SYNOPSIS – PROTOCOL N° UC-0110/1719

A) STUDY IDENTIFICATION	
SPONSOR – PROTOCOL CODE NUMBER: UC-0110/1719 VERSION (NR & DATE): V6.0 – 7.0_24TH NOVEMBER 2023	
STUDY TITLE: Association of Radiochemotherapy and Immunotherapy for the treatment of unresectable Oesophageal caNcer: a comparative randomized phase II trial	
ABBREVIATED TITLE: ARION TRIAL	
COORDINATING INVESTIGATOR: Dr Anouchka MODESTO	
NUMBER OF PARTICIPATING CENTERS (ESTIMATE): 12	NUMBER OF PATIENTS: 120

B) SPONSOR IDENTIFICATION	
NAME:	**UNICANCER** **101, rue de Tolbiac** **75654 Paris Cedex 13 (France)**
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C) TRIAL GENERAL INFORMATION
INDICATION: Localised unresectable adenocarcinoma or squamous cell carcinoma of the oesophagus without any prior chemotherapy, surgery, or radiotherapy
METHODOLOGY: Randomized multicentre, comparative, phase II trial
PRIMARY OBJECTIVE: To assess the efficacy of durvalumab (MEDI4736), initially in combination with radiochemotherapy (FOLFOX and IMRT) and then as maintenance therapy for treating patients with localised unresectable oesophageal cancer, in terms of PFS (centrally reviewed; cPFS).

SECONDARY OBJECTIVE(S):
To assess the efficacy in terms of local PFS.
To assess the efficacy in terms of overall survival.
To evaluate the safety and tolerance of the study treatments.
To evaluate the quality of life.

Ancillary studies :
- Tissue: Biomarkers to predict response to treatment (central pathology review).
- Study of gut microbiota to determine if intestinal bacteria are predictive of tumour response.
- Blood samples: Plasmatic analysis to identify biomarkers of response to radiochemotherapy and / or with anti-PD-L1 (durvalumab) to non-responder to identify biomarkers.

DIAGNOSIS AND INCLUSION CRITERIA:

1. Histologically proven squamous cell carcinoma or adenocarcinoma of the oesophagus,
2. Unresectable disease due to anatomical consideration or medical condition (patient unfit for surgical procedure),
3. Presence of at least one measurable lesion >10 mm with spiral CT scan,
4. No prior therapy for pathology investigated including chemotherapy or radiotherapy prior to the study, except anterior out of field radiotherapy, received for treatment of another primary tumor considered in remission, in the past 5 years,
5. Age ≥18 years old,
6. WHO performance status <2 (i.e., 0 or 1),
7. Body weight >35 kg,
8. Life expectancy of at least 12 weeks ,
9. Adequate haematology laboratory data within the 7 days before randomization
    a. Absolute neutrophils >1.5 x 10^9/L
    b. Platelets >100 x 10^9/L
    c. Haemoglobin ≥9 g/dL,
10. Adequate Biochemistry laboratory data within the 7 days before randomization
    a. Total bilirubin ≤1.5 x upper limit of normal (ULN)
    b. Transaminases ≤2.5 x ULN
    c. Alkaline phosphatases ≤5 x ULN,
    d. Measured creatinine clearance (CL) >40 mL/min by the Cockcroft-Gault formula,
    e. Glycaemia ≤1.5 x ULN
    f. Cholesterolaemia ≤7.30 mmol/L,
    g. Albumin >28 g/L
11. Adequate haemostasis laboratory data within 7 days prior to randomization: prothrombin time (PT) within the normal range,
12. Adequate values for calcium, potassium and magnesium levels measured within 7 days prior to randomization,
13. Women should be post-menopaused or willing to accept the use an effective contraceptive regimen during the treatment period and for at least 6 months after the end of the study. All non-menopausal women should have a negative pregnancy test within 72 h prior to randomization. Men should accept to use an effective contraception during treatment period and at least 6 months after the end of the study especially after the last dose of oxaliplatin treatment.
14. Patients must have provided consent for the study by signing and dating a written informed consent form prior to any study specific procedures, sampling, or analyses,
15. Patient affiliated to a social security regimen.
16. Uracilemia < 16ng/ml
17. Forced expiratory volume (FEV) >1 liter or > 50% of the theoretical value

