GASPAR TRIAL

Perioperative Treatment in Resectable Gastric Cancer with Spartalizumab (PDR001) in Combination with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT): A phase II study (GASPAR)

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REGLEMENTARY CLASSIFICATION OF TRIAL: RIPH 1

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COMPETENT AUTHORITY	Agence Nationale de Sécurité des Médicaments (ANSM)	Date of authorization:2021-01-20
ETHIC COMMITTEE	CPP of Ile de France VII	Date of approval : 2021-01-18

TABLE DES MATIERES

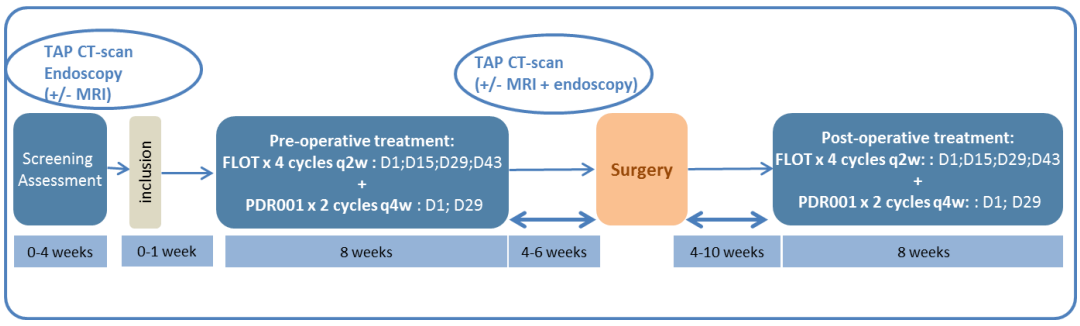
1 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse even of special interest
ANC	absolute neutrophil count
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
CPS	combined positive score
DFS	disease-free survival
CA 19.9	carbohydrate antigen 19.9
CBC	complete blood cells count
CEA	carcinoembryonic antigen
CI	confidence intervals
CPS	combined positif score
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
D	Day
DNA	deoxyribonucleic acid
DFS	Disease-progression Free Survival
EBV	epstein–barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDTA	ethylene diamine tetra-acetic acid
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
G-CSF	granulocyte colony stimulating factor
GEJ	gastroesophageal junction
GGT	gamma glutamyltransferase
GOJ	gastroesophageal junction
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IHC	immunohistochemistry
MASCC	multinational Association of Supportive Care in Cancer
MRI	magnetic resonance imaging
MSI	microsatellits instability
NSAID	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
NCI	national cancer institute
OS	overall survival
PBMC	peripheral blood mononuclear cells
pCR	pathological complete regression
PCR	polymerase chain reaction
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
QTc	corrected QT interval
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
T4	serum thyroxine
TAP	thorax, abdomen and pelvis
TMB	tumor mutational burden
TSH	thyroid stimulating hormone
ULP	upper limit of normal
WBC	white blood cell count

2 SYNOPSIS

TITLE	Perioperative Treatment in Resectable **Ga**stric Cancer with **Spar**talizumab (PDR001) in Combination with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT): A phase II study (**GASPAR**)
Coordinator	Dr Mélanie DOS SANTOS
Indication	Resectable gastric or gastroesophageal junction adenocarcinoma
Design	Multicenter, open-label, nonrandomized, phase 2 trial
Objectives	**Main objective** To evaluate the pathologic response after pre-operative treatment **Secondary objectives** - To evaluate the impact of perioperative treatment on survival outcomes (disease-free and overall survival) - To evaluate the histological R0 resection margin - To establish the association between pCR and survival outcomes outcomes (disease-free and overall survival) - To determine the safety profile of the combination Spartalizumab + FLOT regimen - To evaluate the post-operative morbidity and mortality **Exploratory end point:** To constitute biological collections (blood, tumoral tissue) for further biological explorations such as: - Evaluation of the impact of biomarkers (ctDNA and tissue) in terms of oncological outcomes and response to treatment These biomarkers may include: ❖ ctDNA levels over time ❖ PD-L1 expression measured as the CPS ❖ MSI status ❖ EBV status ❖ TMB - Exploration of tumor organoid cultures
Judgement criteria	**Main criterion** The primary endpoint is the proportion of patients with pCR in the primary tumour defined as: no tumour residue found in the tissue collected during the surgery evaluated by the pathologist **Secondary criteria** The secondary endpoint are: - Disease-free survival (DFS) defined as time between inclusion and first progression according to RECIST v1.1 criteria or death whatever cause (in the absence of progression); patients without disease progression or death at the time of analysis will be censored at the time of the latest date of assessment - Overall survival (OS) defined as the time between inclusion and death whatever cause; any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be aliv. - Proportion of patients with margin-free resection (R0), defined as a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed - Correlation between pCR and DFS

	- Correlation between pCR and OS - Toxicities of the combination Spartalizumab + FLOT regimen according to NCI CTCAE criteria v5.0 - Post-operative morbidity, defined post-operative complications grades II-V according to Clavien-Dindo classification during surgery, within 30 days after surgery or during the hospital stay - Post-operative mortality, defined as the rate of patients died due to any cause during the 30 days post-surgery
Inclusion criteria	- Age ≥ 18 years - Untreated localized gastric or GEJ adenocarcinoma considered resectable (clinical stage ≥cT2 and/or cN+ and no metastasis) - Histologically confirmed adenocarcinoma - ECOG performance status score of 0 or 1 - Tumor tissue must be provided for biomarker analyses (fresh or archival with an FFPE tissue block) - All subjects must consent to allow the acquisition of blood samples for performance of correlative studies - Screening laboratory values must meet the following criteria: o WBC ≥ 2000/ mm³ o Neutrophils ≥ 1500/ mm³ o Platelets ≥ 100 000/ mm³ o Hemoglobin ≥ 9.0 g/dL o Bilirubin ≤ 1.5 x ULN, AST and ALT ≤ 3 x ULN o Measured or calculated creatinine ≥ 50 ml/min clearance (CrCl) (using the Cockcroft-Gault formula) o Potassium ≥ LLN o Magnesium ≥ LLN o Calcium ≥ LLN - Female subject of childbearing potential must have a negative urine or serum pregnancy test within 72h before study start - Subject in reproductive age must be willing to use adequate contraception during the study and at least 9 months in men and 12 months in women after the last dose of investigational drug. In addition, given the toxicities observed on the male reproductive system, a conservation of gametes will be proposed for men, as usually in routine practice - Subject affiliated to a social security regimen - Patient has signed informed consents obtained before any trial related activities and according to local guidelines
Non inclusion criteria	- Subject with any distant metastasis - Subject with no recovering from the effects of major surgery or significant traumatic injury within 14 days before inclusion - Documented significant cardiovascular disease within the past 6 months before the first dose of study treatment, including: history of congestive heart failure (defined as NYHA III or IV), myocardial infarction, unstable angina, coronary angioplasty, coronary stenting, coronary artery bypass graft, cerebrovascular accident or hypertensive crisis - History of anterior organ transplant, including stem cell allograft - Pneumonitis or interstitial lung disease - History of other malignancy within the previous 3 years (except for appropriately treated in-situ cervix carcinoma and non-melanoma skin carcinoma) - Subject with active, known, or suspected autoimmune disease - Subject with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment

