# PROTOCOL SUMMARY

| A) TRIAL IDENTIFICATION | |
|---|---|
| **Sponsor – protocol code number:** PRODIGE 73 – UCGI 40 | |
| **Version (Number & date):** V1.1 – 11 AUGUST 2022 | |
| **Trial title:** Randomised phase II study evaluating trifluridine/tipiracil plus oxaliplatin versus FOLFOX in patients with gastric, oesophagus or gastroesophageal junction adenocarcinoma locally advanced, recurrent or metastatic, ineligible for triplet chemotherapy<br><br>**Phase (for trials on medicinal products):** II | |
| **Trial title for lay people:** Oxaliplatin in combination with trifluridine/tipiracil or 5-fluorouracile in frail patients with advanced, recurrent or metastatic gastric, oesophageal or gastroesophageal junction cancer | |
| **Abbreviated title:** PRODIGE 73 – UCGI 40 – LOGICAN | |
| **Coordinating investigator:** Dr. Christelle DE LA FOUCHARDIERE | |
| **Number of centres (estimate):** 21 | **Number of patients randomised:** 118 |

| B) SPONSOR IDENTIFICATION | |
|---|---|
| **Name:** | **UNICANCER**<br>101, rue de Tolbiac<br>75654 Paris Cedex 13<br>(France) |
| **Contact person:** | **Mr Nicolas DE SOUSA CARVALHO**<br>Project Manager<br>UNICANCER<br>Tel: +33 (0)1 71 93 67 09<br>Fax: + 33 (0)1 6 77 59 49 25<br>email: n-de-sousa@unicancer.fr |

## C) TRIAL GENERAL INFORMATION

**Indication:**

Patients with gastric, oesophagus or gastroesophageal junction adenocarcinoma locally advanced, recurrent or metastatic, ineligible for triplet chemotherapy (e.g. DCF, EOX, ECX, EOF, ECF, TFOX).
Patients ineligible for triplet chemotherapy are patients with ECOG-PS=2 or age ≥70 years old plus one frailty criteria on ADL or IADL score or patients presenting a denutrition defined by albumin <30 g/l.
*The reason of ineligibility to triplet chemotherapy will be collected in the CRF.*

**Trial description/design:**

Randomized, open label, comparative, multicentric, phase II trial comparing Trifluridine/Tipiracil + oxaliplatin vs FOLFOX regimen as first-line palliative therapy

**Primary objective:**

The primary objective is to evaluate the superiority of trifluridine/tipiracil + oxaliplatin over FOLFOX regimen in terms of Progression-Free Survival (PFS), in first-line palliative setting, in patients with gastric, oesophagus or gastroesophageal junction adenocarcinoma locally advanced, recurrent or metastatic, ineligible for triplet chemotherapy.

**Secondary objectives:**

The secondary objectives are the evaluation of:

- The efficacy of the treatments in terms of:
    - Objective Response rate (according to RECIST v1.1) (ORR)
    - Overall Survival (OS)
- Safety and tolerability of treatment (NCI-CTCAE version 5.0)
- Time to PS deterioration >2
- The effect of treatments on Quality of Life (QoL)

**Ancillary studies:**
To evaluate prognostic and predictive values of several biological and radiological biomarkers. A correlation with Geriatric Core Dataset (G-CODE) and overall treatment utility (OTU) (Hall's index) will also be studied in patients ≥70 years old.