EXCLUSION CRITERIA:

1. Previous treatment with another PD-1, PD-L1 including durvalumab or CTLA-4 inhibitor
2. Metastatic disease,
3. Patients should not receive live vaccine 30 days prior to study drug
4. Female patients who are pregnant or breastfeeding
5. Uncontrolled intercurrent illness including, but not limited to diabetes, hypertension, pulmonary failure, chronic renal or hepatic diseases, active peptic ulcer disease or gastritis, active bleeding, diatheses... (non-exhaustive list),
6. Clinically significant cardiac disease or impaired cardiac function, such as:
   a. Congestive heart failure requiring treatment (New York Heart Association [NYHA] grade ≥2), left ventricular ejection fraction (LVEF) <50% as determined by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO), or uncontrolled arterial hypertension defined by blood pressure >140/100 mmHg at rest (average of 3 consecutive readings),
   b. History or current evidence of clinically significant cardiac arrhythmias, atrial fibrillation and/or conduction abnormality, e.g. congenital long QT syndrome, high- grade/complete AV-blockage,
   c. Acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass graft (CABG), coronary angioplasty, or stenting), <3 months prior to screening,
   d. MeanQT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
7. Current or prior use of immunosuppressive medication within 28 days before the first administration of durvalumab (exception: systemic corticosteroids at physiologic doses not exceeding 10 mg/day of prednisone or equivalent are allowed as well as steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) - Topical, inhaled, nasal, and ophthalmic steroids are allowed,
8. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
   a. Patients with vitiligo or alopecia
   b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stabilised with hormone replacement therapy
   c. Any chronic skin condition that does not require systemic therapy
   d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician
   e. Patients with coeliac disease controlled by diet alone
9. Known primary immunodeficiency or active HIV,
10. Patient with a dihydropyrimidine dehydrogenase (DPD) deficiency (Uracilemia ≥ 16 ng/ml, the test should be done for all patients before 5-FU administration)* ,
11. Known active or chronic viral hepatitis or history of any type of hepatitis within the last 6 months indicated by positive HBS antibody test for hepatitis B or hepatitis C virus ribonucleic acid (HCV antibody),
12. History of organ transplantation requiring the use of immunosuppressive medication, including allogenic stem cell transplant
13. History of active tuberculosis or latent disease capable of reactivation,
14. Current pneumonitis or interstitial lung disease,
15. Other invasive malignancy within 2 years prior to entry into the study, except for those treated with surgical therapy only,
16. History of severe allergic reactions or hypersensitivity to any unknown allergens or any components of the study drug (refer to IB of durvalumab section 5.5.1.11).
17. Any prior corticosteroid-refractory immune-related adverse event (irAE),
18. Oeso-tracheal or oeso-bronchial fistulae,Major surgery within 28 days prior to the first dose of study treatment
19. Toxicities of grade ≥1 from any previous therapy,
20. Peripheral sensory neuropathy with functional impairment
21. Severe infection requiring parenteral antibiotic treatment
22. Patients treated with sorivudine or analogues as brivudine
23. Patients treated with phenytoin for prophylaxis
24. Participation in another therapeutic trial within the 30 days prior to study inclusion,
25. Patients deprived of liberty or under guardianship,
26. Patients unable to adhere to the protocol for geographical, social, or psychological reasons.

* As per the ANSM's recommendations the risk of not testing DPD in patient before being administered 5-FU (See Appendices 6 to 9 and Appendices 11-12)

PRIMARY ENDPOINT:
The primary endpoint is defined by a blinded independent centralized revue of progression free survival. cPFS is defined as the time from randomization until progression or death; patients alive and without documented progression at last follow-up news have PFS censored at this date or at initiation of new anticancer treatment (if applicable). Progression will be defined with central external reviewing of TDM per RECIST criteria 1.1, (see appendix 2).