	- Known history of HIV or HBV infection - Known active HCV infection - Known history of active tuberculosis - Vaccination with live vaccine within 30 days before the first dose of study treatment - Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways - Recent or concomitant treatment with brivudine (**herpes virostatic**) - Prior anticancer therapy for the current malignancy - Known hypersensitivity to any of the study drugs or their excipients - Chronic inflammable gastro-intestinal disease - Uracilemia ≥ 16 ng/ml - QT/QTc > 450 msec for men and > 470 msec for women - Peripheral neuropathy ≥ Grade II - Uncontrolled diabetes - Active infection requiring systemic therapy - Participation in another therapeutic clinical study - Patient deprived of liberty or placed under the authority of a tutor - Patient assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol
Experimental Plan	Patients should initiate the combination treatment by FLOT regimen plus Spartalizumab within 7 days after inclusion. Systemic treatment will include: • a pre-operative neoadjuvant 8-week phase of treatment • a post-operative 8-week phase of treatment The administered treatment will be as follows: ❖ **Standard FLOT regimen** ▪ Docetaxel 50 mg/m² IV infusion on D1 ▪ Oxaliplatine 85 mg/m² IV infusion on D1 ▪ Leucovorin 200 mg/m² IV infusion on D1 ▪ Fluorouracile 2600 mg/m² 24 h IV infusion on D1 This regimen will be administered every two weeks (q2w) for 4 pre-operative cycles (8 weeks) and 4 post-operative cycles (8 weeks) ❖ **Spartalizumab PDR001** Patients will received the fixed dose of 400 mg per IV infusion on D1 every four weeks (q4w) for 2 pre-operative cycles (8 weeks) and 2 post-operative cycles (8 weeks) • Localized resectable gastric or GEJ adenocarcinoma • ≥cT2 and/or cN+ • No metastasis • OMS 0/1 

	Surgery For patients with confirmed resectability of the tumor by an imaging assessment (thoraco-abdominopelvic CT-scan and optional MRI and endoscopy), surgery will be realized within 4-6 weeks after the last dose of preoperative chemotherapy. • For gastric tumors: surgery will consist on a total or subtotal distal (for antropyloric tumors) gastrectomy with D2 lymphadenectomy • For type 1 GEJ tumors: transthoracic esophagectomy (Ivor-Lewis procedure) with resection of the proximal stomach and 2-field (mediastinal and abdominal) lymphadenectomy • For type 2 or 3 GEJ tumors: gastrectomy with transhiatal distal oesophagectomy and D2 lymphadenectomy Post-operative systemic treatment will be initiated within 4-10 weeks after surgery.
Statistical considerations	We used an optimal **Simon's two stage** phase II design to estimate the sample size. According to Al-Batran S-E et al outcomes[1], 16% [95%CI: 10-23] of complete responses have been observed in the study (n=128). Assuming a histological complete response of 10% as unacceptable (lower CI limit), and ≥23% as acceptable (upper CI limit), with α=5% and 1-β=80%, 58 assessable patients are required (including 20 in the first stage). Taking into account that 15% of patients will be lost or unevaluable, **we plan to include a total of 67 patients in the present trial (23+44)**. **A safety analysis has been planned and performedone month's follow-up after the surgery of 10th patient. Enrolment has been halted during this safety analysis after inclusion of 10 patients.** Safety analysis of FLOT plus immunotherapy in neoadjuvant treatment on 10 patients showed tolerance observations consistent with the safety profile of similar association in this setting. No safety signal that may have compromised the pursuit of the trial was noticed. Similarly, the type and frequency of toxicities observed during the peri-operative period (up to one month post-surgery) were in line with events usually observed in this setting and compatible with the pursuit of the trial. No death was observed. Overall, the IDMC recommends the Sponsor to pursue the study without modification but to plan a second formal safety analysis after the inclusion of the 30th patient. To be noticed, data concerning surgical pathologic response were available for 9 patients included in the first safety analysis, and reported in the file presented to the IDMC. The results fulfilled the futility criterion of the Simon design. In this context, the IDMC indicated the planned interim analysis will have no more decisional impact on the pursuit of the study. It therefore recommended not to realise the planned interim analysis but to include available efficacy data in the second safety report, to assess the benefit/risk ratio of the combination as approved by authorities.
Participating centres	Around 16 centres
Ancillary studies	Tumor Tissue Collection and Correlative Studies Blood Sampling will be done: • Mandatory tumor tissue (fresh or archival with an FFPE tissue block) at inclusion, before treatment • Mandatory blood samples at inclusion before chemotherapy initiation, after pre-operative treatment, after surgery, after post-operative treatment and 3 months from the end of treatment • Optional fresh tumor biopsies and Peripheral Blood Mononuclear Cell (PBMC) at inclusion, before treatment (only at Centre François Baclesse site)
Study duration	Study duration : 72 months approximately Enrollment period : 30 months Treatment period : 8 months Follow-up period : Up to disease progression

3 STUDY FLOW CHART

	Before inclusion (within 28 days prior inclusion)	DURING TREATMENT									End of treatment 30 days after the end of treatment (+/- 7 days)	Follow-up every 3 months up to progression (+/- 15 days)	Overall survival after disease progression
		Pre-operative treatment [4] +/- 3 days				Before SURGERY	Post-operative treatment [5] +/- 3 days						
		D1	D15	D29	D43	Within 3 weeks before surgery	D1	D15	D29	D43			
FLOT *(q2w)* **Spartalizumab PDR001** *(q4w)*		◆ ◆	◆	◆ ◆	◆		◆ ◆	◆	◆ ◆	◆			No study visit is required. The following treatment/exams are at the discretion of physician
Signed Informed Consent *before any study procedures*	✓												
Clinical assessment Physical examination including weight, ECOG, vital signs Adverse Events collection and concomitant treatments	✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓ ✓	✓	
Biological assessment Hematology and biochemistry[1]	✓	✓[2,3]	✓[3]	✓[3]	✓[3]	✓	✓[3]	✓[3]	✓[3]	✓[3]	✓		
Uracilemia	✓												
Urine or serum pregnancy test		✓[3]		✓[3]			✓[3]		✓[3]				
Thyroid-function: TSH, free T4	✓	✓[2]		✓[3]		✓	✓[3]		✓[3]		✓		
Tumor markers: CEA, CA 19.9	✓	✓[2]				✓	✓[3]				✓		
ECG	✓	✓[7]	✓[7]	✓[7]	✓[7]		✓[7]	✓[7]	✓[7]	✓[7]			
CT-scan (thoracic and abdomino-pelvic) **MRI optional**	✓ ✓					✓ ✓					✓ ✓	✓[8] ✓	
Endoscopy	✓[9]					✓ optional							
Blood samples for translational research[10]	✓					✓	✓				✓	✓[6]	

1 CBC-platelets, Creatininemia, kaliema, magnesemia, calcemia, albumin, glycemia, lipase, bilirubin, ALT, AST, GGT
2 Only if realized more 3 days before D1
3 Within 3 days before treatment administration
4 The initial combination treatment by FLOT regimen plus Spartalizumab should be initiated within 7 days after inclusion
5 The combination treatment by FLOT regimen plus Spartalizumab should be initiated within 4-10 weeks after surgery
6 Blood sample only for follow-up at 3 months
7 To be realized before and after oxaliplatin intravenous infusion
8 Every 3 months (+/- 15 days) for the first 2 years and every 6 months (+/- 1 month) for the next 3 years
9 Within 6 weeks prior to inclusion with available archival tumor (otherwise, fresh tumor)
And optional fresh tumor biopsies only at François Baclesse site for organoids research (additional specific consent form)
10 Mandatory blood samples for ctDNA
And optional PBMC at baseline only at François Baclesse site for organoids research (additional specific consent form).

