last valid tumor assessment. PFS will be provided as assessed by investigators and as adjudicated by the BICR.
- Clinical Benefit Rate (CBR) for each cohort is defined as the percentage of patients with a CR or PR or stable disease (SD) for more than 16 weeks from inclusion assessed according to RECIST1.1. CBR will be provided as assessed by investigators and as adjudicated by the BICR.
- Overall Survival (OS) for each cohort is defined as the time from study registration until death from any cause. Patients who are alive at last follow-up will be censored at this date.
- The safety will be evaluated according to the incidence of adverse events (AEs) graded by NCI-CTCAE v5.0, per cohort and overall.

Exploratory endpoints:

Response and resistance to treatment will be assessed in terms of ORR and survival endpoints (PFS, OS).

D) INVESTIGATIONAL MEDICINAL PRODUCTS

Product names and administration:

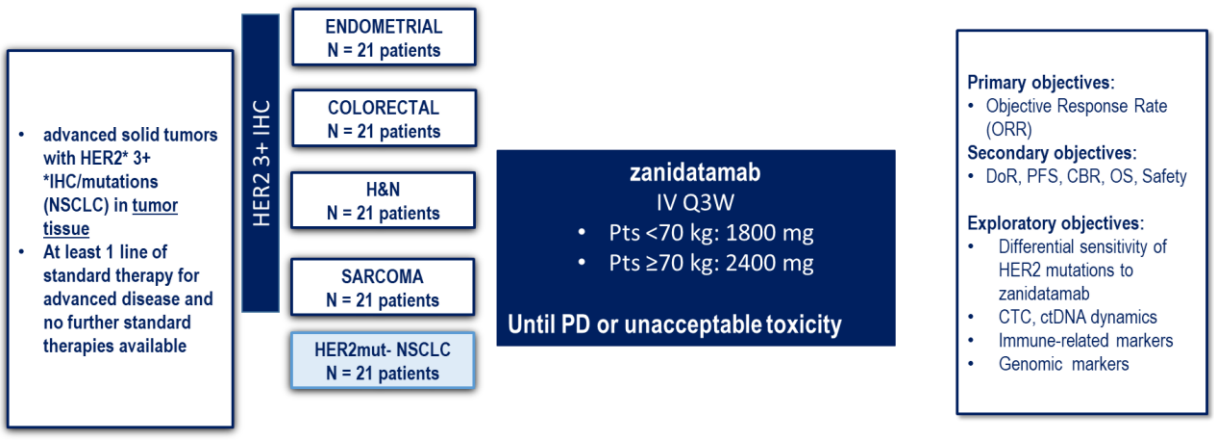
Drug name (INN)	Registered name	Pharmaceutical form	Administration route	Posology
Zanidatamab	NA	300 mg powder for concentrate for solution for infusion	IV	• Participants < 70 kg: 1800 mg Q3W (ie, Day 1 of each 21-day cycle) • Participants ≥ 70 kg: 2400 mg Q3W (ie, Day 1 of each 21-day cycle)

Therapeutic regimens:

Single arm study where the experimental regimen used for all patients will be zanidatamab, administered intravenously every 3 weeks:

- Patients <70 kg: 1800 mg IV Q3W on Day 1 of each 21-day cycle
- Patients ≥70 kg: 2400 mg IV Q3W on Day 1 of each 21-day cycle.

Trial Flowchart:



	Baseline	C2D1	C4D1	C6D1	PD/EoT
Tumor biopsy	x (optional)				x (optional)
Whole blood	x				
Blood for CTC	x	x			x
Blood for ctDNA	x	x	x	x	x

*scored according to ESMO criteria

Treatment duration:

Treatment duration is estimated to 6 to 8 months for a patient.

Patients will be treated until disease progression (RECIST v1.1) as assessed by the investigator. Treatment may also be terminated early at the initiative of either the patient or the investigator for any reason that would be beneficial to the patient, including: unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient request.

Dose escalation (if applicable):

Not applicable

E) STATISTICAL ANALYSIS PLAN

Required number of patients to be included:

Hypothesis : Considering that this study will include heavily pretreated patients with refractory diseases and no longer standard therapeutic options, a null hypothesis with a 10% threshold represents a realistic yet stringent benchmark for evaluating the activity of zanidatamab in this difficult-to-treat population.