SECONDARY ENDPOINT(S):

PFS is defined at the time from randomization until disease progression or death; patients alive without progression at last follow up will be censored at this date.
Overall survival (OS): OS is defined as the time between randomization and death due to any cause. Patients still alive at the time of analysis (including those lost to follow up) will be censored at the last date that they were known to be alive.
Safety will be evaluated using NCI CTCAE v5.0 (see Appendix 3).
Quality of life: EORTC QLQ C30 and Oes18.

Ancillary studies:

- To determine whether the expression level of cytoplasmic peri-tumoral and tumoral PD-L1, macrophages and TILs predicts response to treatment (central reviewing CHU Toulouse).
- Study of gut microbiota to determine if baseline intestinal bacteria correlates with tumor response
- Blood for proteomic analysis comparing long term responder after radiochemotherapy with anti-PD-L1 (durvalumab) to non-responder to identify biomarkers.

D) INVESTIGATIONAL MEDICINAL PRODUCTS

PRODUCT NAMES AND ADMINISTRATION:

Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration route	Posology
Durvalumab	NA	Solution	Intravenous	1500mg
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration route	Posology
Oxaliplatin	Eloxatin® or generic drug	Concentrate for solution for infusion or powder	IV	85 mg/m² IV Infusion over 2 hours
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration route	Posology
Folinic acid	-	solution for injection	IV	200 mg/m² infusion in 2 h (racemic mixture) 100mg/m² in 2 h (L-folinic acid)
Drug name (INN)	Registered name (1)	Pharmaceutical form	Administration route	Posology
5Fluorouracil	-	Concentrate for solution for injection	IV	400mg/m² in 10 mn on D1, followed by 1600 mg/m² infusion continuous in 46 h

(1) *When any generic drug can be is used indicate only the INN name. The choice of the registered name or brand name is left to the decision of the investigation center.*

THERAPEUTIC REGIMENS:

- Standard and experimental arm :

Definitive modulated-intensity radiotherapy will be delivered according to boost integrated technique 5 days a week for 5 weeks at a dose of:

- ✓ 50 Gy delivered in 25 fractions to the macroscopic disease (endoscopic, TDM and fused FDG PET)
- ✓ 45 Gy to the adjacent peri tumoral mucosis and prophylactic lymph node

FOLFOX 4 simplified protocol, 1 infusion every 2 weeks, 6 cycles, during 3 months starting with radiotherapy (+/- 1 day):

- ✓ IV oxaliplatin 85 mg/m² in 2 h on day 1 (D1)
- ✓ IV Leucovorin 200 mg/m² in 2 h on day 1 (D1), followed by
- ✓ IV 5FU 400 mg/m² in 10 minutes on day 1 (D1) followed by
- ✓ IV continuous infusion 5FU 1600 mg/m² in 46 h

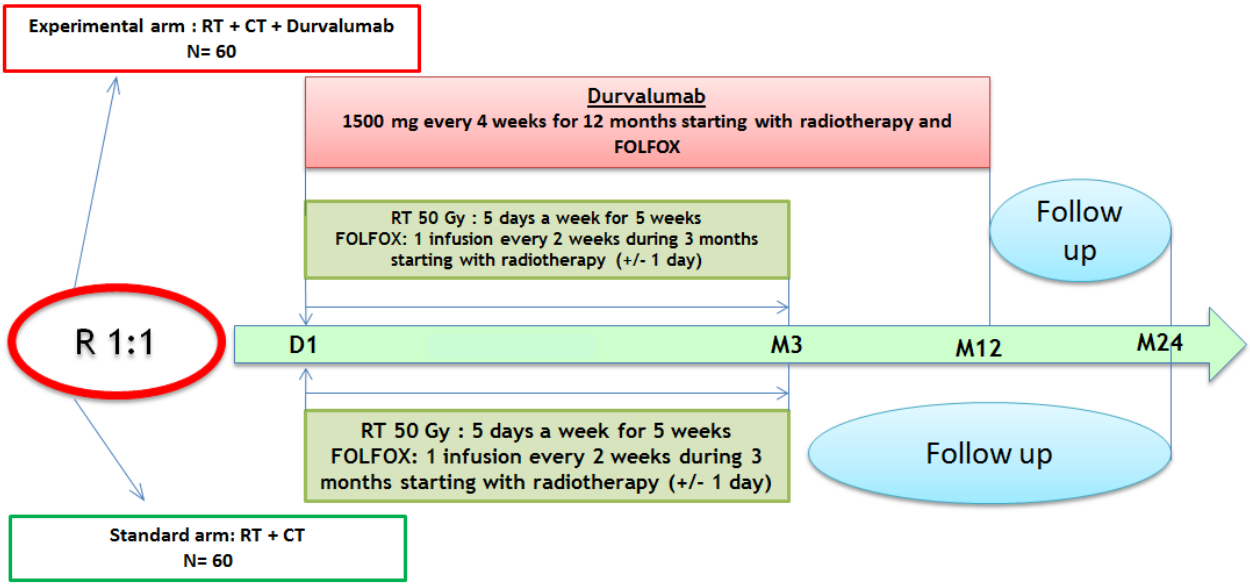
- Experimental arm: Concomitant administration of durvalumab:
  - ✓ Every 4 weeks during concurrent FOLFOX (dose: 1500 mg) and after FOLFOX completion (total of 12 months of treatment)