4 SCIENTIFIC RATIONALE OF THE STUDY

4.1 DISEASE EPIDEMIOLOGY

Gastric cancer is one of the most common and deadly cancers worldwide. It represents the fifth most common cancer and the third leading cause of cancer deaths in the world.[2] Perioperative chemotherapy and surgery is a standard of care for patients with resectable gastric or GEJ adenocarcinoma. Despite this combination of treatment, the prognosis remains poor for this population.

4.2 CURRENT TREATMENTS

Perioperative treatment was considered as the standard compared to surgery alone according to the MAGIC Trial, evaluating ECF (epirubicin, cisplatin and fluorouracile), 3 pre- and 3 post-operative cycles, compared to surgery alone.[3] This large randomized trial was conducted among 503 patients with resectable locally advanced gastric or GEJ adenocarcinoma, and showed an improved OS with a 5-year survival rate of 36% versus 23% for surgery alone. However, in a controlled open-label phase 2/3 trial, conducted among 716 patients, the FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel), 4 pre- and 4 post-operative cycles, was associated with better results compared to ECF as perioperative chemotherapy.[4] OS was increased in the FLOT group compared with the ECF group with a median overall survival of 50 months versus 35 months. Moreover, there was a higher proportion of pCR: 16% [95% CI: 10–23] versus 6% [95% CI: 3–11].[1] Furthermore, a recent meta-analysis investigated the impact of pCR on survival outcomes among 1143 patients with resectable gastric or GEJ cancer, after neoadjuvant chemotherapy and radical surgery.[5] pCR was clearly associated with lower risk of death and recurrence compared with patients with any residual disease.

The FLOT regimen is now considered as the new standard chemotherapy regimen for perioperative strategy of resectable gastric or GEJ adenocarcinoma. However, the 5-year OS rate remains only at 45% following radical surgery.[4] New approaches are needed to improve these outcomes.

4.3 MECHANISM OF ACTION OF PRODUCT

PD-1 is a critical immune checkpoint receptor. Engagement of PD-1 by its ligands, PD-L1 and PD-L2, transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function, attenuating tumor immunity and facilitating tumor progression.[6] PD-1 and its ligand PD-L1 are expressed on up to 50% of gastric or GEJ tumors, with a controversial impact on survival.[7,8]

Immunotherapy with antibodies that inhibit PD-1/ PD-L1 interaction has recently emerged as a new treatment option with promising and encouraging early trial results for patients with advanced or metastatic gastric or GEJ adenocarcinoma.[9] Muro et al, conducted a phase 1b trial (KEYNOTE-012) with 39 patients with PD-L1-positive advanced gastric or GEJ adenocarcinoma to investigated the safety and activity of the anti-PD-1 antibody pembrolizumab.[10] Pembrolizumab demonstrated a 22% objective response rate with a manageable toxicity profile. Fuchs et al, conducted a phase II trial (KEYNOTE-059) with pembrolizumab monotherapy in 259 patients with previously treated advanced gastric and GEJ cancer (at least 2 lines of treatment).[11] They showed durable responses, with great response rate, especially for PD-L1–positive tumors. Results from these studies allowed approval of pembrolizumab by the US FDA as third line treatment for patients with advanced or metastatic gastric or GEJ cancer PD-L1–positive. Moreover, an update of the KEYNOTE-059 trial demonstrated a manageable safety and promising efficacy of first-line immunotherapy combined with chemotherapy (cisplatin and fluorouracil).[12] In a first-line study (KEYNOTE-062), Shitara et al showed encouraging benefit with pembrolizumab versus chemotherapy among patients with untreated advanced gastric and GEJ cancer with higher levels

of PD-L1 and microsatellite instability–high (MSI-H) tumours.[13] The CheckMate 649 trial recently showed that nivolumab and chemotherapy versus chemotherapy alone improved OS and PFS as first-line treatment in patients with non-HER-2-positive advanced gastric, GEJ or oesophageal cancer.[14]

Currently, no trials have investigated the impact of neoadjuvant immunotherapy in combination with chemotherapy for resectable gastric or GEJ adenocarcinoma. Nevertheless, some studies suggest a change in the tumor immune micro-environment following neoadjuvant chemotherapy in locally advanced gastric cancer, with an increased expression of immune markers.[15] Tumor samples, before and after neoadjuvant chemotherapy, of 60 patients with locally advanced gastric cancer were retrospectively identified and analyzed by multiplex immunohistochemistry, with a panel including PD-1 and PD-L1. Following neoadjuvant chemotherapy, the overall median expression levels of PD1 and PD-L1 were significantly increased. Moreover, high upregulation levels of these checkpoint molecules were correlated with survival benefits.

4.4 STUDY RATIONALE AND PURPOSE

All these data are encouraging in the use of immunotherapy in combination with perioperative chemotherapy, with the aim of improving treatment efficacy and survival outcomes.

PDR001 (Spartalizumab) is a high-affinity, ligand-blocking, humanized Immunoglobulin G4 antibody directed against PD-1 that blocks the binding of PD-L1 and PD-L2. Spartalizumab has demonstrated pharmacodynamic activity and a favorable toxicology profile in preclinical studies. The available safety data from clinical studies indicate that PDR001 is generally well tolerated.

As of the safety cut-off date of 26-Mar-2020, 1702 patients across the 17 Novartis-sponsored clinical studies described have been treated with PDR001. In the open label multicenter phase I/II study of the safety and efficacy of PDR001 administered to patients with advanced malignancies, the results of phase I dose escalation among 58 patients have been published.[16] The maximum tolerated dose was not reached. The recommended phase 2 doses were selected as 400 mg Q4W or 300 mg Q3W. No dose-limiting toxicities were observed, and adverse events included those typical of other PD-1 antibodies. In this phase I trial [16], the most common treatment-related adverse events of any grade were fatigue (22%), diarrhea (17%), pruritus (14%), hypothyroidism (10%), and nausea (10%).

In this study, we aim to evaluate the efficacy and safety of Spartalizumab in combination with the FLOT regimen as perioperative treatment for resectable gastric or GEJ adenocarcinoma.

4.5 ANCILLARY STUDIES

The Cancer Genome Atlas studies have identified four molecular subgroups of gastric cancer: tumors positive for EBV, MSI tumors, genomically stable tumors, and tumors with chromosomal instability.[17] Immune-checkpoint blockade seems to have durable antitumor activity and improved survival in a subset of patients with PD-L1-expressing, MSI, and EBV-positive tumors.[18]

Moreover, a recent study, showed that TMB high was independent predictor of prolonged PFS for patients with advanced gastric cancer treated with immune checkpoint blockade.[19] ctDNA has shown potential in some studies as a biomarker with predictive and prognostic implications. Correlation of ctDNA with treatment response has been noted, implicating a possible role in monitoring treatment response.[20]

However there is a need to confirm this data and for additional predictive biomarkers to improve patient selection, especially in the neoadjuvant setting.