**Diagnosis and Inclusion criteria:**

1. Histologically confirmed locally advanced, recurrent or metastatic non resectable adenocarcinoma of the stomach, oesophagus or gastroesophageal junction (GEJ) ineligible to curative treatment and ineligible to immunotherapy (CPS <5 or patient presenting any contra-indication preventing the use of immunotherapy).
2. No dysphagia or difficulty in swallowing.
3. No overexpression/amplification of HER2 (IHC 0 or 1+; if IHC is 2+, HIS must be negative). Known CPS PD-L1 score (result in % with the name of the method used). The microsatellite and MMR status of patient's tumour (MSI/MSS and pMMR/dMMR) must also be known at the time of screening (IHC and PCR tests have to be done).
4. At least one evaluable lesion according to RECIST v1.1 outside any previously irradiated area.
5. No prior palliative chemotherapy.
6. Age ≥18 years old.
7. Patient unfit for triplet chemotherapy = ECOG-PS=2 or age ≥70 year old **PLUS** one frailty criteria on ADL/IADL score or denutrition defined by albumin <30 g/L
   *The reason of ineligibility to triplet chemotherapy will be collected in the CRF.*
8. Adequate organs function:
   - ✓ Absolute neutrophils count ≥1.5x$10^9$/L
   - ✓ Platelets count ≥100x$10^9$/L
   - ✓ Haemoglobin ≥9 g/L
   - ✓ Serum bilirubin levels <2 times upper limit of normal (ULN), up to 2.5 times ULN in case of hepatic metastasis (biliary drainage allowed)
   - ✓ Transaminases <5 times ULN
   - ✓ Creatinine clearance >40 mL/min
9. No Dihydropyrimidine dehydrogenase (DPD) deficiency (uracilemia <16 ng/ml)
10. Women of childbearing potential must have a negative serum or urine pregnancy test done within 14 days before the first study treatment.
11. Patients must agree to use adequate contraception methods for the duration of study treatment and within 6 months after completing treatment.
12. Patients must be affiliated to a Social Security System (or equivalent).
13. Patient must have signed and dated 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 writing the patient's consent.
14. Availability of archived tumour material for ancillary studies

**Non-inclusion criteria:**

1. Patient with a performance status ECOG PS >2.
2. Other current or previous malignancy within the past 3 years (with the exception of squamous cell carcinoma of the skin treated by surgery).
3. Adjuvant chemotherapy or radio-chemotherapy completed for less than 6 months.
4. Peripheral neuropathy of NCI-CTCAE grade ≥2 at baseline.
5. Patients with known allergy or severe hypersensitivity to any of the trial drugs or any of the trial drug excipients.
6. Patients unwilling or unable to comply with trial obligations for geographic, social, or physical reasons, or who are unable to understand the purpose and procedures of the trial.
7. Previous treatment with trifluridine/tipiracil.
8. Known Human Immunodeficiency Virus (HIV) infection.
9. Active Hepatitis B virus (HBV, defined as having a positive hepatitis B surface antigen [HBsAg] test prior to inclusion) or hepatitis C virus (HCV).
10. Interstitial lung disease.
11. Prior pneumonitis requiring systemic corticosteroid therapy.
12. Active infections.
13. Pregnant or breastfeeding woman.
14. Participation in another therapeutic trial within the 30 days prior to randomisation.
15. Persons deprived of their liberty or under protective custody or guardianship.
16. Clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months, or high risk of uncontrolled arrhythmia (for men: QTc ≥450 msec, for women: QTc ≥470 msec)

**Primary endpoint:**

PFS defined as the time from the date of randomisation to date of disease progression (radiological or clinical) or death from any cause, whichever occurs first. Patients without tumour progression or death at the time of analysis will be censored at the date of their last tumour assessment.

**Secondary endpoint(s):**

- Efficacy endpoints:
  - ORR (according to RECIST v1.1) defined as the percentage of patients with Complete Response (CR) or Partial Response (PR). Patients who discontinue treatment without a tumour assessment will be considered non-responders for the analysis
  - Overall survival (OS), defined as the time from date of randomisation to the date of death from any cause. Patients alive at the database cut-off date will be censored at the last date of follow-up.

- Safety and tolerability of treatment (NCI-CTCAE version 5.0) determined through the incidence of adverse events, treatment related adverse events, serious adverse Events (SAE), and death.