TREATMENT DURATION:

Radiochemotherapy in standard and experimental arm: 12 weeks (RT 50 Gy and FOLFOX q2w)

Immunotherapy in experimental arm only: Patients will received concomitantly a maximum of 12 infusions of Durvalumab at fixed dose(s) or until one of the following occurs:

- Unacceptable toxicity
- Investigator's decision to discontinue treatment
- Patient's decision to discontinue treatment



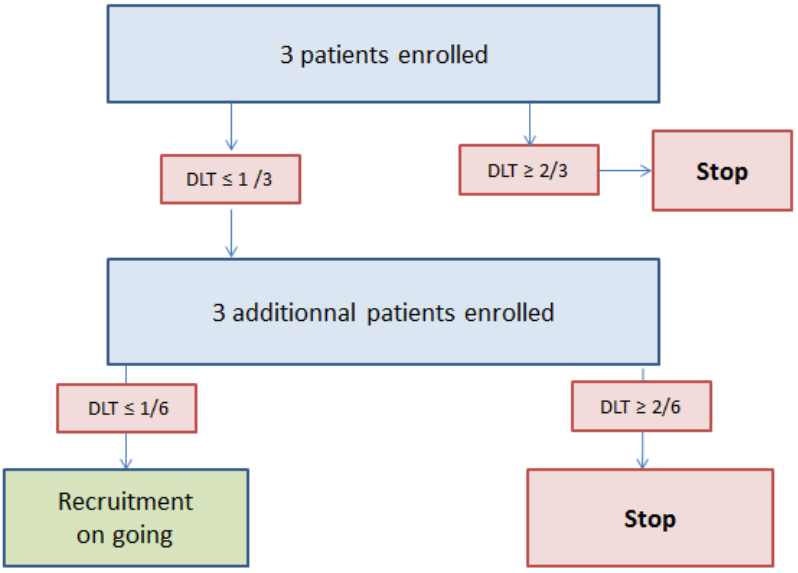
Safety run:

Given the lack of safety data from this association, a safety run-in of 6 patients is planned. A minimum of 3 patients and a maximum of 6 patients will be included in the safety run-in to assess the absence of dose limiting toxicity (DLT) (see figure below).

To be considered a DLT, a treatment stop related to the combination of durvalumab with radiochemotherapy have to be initiated within the DLT period but can last after the end of the DLT period. Toxicity that is clearly and directly related to the primary disease (ie disease progression), or expected AE related to radiotherapy or FOLFOX or to another etiology is excluded from this definition.

During the DLT observation period, a review of safety and tolerability data will be perform every 2 weeks by teleconference between an investigator from each participating centre and the sponsor.

The first three patients randomized in the experimental arm will be treated simultaneously with the expected doses of durvalumab 1500mg. The patients will be observed for an observation period of DLT (DLT will be evaluated during 3 months after the first durvalumab infusion). If no or one DLT is observed, the treatment of 3 additional patients will be permitted.



After the first three patients randomized in the experimental arm.