Organoids (and cancer-derived organoids), are three-dimensional tissue-resembling cellular clusters derived from tissue or tumor specific stem cells that mimic the in vivo characteristics, as well as cell heterogeneity.[21] They are very similar morphologically and genetically to the tumor from which they are derived.[22,23] The emergence of tumor organoid cultures has recently opened up new

opportunities in preclinical personalised therapy testing. These organoids are obtained after inclusion of the cells derived from the tumor in the Matrigel and placed in culture in the presence of growth factors essential for stem cells. Advantages of the organoid cultures are a rapid amplification, a high rate of establishment success and unlimited potential proliferation. Moreover, they can be transfected and cryopreserved. Tumor organoid panels were thus established and characterized from tumor samples from the colon, liver, breast, prostate, bladder, ovary, glioblastoma, squamous cell carcinoma of the head and neck, and also gastric and esophageal cancer.[23–28] Tumor organoid cultures have shown interesting results to predict individual therapy response and patient outcome. A study evaluated the benefit of using organoids derived from metastatic colorectal and esogastric tumors to predict the response of patients to anticancer treatments (100% sensitivity, 93% specificity, 88% positive predictive value and 100% negative predictive value).[29] Other studies have shown a correlation between the organoid response and the clinical response for patients with colorectal cancer treated with irinotecan-based therapies and for patients with for rectal cancer treated with radiochemotherapy.[30–32] Several clinical trials are underway to determine whether tumor organoids can predict patient response and help treatment decisions. In particular, two of them involve the use of tumor organoids in immunotherapy (NCT03778814, NCT02718235). In fact, some works are currently underway to make organoid culture systems more complex by incorporating immune cells and to test treatments based on immunotherapy. A study was able to demonstrate the maintenance of the stromal and immunological environment around tumor organoids within an air-liquid interface system.[33] In addition, organoids from colorectal and lung tumors of patients have been cultured with autologous peripheral blood, allowing specific activation and expansion of T-cells for some patients.[34] Finally, the proof of the feasibility of a functional test predictive of the response to immunotherapies was recently carried out on co-cultures of organotypic tumor spheroids and their autologous immune cells derived from murine syngeneic models.[35] The response of spheroids to an anti-PD-1 strategy has been correlated with the response of the mouse model in vivo, suggesting that such predictive functional tests based on tumor organoids could eventually be implemented from samples of human origin.

In this study, the main objective of ancillary biological exploration is therefore to identify subgroups of responder patients. Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered. These efforts may identify predictive biomarkers and generate information that could help in patient selection with personalized medicine programs.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

The primary objective is to assess the pathologic response after pre-operative treatment.

5.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the impact of perioperative treatment on survival outcomes (outcomes (disease-free and overall survival)
- To evaluate the histological R0 resection margin
- To establish the association between pCR and survival outcomes (outcomes (disease-free and overall survival)
- To determine the safety profile of the combination Spartalizumab + FLOT regimen
- To evaluate the post-operative morbidity and mortality

5.3 FURTHER ANCILLARY STUDIES

Tumoral and blood samples will be collected for further biological explorations such as:

- Evaluation of the impact of biomarkers (ctDNA and tissue) in terms of oncological outcomes and response to treatment,

  These biomarkers may include:
  - ctDNA levels over time
  - PD-L1 expression measured as the CPS
  - MSI status
  - EBV status
  - TMB
- Exploration of tumor organoid culture

6 ENDPOINTS

6.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of patients with pCR in the primary tumor, defined as no tumor residue found in the tissue collected during the surgery evaluated by the pathologist.

6.2 SECONDARY ENDPOINTS

The secondary endpoints are:

- Disease-free survival (DFS) defined as time between inclusion and first progression according to RECIST v1.1 criteria or death whatever cause (in the absence of progression); patients without disease progression or death at the time of analysis will be censored at the time of the latest date of assessment.
- Overall survival (OS) defined as the time between inclusion and death whatever cause; any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.
- Proportion of patients with margin-free resection (R0), defined as a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed
- Correlation between pCR and DFS
- Correlation between pCR and OS
- Toxicities of the combination Spartalizumab + FLOT regimen according to NCI CTCAE criteria v5.0

- Post-operative morbidity, defined post-operative complications grades II-V according to Clavien-Dindo classification during surgery, within 30 days after surgery or during the hospital stay
- Post-operative mortality, defined as the rate of patients died due to any cause during the 30 days post-surgery

7 STUDY DESIGN

7.1 METHODOLOGY

We propose to implement a multicenter, open-label, non-randomized phase II trial to evaluate the efficacy and safety of Spartalizumab in combination with the FLOT regimen as perioperative treatment for resectable gastric or GEJ adenocarcinoma in patients.

7.2 STUDY DURATION

Overall study duration: 72 months approximatively
Enrollment period: 30 months
Treatment period: 8 months
Follow-up period: Up to disease progression

7.3 SUBJECTS SELECTION

7.3.1 Inclusion criteria

- Age ≥ 18 years
- Untreated localized gastric or GEJ adenocarcinoma considered resectable (clinical stage ≥cT2 and/or cN+ and no metastasis)
- Histologically confirmed adenocarcinoma
- ECOG performance status score of 0 or 1
- Tumor tissue must be provided for biomarker analyses (fresh or archival with an FFPE tissue block)
- All subjects must consent to allow the acquisition of blood samples for performance of correlative studies
- Screening laboratory values must meet the following criteria:
- WBC ≥ 2000/ mm³
- Neutrophils ≥ 1500/ mm³
- Platelets ≥ 100 000/ mm³
- Hemoglobin ≥ 9.0 g/dL
- Bilirubin ≤ 1.5 x ULN, AST and ALT ≤ 3 x ULN
- measured or calculated creatinine ≥ 50 ml/min clearance (CrCl) (using the Cockcroft-Gault formula)
- Potassium ≥ LLN
- Magnesium ≥ LLN
- Calcium ≥ LLN
- Female subject of childbearing potential must have a negative urine or serum pregnancy test within 72h before study start
- Subject in reproductive age must be willing to use adequate contraception during the study and at least 9 months in men and 12 months in women after the last dose of investigational drug. In addition, given the toxicities observed on the male reproductive system, a conservation of gametes will be proposed for men, as usually in routine practice
- Subject affiliated to a social security regimen
- Patient has signed informed consents obtained before any trial related activities and according to local guidelines

7.3.2 Non-inclusion criteria

- Subject with any distant metastasis
- Subject with no recovering from the effects of major surgery or significant traumatic injury within 14 days before inclusion
- Documented significant cardiovascular disease within the past 6 months before the first dose of study treatment, including: history of congestive heart failure (defined as NYHA III or IV), myocardial infarction, unstable angina, coronary angioplasty, coronary stenting, coronary artery bypass graft, cerebrovascular accident or hypertensive crisis
- History of anterior organ transplant, including stem cell allograft
- Pneumonitis or interstitial lung disease
- History of other malignancy within the previous 3 years (except for appropriately treated in-situ cervix carcinoma and non-melanoma skin carcinoma)
- Subject with active, known, or suspected autoimmune disease
- Subject with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment
- Known history of HIV or HBV infection
- Known active HCV infection
- Known history of active tuberculosis
- Vaccination with live vaccine within 30 days before the first dose of study treatment
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- Recent or concomitant treatment with brivudine (herpes virostatic)
- Prior anticancer therapy for the current malignancy
- Known hypersensitivity to any of the study drugs or their excipients
- Chronic inflammable gastro-intestinal disease
- Uracilemia ≥ 16 ng/ml
- QT/QTc > 450 msec for men and > 470 msec for women
- Peripheral neuropathy ≥ Grade II
- Uncontrolled diabetes
- Active infection requiring systemic therapy
- Participation in another therapeutic clinical study
- Patient deprived of liberty or placed under the authority of a tutor
- Patient assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

7.4 STUDY PLAN

7.4.1 Consent sign

The study will be proposed by oncologists, gastroenterologists or digestive surgeons to patients meeting all the eligibility criteria. Patients will be given study information (explanation on the study, reading and giving of the information notice). Patients will have a reflection period of the duration of their choice.
The specific exams/procedure requested in the study before inclusion (baseline visit) will be realized after signed consent and before inclusion.