10% vs 35%, alpha=5%, power=85%

Each cohort will be considered independent and conducted as a phase II trial using an A'Hern design. The following hypotheses are used:

- p0 = 10%, maximal unacceptable rate of patients presenting a confirmed objective response for whom the experimental treatment will be considered as insufficiently active.
- p1 = 35%, minimal acceptable rate of patients presenting a confirmed objective response for whom the experimental treatment will be considered as sufficiently active.

Using an A'Hern design (alpha = 5%, 1-beta = 85%) and (p0 = 10%; p1 = 35%), 19 patients evaluable need to be included. The decision rules are summarized in the table below

Nb of patients evaluable	Insufficiently active	Sufficiently active
19	≤ 4 successes	≥ 5 successes

* Success: Confirmed objective response

Supposing a 10% drop out rate, 21 patients will be included in each cohort.

For the 5 pre-planned cohorts, the required number of patients is 105.

Statistical analysis:

Demographic and clinical data

Demographic and clinical characteristics (including HER2 status) will be presented in the overall population and per cohort using usual statistics. Quantitative variables will be summarized as median, min, max, and number of missing data. Qualitative variables will be described as number, percentage, and number of missing data.

Population definition

The following populations will be considered for analyses:

- Per-protocol: all eligible patients with at least one valid post-baseline disease assessment (or with early death due to disease progression before first disease assessment) and have received any amount of zanidatamab treatment.
- Safety population: all patients who initiated allocated treatment (i.e. received any amount of zanidatamab treatment).

Primary endpoint

The primary endpoint will be assessed in the per protocol population and will be reported per cohort. The primary endpoint is the rate of evaluable patients for response presenting a confirmed objective response assessed by the investigators according to RECISTv1.1. It will be presented as number, percentage, and 95% confidence interval (CI): by the binomial exact distribution.

Secondary endpoints

The secondary efficacy endpoints will be assessed in the per protocol population and will be reported per cohort.

ORR by BICR, CBR and CBR by BICR will be presented using frequency, percentage, and the 95% CI (Binomial exact distribution).

DOR, DOR by BICR, PFS, cPFS and OS will be estimated at different time points using the Kaplan-Meier method. Median survival times will be estimated and reported with the corresponding 95% CI.

The secondary safety endpoints will be assessed in the safety population and will be reported per cohort and on the overall population. Incidence rates of adverse events and serious adverse events will be presented using frequencies and percentages by system organ class and MedDRA preferred term. Pharmacovigilance will be handled by UNICANCER.

Exploratory endpoints

Biological parameters (immune biomarkers, genomic alterations, mutations, …) will be described using usual statistics.

Comparisons between groups will be performed using the Kruskal-Wallis test for continuous parameters and the Chi-squared or Fisher's exact test for qualitative parameters. Correlation between continuous parameters will be evaluated using the Spearman rank correlation coefficient.

Associations between biological parameters and ORR will be studied using a logistic regression model.

Associations between biological parameters and PFS and OS will be performed using the Logrank test and the Cox proportional hazards model.

D) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

Sample types:

- At baseline:
  - archival FFPE tumor from previous biopsies (primary tumor of metastatic lesion) or tumor surgeries or optional newly performed tumor biopsy under the study
  - blood for CTC and ctDNA
  - whole blood
- On treatment at C2D1
  - Blood for CTC and ctDNA
- On treatment at C4D1, C6D1
  - Blood for ctDNA
- At end of treatment/progression:
  - Blood for CTC and ctDNA
  - optional newly performed tumor biopsy

Sample quantities:

Archived tumor or new biopsy: 1 to 2 FFPE blocks, 1 frozen core biopsy when possible

Whole blood sample: 1 X 5 mL EDTA tube

Blood for CTC: 3 x 10 mL Cell Save Tubes (for Paris and Ile de France centers only)