- If 0 or 1 DLT among 3 patients, randomization continue until 3 additional patients will be randomized in the experimental arm
    - If one patient or less among 6 (randomized in the experimental arm) presents a DLT, the experimental arm will be considered as safe.
    - If 2 patients or more among 6 present a DLT, the experimental arm will be defined as unsafe.
- If at least 2 DLT among 3 patients (randomized in the experimental arm), this combination will be defined as unsafe

According to results observed in the safety run, accrual will be stopped or randomization will continue until complete accrual.

Once all patients evaluable for DLT have been included and treated during the period for DLT reporting a review of the toxicities in terms of DLT and of safety data will be made by the sponsor and an investigator from each participating center.

Additionally an Independent Data Monitoring Committee (IDMC), with expertise and experience in the pathology, will be set up to evaluate safety and tolerability at the end of the safety-run. The IDMC will then meet on regular basis (at least once a year after the safety run). The IDMC has only a consultative role. The steering committee and the Sponsor will jointly decide whether the IDMC recommendation will be followed.

Patients who required discontinuation of treatment before the end of the DLT observation period for reasons other than the occurrence of a dose-limiting toxicity will be replaced after a review in the independent data monitoring committee (IDMC).

If the patient presents a DLT, durvalumab will be suspended and the patient will receive definitive RT and FOLFOX.

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED / INCLUDED: 120

The main objective is to increase 12-months cPFS from 50% to 68%. This corresponds to detecting a hazard ratio of 0.55. A total of 74 events are necessary for 90% power to detect this difference if it is true using a one–sided logrank test at the 10% level of significance and a 1:1 randomization (arm A: arm B). Target difference, type I and II error rates are compatible with recommendations performed by Rubinstein for comparative phase II trial (Rubinstein, JCO 2005).
Based on an estimated accrual rate of approximately 4 patients per month for the randomization of 120 patients and a fixed follow-up of two years, we can expect to see this number of events 53 months after the start of the study.

STATISTICAL ANALYSIS:
Continuous variables will be summarized by arm, using median, minimum, maximum and number of available observations. Qualitative variables will be summarized by arm using: counts, percents, number of missing data.
Primary endpoint will be analyzed on the ITT population when the required number of events has been reached. The Kaplan-Meier approach will be used to estimate cPFS rates for each treatment arm. The primary endpoint analysis will be a Cox regression analysis with 90% confidence interval (one sided).
In a sensitivity analysis primary endpoint will be analysis in full analysis set.
Secondary endpoints will be analysed in the ITT population and sensitivity analysis will be performed in the full analysis set. For each treatment arms, survival rates (PFS and OS) will be estimated at 12, 18 and 24 months using the Kaplan-Meier method (with their respective confidence interval). Median survival times will be estimated by arms with corresponding 90%confidence interval. The hazard ratio and corresponding one-sided 90% confidence interval (CI) will be estimated using a Cox proportional hazards model. Quality of life scores (EORTC QLQ C30 + OES28) will be described at each assessment time by means, standard deviations, medians and percentages. The percentage of missing Quality of life scores will be also provided at each follow-up. Patients' missing score profiles will be then generated to study the impact on QoL scores.

The randomization will be performed according to a 1:1 ratio using minimization method according to the following stratification factors:

- Center
- Histological Type: Adenocarcinoma or adenosquamous carcinoma vs epidermoid (=Squamous cell carcinoma).
- Stage: I/II vs III/IV vs unknown

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES:
Blood
Stool
Baseline biopsies

SAMPLE QUANTITIES:
Blood: 2 tubes of 7 mL of blood per patient will be drawn at screening, M2 (before C4 FOLFOX), M12.
Gut microbiota: 1 stool sample per patient before any study treatment
Tumour biopsies blocks at baseline.

G) STUDY DURATION

INCLUSION PERIOD: 60 MONTHS
TREATMENT PERIOD: 12 MONTHS (EXPERIMENTAL ARM) AND 3 MONTHS (STANDARD ARM)
FOLLOW-UP: 24 MONTHS
PRIMARY ENDPOINT EVALUATION: AT 74 EVENTS (EXPECTED 53 MONTHS AFTER THE START OF THE STUDY)
OVERALL STUDY DURATION (INCLUDING FOLLOW-UP): 8 YEARS (96 MONTHS)