7.4.2 Inclusion procedure

After collection of the signed informed consent and checking of all eligibility criteria, inclusion will be performed before initiation of treatment.

The inclusion will be recorded on the software dedicated to the study via an internet portal.

An inclusion number will be assigned to the patient and will be used during the whole study.

7.4.3 Drug administration

Patients should initiate the combination treatment by FLOT regimen plus Spartalizumab within 7 days after inclusion.

Systemic treatment will include:

- a pre-operative neoadjuvant 8-week phase of treatment
- a post-operative 8-week phase of treatment.

The administered treatment will be FLOT associated to spartalizumab as follows:

❖ **Standard FLOT regimen**

Docétaxel 50 mg/m² IV infusion on D1

Oxaliplatine 85 mg/m² IV infusion on D1

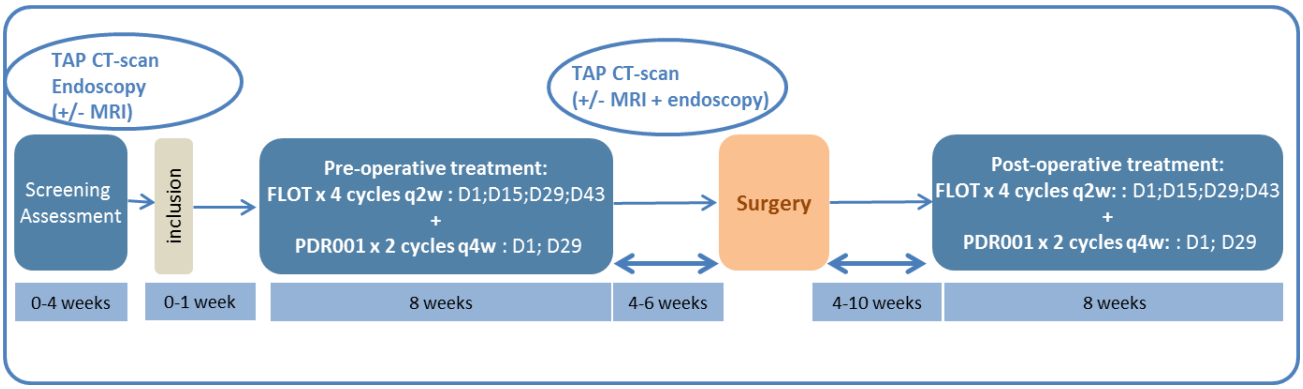
Leucovorin 200 mg/m² IV infusion on D1

Fluorouracile 2600 mg/m² 24 h IV infusion on D1

Chemotherapy will be administered every two weeks (q2w) for 4 pre-operative cycles (8 weeks) and 4 post-operative cycles (8 weeks).

❖ **Spartalizumab PDR001**

Patients will receive the fixed dose of 400 mg per IV infusion over 30 minutes on D1 every four weeks (q4w) for 2 pre-operative cycles (8 weeks) and 2 post-operative cycles (8 weeks).



7.4.4 Surgery

For patients with confirmed resectability of the tumor by an imaging assessment (TAP CT-scan and optional MRI and endoscopy), surgery will be realized within 4-6 weeks after the last dose of preoperative chemotherapy.

- **For gastric tumors:** surgery will consist on a total or subtotal distal (for antropyloric tumors) gastrectomy with D2 lymphadenectomy
- **For type 1 GEJ tumors**: transthoracic esophagectomy (Ivor-Lewis procedure) with resection of the proximal stomach and 2-field (mediastinal and abdominal) lymphadenectomy
- **For type 2 or 3 GEJ tumors:** gastrectomy with transhiatal distal oesophagectomy and D2 lymphadenectomy

Local pathologists from expert centers selected will perform standardized evaluation of pathological response in surgically resected specimens.

Tumour regression grade will be assessed according to the Becker regression criteria.[36]

Post-operative systemic treatment will be initiated within 4-10 weeks after surgery.

7.4.5 Premedication

- **For FLOT regimen:**

It is recommended to use antiemetic treatment according to the ASCO/MASCC recommendation guideline (moderate risk of nausea / vomiting) with aprepitant and setron.
Corticoid as premedication to doxetaxel should be avoided. However, if usually used as standards-of-care, a single dose of 60 mg on the day of administration of Taxotere will be allowed, but must be documented in the eCRF.

- **For Spartalizumab**

Premedication is not recommended for Spartalizumab.

7.5 SCHEDULE OF ASSESSMENT

7.5.1 Inclusion Assessments

For the patients will be given their written informed consent, an inclusion assessment will be performed within 28 days prior inclusion and will include:

- Clinical assessment (medical history) with complete physical examination (including weight, height, ECOG, vital signs)
- Laboratory Assessments
  - CBC-platelets
  - Creatininemia, kaliema, magnesemia, calcemia, albumin, glycemia, lipase, bilirubin, ALT, AST, GGT
  - Uracilemia
  - TSH, free T4
  - CEA, CA19.9
- Cardiac assessment with ECG. *The Fridericia correction method for calculating QTc will be used.*
- Tumor Assessments
  - Endoscopy (within 6 weeks prior to inclusion)
  - CT-scan (thoracic and abdomino-pelvic)
  - MRI in optional

For translational research:

- Blood sample for ctDNA (mandatory)
- Optional fresh tumor biopsies and blood sample PBMC for organoids research only at François Baclesse site (additional specific consent form)

7.5.2 Assessments during treatment

❖ **PRE-OPERATIVE TREATMENT**

✓ **Day 1 (D1)**

- Complete physical examination (including weight, ECOG, vital signs, concomitant treatments)
- Laboratory Assessments *(only if realized more 3 days before D1)*
  - CBC-platelets
  - Creatininemia, kaliema, magnesemia, calcemia, albumin, glycemia, lipase, bilirubin, ALT, AST, GGT
  - TSH, free T4
  - CEA, CA19.9
  - Negative urine or serum pregnancy test within 72h before study start
- Cardiac assessment with electrocardiogram : ECG to be realized before and after oxaliplatin intravenous infusion

✓ **D15, D29 and D43** (+/- 3 days)

- Complete physical examination (including weight, ECOG, vital signs, concomitant treatments)
- Laboratory Assessments *(within 3 days before drugs administration)*
  - CBC-platelets
  - Creatininemia, kaliema, magnesemia, calcemia, albumin, glycemia, lipase, bilirubin, ALT, AST, GGT
  - TSH, free T4 only on D29
  - Negative urine or serum pregnancy test within 72h before study start only on D29
- Cardiac assessment with electrocardiogram : ECG to be realized before and after oxaliplatin intravenous infusion

❖ **BEFORE SURGERY**

The assessment will be performed within 3 weeks before surgery and will include:

- Complete physical examination (including weight, ECOG, vital signs, concomitant treatments)
- Laboratory Assessments
  - CBC-platelets
  - Creatininemia, kaliema, magnesemia, calcemia, albumin, glycemia, lipase, bilirubin, ALT, AST, GGT
  - TSH, free T4
  - CEA, CA19.9
- Tumor Assessment
  - CT-scan (thoracic and abdomino-pelvic)
  - MRI in optional
  - Endoscopy in optional

For translational research:

- Blood sample for ctDNA

❖ **POST-OPERATIVE TREATMENT**

Post-operative systemic treatment will be initiated within 4-10 weeks after surgery.