Blood for ctDNA: 2 x 10 mL EDTA tubes

G) TRIAL DURATION

Inclusion period: 20 months

Estimated trial treatment period: 6 to 8 months

Post-treatment follow-up: 24 months

Duration until primary endpoint evaluation: 26 to 28 months

Overall trial duration (First patient in- Last patient out): 28+24 = 52 months

SCHEDULE OF VISITS AND ACTIVITIES

VISITS	**Baseline**	**Follow-up during treatment**								**EoT**	**Post-treatment follow-up[7]**
Visit Dates	**D0**	**D1**	**D21**	**D42**	**D63**	**D84**	**D105**	**D126**		**+ 30 days post-treatment**	**Every 12 weeks**
Cycles [Range days]		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**Cn**		
Inclusion/Exclusion criteria	[-28 - 0]										
Signed informed consent form	[-28 - 0]										
Demographic data collection	[-28 - 0]										
Cancer description and history	[-28 - 0]										
Relevant medical history	[-28 - 0]										
Significant concomitant medications and therapies	[-14 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	
Contraception use confirmation	[-28 - 0]										
HER2 overexpression/mutation status	[-28 - 0]										
Verification that a suitable FFPE tissue is available	[-28 - 0]										
Study registration/enrolment	***0***										
TREATMENT ADMINISTRATION											
Zanidatamab infusion		D1	D1	D1	D1	D1	D1	D1	D1		
SAFETY ASSESSMENTS											
PHYSICAL EXAMINATION											
Height, Weight,	[-28 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	
Physical examination : organ or body systems	[-3 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	
Vital signs & ECOG PS	[-3 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	
Collection of adverse events	[-3 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-14 - + 14][7]
PARACLINICAL EXAMINATION											
ECG	[-3 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	
LVEF measurement (echocardiogram or MUGA)[1]	[-14 - 0]			[-7]				[-7]	[-7][1]	[-3]	
BIOLOGICAL TESTS											
CBC, platelets	[-7 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	
Ionogram and biochemistry	[-7 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	
Renal and hepatic function	[-7 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	
Coagulation function[2]	[-7 - 0] [2]									[-3] [2]	

VISITS	**Baseline**	**Follow-up during treatment**								**EoT**	**Post-treatment follow-up[7]**
Visit Dates	**D0**	**D1**	**D21**	**D42**	**D63**	**D84**	**D105**	**D126**		**+ 30 days post-treatment**	**Every 12 weeks**
Cycles [Range days]		**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**Cn**		
WOCBP only: Pregnancy test (serum or urine)[3]	[-3 - 0]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3]	[-3][3]
EFFICACY ASSESSMENTS											
Clinical assessment or palpable/visual lesions	[-28 - 0]			[-3]		[-3]		[-3]	[-3][5]	[-30][6]	
Radiological tumour assessment (RECIST v1.1)[4,5,6]	[-28 - 0]			[-3]		[-3]		[-3]	[-3][5]	[-30][6]	
FOLLOW-UP INFORMATION											
Disease status, survival & subsequent anticancer therapy[7]											[-14 - + 14] [7]
TRANSLATIONAL RESEARCH											
Tumor biopsy (optional)	[-28 - 0]									[-3]	
Blood collection	[-7 - 0]		[-3]	[-3]		[-3]				[-3]	

1. LVEF measurement are to be performed pre-dose zanidatamab within 14 days prior zanidatamab initiation, at Cycle3-Day1, and every 4 subsequent cycles.
2. Coagulation test results must be made available before the optional tissue biopsy is engaged.
3. Serum testing at baseline and EoT, urine testing during treatment phase and monthly urine or serum testing during post-treatment 4-month-follow-up phase.
4. Radiological tumor assessment will be performed using CT scan or MRI of the thorax, abdomen and pelvis (as per standard practice). Other explorations are left to physician's decision.
5. Radiological and clinical assessments will be performed every 42 (±7) days, and every 84 (±7) days beyond 18 months on treatment,
6. Patients who discontinue study treatment for reasons other than disease progression (RECIST v1.1), death or consent withdrawal will continue to perform disease evaluations according to this 42 (±7) day schedule (or 84 (±7) days beyond 18 months on treatment) during the follow-up period, until PD.
7. Long Term Follow-Up will follow standard practice and frequency. During this time, information will be collected every 84 (±14) days from the patient's chart.