- Time to PS deterioration >2 defined as the time between patient randomisation and the first date when PS>2

- Quality of Life (QoL) according to QLQ-C30 questionnaire

- Ancillary studies will address:
  - Specific pathological features and expression of biomarkers: microsatellite status (MS), PD1 and PDL1 expression, TMB, CD8+ cell infiltration, Epstein Barr Virus (assessed by in situ hybridization), TP53, E-cadherin, HER3.
  - Circulating tumour DNA (ctDNA) and its value for prognosis and treatment monitoring (monitoring of DNA levels at different point during the treatment: pretreatment ctDNA and then every two months during the first year or till disease progression whatever occurs first). Genetic changes on several genes will also be evaluated.
  - Correlation of Geriatric Core Dataset (G-CODE) (including social assessment, functional autonomy, mobility, nutrition, cognition, mood and comorbidity analysis) and Overall survival.
  - Correlation of different biological prognostic scores (Glasgow and modified Glasgow Prognostic Score (GPS; mGPS), NLR (Neutrophil to Lymphocyte Ratio) with patient outcome.

## D) INVESTIGATIONAL MEDICINAL PRODUCTS

**PRODUCT NAMES AND ADMINISTRATION:**

| Drug name (INN) | Registered name (1) | Pharmaceutical form | Administration route | Posology |
|---|---|---|---|---|
| Trifluridine/Tipiracil 15mg/6.14 mg | Lonsurf® | Film-coated tablet | Oral | 35 mg/m² BID for 5 days (D1=D15) |
| Trifluridine/Tipiracil 20mg/8.19 mg | Lonsurf® | Film-coated tablet | Oral | 35 mg/m² BID for 5 days (D1=D15) |
| 5FU | - | Concentrate for solution for infusion | Intravenous (IV) | 46-hour continuous infusion 5-FU 2400 mg/m² at day1, every 14 days |
| 5FU | - | Concentrate for solution for infusion | Intravenous (IV) | Bolus<br>5-FU 400 mg/m² at day 1, every 14 days |
| Capecitabine | - | Film-coated tablet | Oral | 1000 mg/m² BID during 2 weeks, every 3 weeks |
| Oxaliplatin | - | Concentrate for solution for infusion | Intravenous (IV) | 70-85 mg/m² at day 1, every 14 days |
| Folinic acid | - | Solution for injection or infusion | Intravenous (IV) | 400 mg/m² at day 1, every 14 days |
| L-folinic acid | - | Solution for injection or infusion | Intravenous (IV) | 200 mg/m² at day 1, every 14 days |

*(1) When any generic drug can be is used indicate only the INN name. The choice of the registered name or brand name used in the trial is at the investigation centre discretion.*