✓ **D1, D15, D29 and D43** (+/- 3 days)

- Complete physical examination (including weight, ECOG, vital signs, concomitant treatments)
- Laboratory Assessments *(within 3 days before drugs administration)*
  - CBC-platelets
  - Creatininemia, kaliema, magnesemia, calcemia, albumin, glycemia, lipase, bilirubin, ALT, AST, GGT
  - TSH, free T4 only on D1 and D29
  - CEA, CA19.9 only on D1
  - Negative urine or serum pregnancy test within 72h before study start only on D1 and D29
- Cardiac assessment with electrocardiogram: ECG to be realized before and after oxaliplatin intravenous infusion

For translational research, only at D1:

- Blood sample for ctDNA

7.5.3 End of treatment assessments

Patients who discontinue the treatment for another reason than disease progression will be followed-up 30 days (+/- 7 days) after the last dose of study treatment:

- Complete physical examination (including weight, ECOG, vital signs, concomitant treatments)
- Laboratory Assessments
  - CBC-platelets
  - Creatininemia, kaliema, magnesemia, calcemia, albumin, glycemia, lipase, bilirubin, ALT, AST, GGT
  - TSH, free T4
  - CEA, CA19.9
- Tumor Assessments
  - CT-scan (thoracic and abdomino-pelvic)
  - MRI in optional

For translational research:

- Blood sample for ctDNA

7.5.4 Follow-up assessments

Patients who discontinue the treatment for another reason than disease progression will be followed-up every 3 months (+/- 15 days) up to progressive disease with:

- Complete physical examination (including weight, ECOG, vital signs, concomitant treatments)
- Tumor Assessments *(every 3 months for the first 2 years and every 6 months for the next 3 years)*
  - CT-scan (thoracic and abdomino-pelvic)
  - MRI in optional

For translational research:

- Blood sample for ctDNA at 3 months from the end of treatment

For patients withdrawn from treatment due to progression, a follow-up for survival will be performed about every 6 months (+/- 1 month). The following anti-cancer treatment is at the discretion of physician and will be collected in the e-CRF.

7.6 CRITERIA FOR PREMATURE WITHDRAWAL

The treatment will be interrupted at any time under the following circumstances:

- Disease progression
- Need to initiate another anti-tumor treatment such as radiotherapy. Antalgic radiotherapy is also a criterion for stopping treatment of the study
- Unacceptable toxicity, not compatible with study treatment
- Patient's decision (the data already collected during the search can be kept and exploited unless the patient opposes it)
- Intercurrent illness or other reason that necessitates stopping treatment of the study
- Patient lost to view
- Investigator's decision

Any patient who prematurely withdraws from the study treatment only will continue to be followed, unless he/she withdraws from the study.

7.7 CONCOMITANT MEDICATION

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded.

The following treatments/procedures are permitted:

- G-CSF is recommended as a secondary prophylaxis of severe neutropenia or febrile neutropenia. A systemic primary G-CSF prophylaxis from the first cycle of treatment is allowed and at the discretion of the investigator.
- Erythropoietin and/or transfusions at the discretion of the Investigator.
- The systematic administration of antiemetic by aprepitant and setron is recommended.
- Anti-diarrheal medications (e.g. loperamide) for patients who develop diarrhea.
- Pain medication to allow the patient to be as comfortable as possible.
- Nutritional support.
- The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

The following treatments are not permitted:

- Treatment with other systemic anticancer agents (e.g., chemotherapy, hormonal therapy other than megestrol acetate, immunotherapy) or other treatments not part of protocol-specified anticancer therapy
- Live vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  <u>Notes</u>:
  - *A short course of steroids may be used as concomitant medication for either treatment of an AE or medical condition with Sponsor approval.*
  - *Use of prophylactic corticosteroids to avoid allergic reactions (eg, IV contrast dye or transfusions) is permitted.*
  - *The use of intermittent inhaled steroids or intranasal or local injection of corticosteroids is permitted.*
  - *Use of steroids for premedication is not recommended. However, a single dose of 60 mg on the day of administration of Taxotere is permitted but must be documented.*

Other Restrictions and Precautions:

- Drugs known to prolong the QTc interval should be used with caution. The list of those drugs can be found on https://www.crediblemeds.org/.

8 PHARMACEUTICAL FORM OF STUDY MEDICATION: SPARTALIZUMAB

SPARTALIZUMAB (PDR001) is the Investigational Medicinal Product (IMP) in this study. It will be supplied by Novartis firm.

8.1 PRESENTATION OF THE PRODUCT

The chemical name of the study treatment is spartalizumab (PDR001).

8.2 PACKAGING AND LABELLING

Spartalizumab (PDR001) will be provided as concentrate for solution for infusion (100 mg / 4 mL).

8.3 STORAGE CONDITIONS

PDR001 drug product should be stored at 2 to 8 °C, protected from light. Do not freeze.

The Investigator, or an approved representative (e.g., pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements. Screening will be required for staff members authorized to handle controlled substances who are not medical practitioners.

8.4 METHOD OF ADMINISTRATION

Spartalizumab (PDR001) will be administered intravenously as a 30-minute infusion (up to 2 hours, if clinically indicated).

8.5 LABEL

The product will be labeled according to current legal requirements.

9 DOSE ADJUSTMENTS OF ANTICANCER PRODUCTS

9.1 GENERAL RULES

- No dose reduction will be applied for **Spartalizumab**
- 2 dose reductions is possible for **FLOT regimen**
- Once doses are reduced, **no dose increase** will be possible.
- The maximum interruption **allowed is 28 successive days** for the study treatments, starting from the day of onset of toxicity. Beyond this time, the patient will be withdrawn from the study treatment.
- For FLOT regimen, participants must have ANC ≥1500/mm³ AND platelets ≥100 000/mm³ on day of infusion or within 72 hours prior to receiving treatment. Participants who do not meet these values will have their cycle start delayed and Spartalizumab will also be delayed.
- In case of Spartalizumab delay for reasons of toxicity, chemotherapy could be either delayed or administered according to investigator opinion (depending on the severity of the toxicity and the estimated delay: < or ≥ 2 weeks) and after contact with the sponsor.
- The decision to reduce the doses will be based on the maximum toxicity observed during the intercourse. The dose adjustments should be based on the most significant toxicity grades. If a patient has several types of toxicity, the dose administered will be the one with the least risk to the patient.

9.2 DOSE LEVELS

Agent	Starting Dose	Dose Level - 1	Dose Level - 2
Docetaxel	50 mg/m²	40 mg/m²	30 mg/m²
Oxaliplatin	85 mg/m²	65 mg/m²	50 mg/m²
Leucovorin	200 mg/m²	Not applicable	Not applicable
Fluorouracil	2600 mg/m²	2000 mg/m²	1600 mg/m²
Spartalizumab	400 mg	Not applicable	Not applicable

Any subjects with two prior dose reductions for one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

9.3 ADJUSTEMENT FOR FLOT REGIMEN

The chemotherapy doses must be adapted in case of severe hematological or non-hematological toxicities.

Subjects who discontinue one of the study drugs on the FLOT regimen may, at the investigator discretion, continue administration of the other study drugs. For example, if Oxaliplatin is discontinued, Docetaxel and Fluorouracil may be continued at the intended dose and schedule.

For the management of patients, especially concerning contraindications, duration of contraception, special warnings and precautions, posology adaptation (only is not referencing in the protocol), monitoring, as well as medications that are contraindicated or must be used with caution, please refer to the SmPC of the products on the website : http://base-donnees-publique.medicaments.gouv.fr

9.3.1 Dose Modifications for hematologic toxicity

Before any chemotherapy administration, the following laboratory parameters should be checked:

- ANC ≥ 1 500/mm³
- platelets ≥ 100 000/mm³

NEUTROPENIA				
If ANC < 1.5 on Day 1: hold treatment. **If ANC ≥ 1.5 within 2 weeks (G0/G1), start treatment at the dose level noted across from the lowest ANC result of the delayed week(s).** **If delayed 2 weeks consider**				
Dose after toxicity:				
Grade	**ANC (x10⁹/L)**	**Docetaxel**	**Oxaliplatin**	**Fluorouracil**
I	≥ 1.5	no dose reduction		
II	1 to 1.5	no dose reduction		
III	0.5 to 1	-1 dose level	-1 dose level	no dose reduction
IV **Or febrile neutropenia**	< 0.5	-1 dose level	-2 dose levels	-1 dose level

G-CSF is recommended as a secondary prophylaxis of neutropenia.

THROMBOPENIA				
If Platelets < 100 on Day 1: hold treatment. **If Platelets ≥ 100 within 2 weeks, start treatment at the dose level noted across from the lowest result of the delayed week(s).** **If delayed 2 weeks consider discontinuing.**				
Dose after toxicity:				
Grade	**Platelets ($x10^9$/L)**	**Docetaxel**	**Oxaliplatin**	**Fluorouracil**
I	≥ 75	no dose reduction		
II	50 to 75	no dose reduction		
III	25 to 50	-1 dose level	-1 dose level	no dose reduction
IV	< 25	-1 dose level	-2 dose levels	-1 dose level

9.3.2 Dose Modifications for oxaliplatin neurologic toxicity

Grade	**Duration**		
	1-7 days	**7-14 days**	**Persisting between cycles**
I: Paresthesias/dysesthesias of short duration that resolve; do not interfere with function	no dose reduction		
II: Paresthesias / dysesthesias interfering with function, but not activities of daily living	no dose reduction	-1 dose level	-1 dose level
III: Paresthesias / dysesthesias with pain or with functional impairment which interfere with activities of daily living	Interrupt until resolved to Grade 2 And restart at -1 dose level	Interrupt until resolved to Grade 2 And restart at -1 dose level	Discontinue therapy
IV: Persistent paresthesias / dysesthesias that are disabling or life-threatening	Discontinue therapy	Discontinue therapy	Discontinue therapy
Acute laryngopharyngeal dysesthesia	If during Oxaliplatin infusion: premedication + increase duration to 6 hours If during Docetaxel infusion: treat as per anaphylactic reaction		

If oxaliplatin is stopped because of neurotoxicity, 5-FU should be continued.

Docetaxel may also cause neurologic toxicity. Docetaxel dose reductions in addition to oxaliplatin reductions will be determined by clinician at their discretion.

9.3.3 Dose modifications for diarrhea

Grade	**Docetaxel**	**Oxaliplatin**	**Fluorouracil**
I or II 1st episode	no dose reduction, start supportive treatment		
II 2nd episode	no dose reduction		-1 dose level
III	Interrupt until resolved to Grade 2 And restart at -1 dose level		Interrupt until resolved to Grade 2, and restart at: 1st episode: -1 dose level 2nd episode: -2 dose levels
IV	Discontinue therapy		

NB: rare case of enterocolitis. If suspected, the patient will be referred urgently to a specialist (gastroenterologist).

We recommend a permanent discontinuation of docetaxel in case of enterocolitis.

9.3.4 Dose modification for liver toxicity

Grade	AST/ALT		Bilirubin	Docetaxel	Oxaliplatin	Fluorouracil
I	< 3 x ULN	and	≤ 1.5 ULN	no dose reduction	no dose reduction	
II	3 - 5 x ULN	or	1.5 - 3 ULN	-1 dose level	no dose reduction	
III	5 -20 ULN	or	3 -10 ULN	Interrupt until resolved to Grade 2 -1 dose level	Interrupt until resolved to Grade 2 no dose reduction	
IV	> 20 x ULN	or	>10 ULN	Discontinue therapy		

9.3.5 Dose modification for mucositis or hand-foot syndrome

These toxicities are caused by Fluorouracil. If grade 3-4 toxicity occurs, stop chemotherapy until recovery (≤ grade 2) and Fluorouracil infusion will be reduced by 1 dose level for the remaining courses.

9.3.6 Adjustments for cardiac toxicity

- In case of prolongation of the QT/QTc interval to > 500 msec, oxaliplatin treatment should be discontinued. In the event of QT/QTc interval prolongation greater than 500 ms (grade 3 toxicity):initiation of close and appropriate ECG monitoring (continuously) in hospital until a cardiologist's opinion is issued.
- In case of suspicion of cardiac toxicity related to Fluorouracil (chest pain, arrhythmia, acute coronary syndrome), Fluorouracil must be suspended until confirmation or exclusion of its causality by a cardiologist. Fluorouracil can be restart if any relationship was eliminated. The others agents can be continued without modification at the discretion of the Investigator.

9.3.7 Adjustments for Docetaxel hypersensitivity reaction

Grade	Docetaxel
I	As per institutional guidelines or at the discretion of the Investigator
II	STOP docetaxel temporarily. Administration of an anti H1 (Polaramine 5mg IV or equivalent), an anti H2 (Ranitidine 50mg IV) and corticoid (Solumedrol 1mg/kg IV or equivalent). Restart docetaxel perfusion if complete resolution. For subsequent cycles, systematic use of the same premedication protocol.
III / IV	STOP docetaxel definitively. Administration of an anti H1 (Polaramine 5mg IV or equivalent), an anti H2 (Ranitidine 50mg IV) and corticoid (Solumedrol 1mg/kg IV or equivalent). Administration of atropine or epinephrine if necessary.
IV	Discontinue therapy

9.3.8 Adjustments for other toxicities

- Other toxicities ≥ grade 3, except anemia and alopecia, may justify an interruption of chemotherapy until recovery (≤ grade 2) and a dose reduction of 1 dose level of the drug(s) involved according to the investigator.
- Any oxaliplatin-related decrease in creatinine clearance to < 30 mL/min requires discontinuation of oxaliplatin.
- Any grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- In the event of infection, fever, digestive disorders suggestive of enterocolitis, a blood count (NFS) will be performed.

9.4 ADJUSTMENT FOR SPARTALIZUMAB

There is no dose adaptation for Spartalizumab. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Investigators must be vigilant and carefully identify AEs that may be suggestive of potential immune-mediated AEs, as their appearance may be sub-clinical (for example an asymptomatic laboratory abnormality) and early diagnosis is critical for appropriate management.

Some symptoms, that potentially may involve every organ system, may evocate immune-mediated mechanisms. In such cases, a particular attention may be paid by investigators. For example, these symptoms may include:

- Fatigue
- Decreased appetite
- Anaemia
- Dyspnea
- Nausea
- Pyrexia
- Cough
- Constipation and diarrhea
- Vomiting
- Back pain and abdominal
- Pruritus and rash

The Investigator Brochure of Spartalizumab should be consulted in case of Adverse Event.