**Therapeutic regimens:**

**ARM A**: **Experimental group (Trifluridine/Tipiracil + Oxaliplatin)**

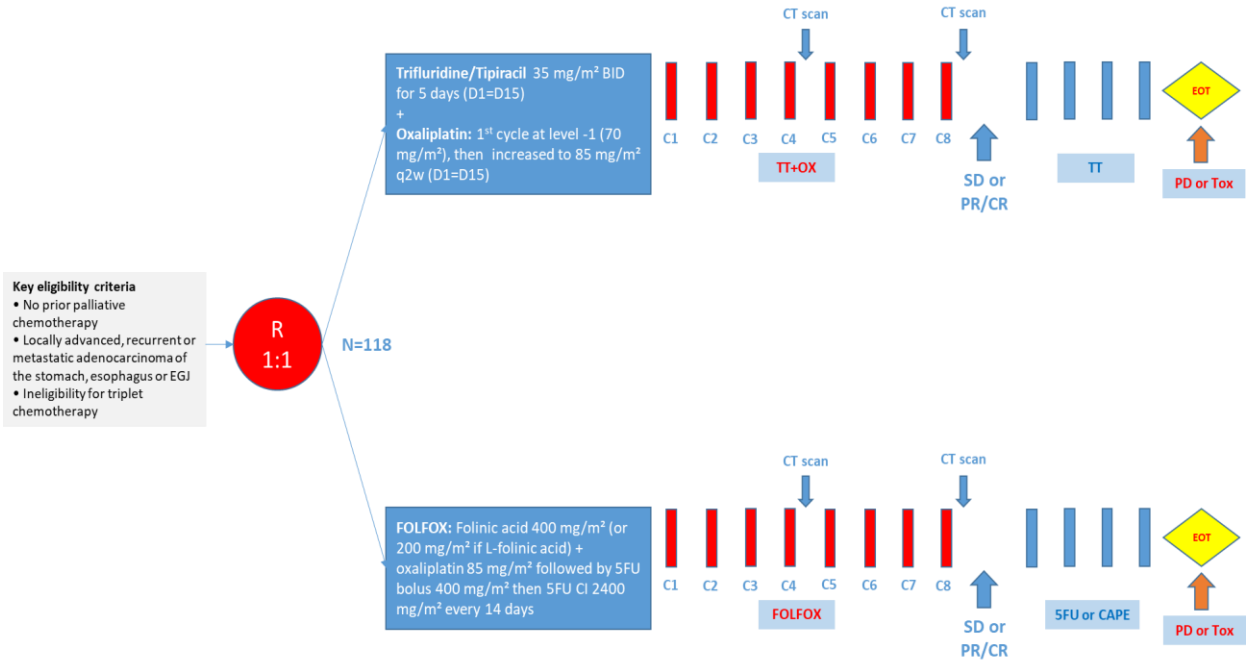
Trifluridine/Tipiracil will be administered with a 14-day schedule (35 mg/m² twice-daily [BID] for 5 days followed by 9 days of recovery) until disease progression or intolerable toxicity.

Oxaliplatin will be administered intravenously on day 1 of each treatment cycle (infusion duration: 2 hours), every 2 weeks. The first cycle will be administered at level -1 (70 mg/m²) and then increased to 85 mg/m² (if feasible) from the cycle 2 to 8 or until disease progression, whatever occurs first. In case of limitant-oxaliplatin neuropathy (see section 5.5.3) and in all cases after 8 cycles, oxaliplatin will be stopped and Trifluridine/Tipiracil will be continued alone until disease progression or intolerable toxicity.

**ARM B : Comparator group (FOLFOX)**

Folinic Acid 400 mg/m² (or 200 mg/m² if L-folinic acid) + oxaliplatin 85 mg/m² (infusion duration: 2 hours) followed by 5-FU bolus 400 mg/m² and then 5-FU 2400 mg/m² as a 46-hour continuous infusion. Treatment repeated every 14 days. In case of limitant-oxaliplatin neuropathy (see section 5.5.3) and in all cases after 8 cycles, oxaliplatin will be stopped and 5-FU (simplified LV5FU2 regimen) or capecitabine (1000 mg/m² BID during 2 weeks every 3 weeks) will be continued alone until disease progression or intolerable toxicity.

**Trial Flowchart:**



| |
|---|
| **Treatment duration:** The patient will be randomized in one of the two treatments arms and will receive their treatment every 14 days until disease progression or intolerable toxicity. Oxaliplatin will be stopped after 8 cycles or earlier in case of limitant-oxaliplatin neuropathy. |
| **Dose escalation (if applicable):** NOT APPLICABLE |

| **E) STATISTICAL ANALYSIS PLAN** |
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| **Required number of patients to be screened/included:** |
| 118 randomized patients (59 per arm) |

**STATISTICAL ANALYSIS:**

Statistical analysis: randomized comparative phase II study.

**Sample size justification**

The study was calibrated to detect a treatment effect hazard ratio (HR) of 0.65 under the proportional hazards assumption, translating in an improvement in median PFS from 7.7 months (control arm) to 11.8 months (experimental arm).
With a 1:1 randomisation, a total of 97 events observed in the study would have 80% power to show statistically significant PFS at a 1-sided alpha level of 10%. Considering a recruitment duration of 36 months and a 24-month follow-up for the last included patient (estimated total duration of the study: 60 months), and assuming a common exponential dropout rate of 1%, 118 patients will be randomized in the study (59 patients by arm) so that maturity of the PFS data is approximately 82%.

**Analysis populations**

ITT Population: The ITT population is defined as all patients randomized in the trial.
Per-Protocol population: The Per-Protocol population is a subgroup of the ITT population containing all randomized patients with no major protocol violation who received at least one dose of study treatments.
Safety analysis set: The safety analysis is defined as all randomized patients having received at least one dose of study treatment, whether withdrawn prematurely or not.

Baseline characteristics and Efficacy endpoints will be described among the ITT population. The safety population will be used for safety analyses.

**General methods**

Qualitative variables will be described using frequency and percentage distributions. The number of missing data will be given, but will not be considered for the calculation of proportions. Quantitative data will be described using the number of observations, mean, standard deviation, median, minimum and maximum values. The date of randomisation will serve as a reference for calculation of durations unless otherwise indicated.
Statistical analyses will be performed using SAS® software version 9.4 or later.

**Randomisation stratification**:

Randomisation will be stratified on:

- PS 0-1 vs 2
- Age <75 vs ≥75

**Timing**

No interim analysis is planned. Final analysis will be performed after that required number of events (97 progression or death) are notified in order to ensure the expected statistical power and will be performed on frozen database after blind review.

**Analysis methods**

PFS will be estimated using the Kaplan-Meier method, and will be described in terms of median PFS and 1 year PFS rate, along with the associated 1-sided 90% confidence interval (CI; in accordance with sample size calculation) for the estimates.

OS will be estimated using the Kaplan-Meier method, and will be described in terms of median OS and 2-years OS rate, along with the associated 2-sided 95% CIs for the estimates.

PFS and OS analyses will be supplemented by a Cox model in order to measure the effect of the treatment throughout the follow-up (Hazard Ratio and its 95% CI).

Overall Response will be assessed according to RECIST v1.1 criteria. Percentage of responders will be presented with its 95% confidence interval.

Safety will be assessed in terms of AEs, SAEs and Toxic deaths. AE will be described according to MedDRA terms and graded according to CTCAE version 5.0. Descriptive statistics will be provided for characterizing and assessing patient tolerance to treatment.

QoI analysis will be performed according to the QLQ-C30 scoring manual provided by EORTC. Descriptive statistics will be used to summarize the scored scales at each scheduled assessment time point. Variation from baseline will be described.

## F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

**Sample types:** Tumour tissues and blood samples

**Sample quantities:**

Archived tumour tissues available will be collected for analysis (frozen and/or FFPE tissues) at baseline. Optional biopsy will be proposed to patients to collect tumour tissues at disease progression.

Blood samples will be collected for ctDNA testing: Blood samples will be collected at baseline before the experimental treatments and then every two months during the first year following randomisation or till disease progression, whatever occurs first. 30 mL of blood (5 EDTA tubes of 6 mL) will be collected at each sampling point (total: 210 mL of blood collected per patient)

| G) TRIAL DURATIONS |
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| **Inclusion period:** 36 months |
| **Trial treatment period:** 12 months |
| **Follow-up:** 12 months |
| **Duration until primary endpoint evaluation:** approximately 48 months |
| **Overall trial duration (including follow-up):** 60 months |

# H-SCHEDULE OF VISITS AND ACTIVITIES (SOA)

| | Baseline | Visits during study treatment | End of Treatment (EOT) visit | Follow-up visits |
|---|---|---|---|---|
| | Within 14 days prior to first study treatment. Imagery can be done within 28 days prior to first study treatment | Day 1 of each cycle (delay ≤3 days allowed) | 35 days (±5 days) after last study treatment | Every 8 (±2) weeks after EOT. Every 12 (±2) weeks after progressive disease |
| Consent signature | X | | | |
| Eligibility criteria | X | | | |
| Randomisation | X | | | |
| Diagnosis & prior anticancer therapies | X | | | |
| Demographics, Medical history & signs and symptoms | X | | | |
| Prior medication & concomitant medication | X | X | X | |
| Clinical exam (physical exam, PS) + vital signs[1] | X | X | X | X[5] |
| Glasgow and Modified Glasgow Prognostic Scores evaluation[6] | X | | | |
| Adverse events | | X | X | X |
| Electrocardiogram (ECG)[10] | X | X | | |
| Serology (HIV, hepatitis B/C) | X | | | |
| Serum or urine pregnancy test (for all women of childbearing potential) | X | X[11] | X | |
| Complete Blood Count[2] | X | X | X | |
| Neutrophil/Lymphocyte Ratio (NLR) evaluation | X | | | |
| Coagulation factors[3] | X | | | |
| Serum chemistries[4] | X[7] | X | X | |
| Uracilemia | X | | | |
| Tumour biomarkers (every 8 weeks from D1C5 till disease progression) - CEA and CA19-9 | X | every 8 weeks from D1C5 till disease progression | X | X |
| CT-Scan (Thorax, Abdomen, Pelvis) (every 8 weeks from D1C5 till disease progression) | X | every 8 weeks from D1C5 till disease progression | X | X |
| Tumour assessments (RECIST v1.1) (every 8 weeks from D1C5 till disease progression) | X | every 8 weeks from D1C5 till disease progression | X | X |
| QoL questionnaire (QLQ-C30) (every 8 weeks from D1C5 till disease progression) | X | every 8 weeks from D1C5 till disease progression | X | X |
| G-CODE evaluation (only in patients ≥ 70 years)[8] | X | X | X | X |
| Archived tumour material preparation and shipment | X | | | |
| **Optional procedures if patient consented to translational research** | | | | |

| | Baseline | Visits during study treatment | End of Treatment (EOT) visit | Follow-up visits |
|---|---|---|---|---|
| | Within 14 days prior to first study treatment. Imagery can be done within 28 days prior to first study treatment | Day 1 of each cycle (delay ≤3 days allowed) | 35 days (±5 days) after last study treatment | Every 8 (±2) weeks after EOT. Every 12 (±2) weeks after progressive disease |
| Blood samples for ctDNA testing (5 EDTA tubes of 6 mL at each sampling point) | X[9] | every 8 weeks from D1C5 during the first year after randomisation or till disease progression, whatever occurs first) | | |
| Optional tumour biopsy | | at disease progression, before any new anticancer treatment initiation | | |

1) Vital signs: height, weight, blood pressure, pulse, body temperature. Height only at baseline.
2) CBC: haemoglobin, RBC counts, WBC and differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelets
3) Coagulation factors: partial thromboplastin time, fibrin, prothrombin ratio, sedimentation rate
4) Serum chemistries: Na, Ca, P, Mg, K, Cl, HCO3-, creatinine, urea, creatinine clearance, total protein, albumin, glucose, alkaline phosphatase, total and conjugated bilirubin, AST, ALT, LDH, γGT
5) During follow-up visits: only physical examination and evaluation of PS (vital signs are not to be done)
6) Glasgow and Modified Glasgow Prognostic Scores calculation method: see protocol Appendix 8
7) At baseline, in addition to parameters reported at item 4), serum chemistries must also include the C-reactive protein to allow Glasgow and Modified Glasgow prognostic scores calculation
8) G-CODE evaluation will be done at baseline, every 4 cycles during treatment, at the EOT visit and at the first follow-up visit (2 months after the EOT visit). For G-CODE evaluation method, please refer to protocol Appendix 9
9) If blood samples cannot be collected during the baseline visit, sampling can be done at Day 1 of Cycle 1 prior to any experimental treatment.
10) ECG at day 1 will be done prior and at the end of oxaliplatin infusion in both treatment arms
11) Pregnancy test will be performed monthly during all treatment period for women of childbearing potential