9.4.1 Management of infusion-reactions related to Spartalizumab

Patients should be monitored for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria.

Toxicity grade (CTCAE v 5.0)	Treatment	Premedication at Subsequent Dosing
Grade 1 **Mild reaction; infusion interruption not indicated; intervention not indicated**	・Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. ・Consider slowing infusion rate until recovery of symptoms	None
Grade 2 **Requires infusion interruption but responds promptly to symptomatic treatment Prophylactic medications indicated for ≤ 24 hrs**	・Stop Infusion and keep line open. ・Additional appropriate medical therapy (eg, IV fluids, antihistamines, NSAIDs, paracetamol, oxygen, corticostreroids, bronchodilators...). Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable. ・If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate.	Premedication prior to Spartalizumab infusion with: ・Antihistamine ・Paracetamol (500 to 1000 mg) Permanently discontinued in case of recurring infusion reaction despite adequate premedication and prolonged infusion/slow infusion rate.
Grade 3 **Prolonged; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae** **or Grade 4** **Life-threatening; pressor or ventilatory support indicated**	・Stop Infusion. ・Additional appropriate medical therapy (eg, epinephrine, IV fluids, antihistamines, NSAIDs, paracetamol, narcotics, oxygen, bronchodilators, corticosteroids…). ・Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable. ・Hospitalization as indicated. ・In cases of anaphylaxis, epinephrine should be used immediately. ・Permanently discontinue Spartalizumab.	No subsequent dosing

9.4.2 Toxicity management guidelines for immune-related AEs associated with Spartalizumab

AEs	Toxicity grade (CTCAE v 5.0)	Action with Spartalizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Nephritis	**Grade 2** 1.5-3 x baseline;1.5-3 x ULN	Withhold until resolved to Grade ≤ 1	• Corticosteroids (0.5-1 mg/kg prednisone or equivalent) followed by taper.	·Monitor creatinine. ·Rule-out other causes (e.g. fluids, medications, IV contrast). ·Promote hydration and cessation of nephrotoxic drugs. ·Consult with nephrologist and consider renal biopsy.
	Persistent Grade 2 despite management **Or** **Grade 3 or 4** >3 baseline or ULN	Permanently discontinue	• Corticosteroids (1-2 mg/kg) followed by taper.	
Skin events	**Grade 1** (e.g. rash, pruritus)	Continue	• Consider treatment with topical corticosteroids and/or other symptomatic therapy (eg, antihistamines).	
	Grade 2 (e.g. rash, pruritus)	Consider dose interruption until resolved to Grade ≤ 1	• Topical corticosteroids. • Consider adding low dose systemic corticosteroid as needed (0.5-1 mg/kg/day).	·Consider patient referral to dermatologist.
	Grade 3 (e.g. rash, pruritus) Other severe cutaneous adverse reactions, Bullous dermatitis	Withhold until resolved to Grade ≤ 1	• High-potency topical steroids • Corticosteroids 1mg/kg/day followed by taper.	·Refer patient to dermatologist and consider skin biopsy.
	Persistent Grade 2 or 3 despite management **Or** **Grade 4** Life-threatening	Permanently discontinue	• Corticosteroids (1-2 mg/kg prednisone or equivalent) followed by taper.	·Refer patient to dermatologist and obtain a skin biopsy.
	Stevens-Johnson syndrome, toxic epidermal necrolysis	Permanently discontinue	• Hospitalization and urgent dermatology consultation • Supportive care immediately as per institutional guidelines.	
Hyperthyroidism	**Grade 2** Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Withhold until resolved to Grade ≤ 1	· Initiate treatment with anti-thyroid drug (eg,methimazole or carbimazole) as needed.	· Monitor for signs and symptoms of thyroid disorders. · Monitor TSH and free T4 levels. · Consider patient referral to endocrinologist.
	Grade 3 Severe symptoms; limiting self-care ADL; hospitalization indicated	Withhold until resolved to Grade ≤ 1	· Initiate treatment with anti-thyroid drug as needed. · Consider beta-blocker.	· Monitor for signs and symptoms of thyroid disorders. · Monitor TSH and free T4 levels. · Refer to endocrinologist.
	Persistent Grade 2 or 3 despite management **Or** **Grade 4** Life-threatening	Permanently discontinue		

AEs	Toxicity grade (CTCAE v 5.0)	Action with Spartalizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Hypothyroidism	**Grade 2** Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Continue	· Initiate thyroid replacement hormones (eg, levothyroxine) per standard of care.	· Monitor for signs and symptoms of thyroid disorders. · Monitor TSH and free T4 levels. · Consider patient referral to endocrinologist.
	Grade 3 Severe symptoms; limiting self-care ADL; hospitalization indicated	Withhold until resolved to Grade ≤ 2		
	Persistent Grade 2 or 3 despite management Or Grade 4 Life-threatening	Permanently discontinue		
Hypophysitis	**Grade 3** Severe or medically significant; hospitalization indicated; limiting self-care ADL	Withhold until resolved to Grade ≤ 2	· Corticosteroids (1-2 mg/kg prednisone or equivalent) followed by taper and initiate hormonal replacements as clinically indicated.	· Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Persistent Grade 2 or 3 despite management Or Grade 4 Life-threatening	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	**New onset T1DM or hyperglycemia Grade 3** Insulin therapy initiated; hospitalization indicated	Withhold until resolved to Grade ≤ 2	· Initiate insulin replacement therapy.	· Monitor participants for signs and symptoms of diabetes. · Monitor glucose levels. · Refer to endocrinologist.
	Persistent Grade 2 or 3 despite management Or Grade 4 Life-threatening	Permanently discontinue		
Guillain-Barré, encephalitis,	**Grade 2** Moderate	Consider interruption until resolved to Grade ≤ 1	· Initiate symptomatic treatment. · Consider corticosteroids.	· Ensure adequate evaluation to confirm etiology or exclude other causes. · Refer to a specialist.

	Grade 3 or 4	Permanently discontinue	· Corticosteroids based on severity of AE (1-2 mg/kg prednisone or equivalent) followed by taper.	
Myasthenic syndrome/myasthenia gravis	**All grade**	Permanently discontinue		▪ Ensure adequate evaluation to confirm etiology or exclude other causes. ▪ Refer to a specialist.
Other immune-related AEs (including myositis, myocarditis, hypopituitarism, uveitis, etc.)	**Grade 2** Moderate	Consider interruption until resolved to Grade ≤ 1	· Initiate symptomatic treatment. · Consider corticosteroids.	▪ Ensure adequate evaluation to confirm etiology or exclude other causes. ▪ Refer to a specialist.
	Grade 3 Severe	Withhold until resolved to Grade ≤ 1 Except for myocarditis : Permanently discontinue	· Corticosteroids based on severity of AE (1-2 mg/kg prednisone or equivalent) followed by taper.	
	Recurrent grade 3 immune-related adverse reactions	Permanently discontinue		
	Grade 4 Life-threatening	Permanently discontinue	· Hospitalization. · Corticosteroids based on severity of AE (1-2 mg/kg prednisone or equivalent) followed by taper.	

10 BIOLOGICAL BANKING FOR FURTHER ANCILLARY STUDIES

10.1 TUMOR SAMPLES

Possible approaches will be developed with additional grants.

Tumour samples will be collected for further explorations in baseline tumor tissue.

These analyses may include for example:

- PD-L1 expression by IHC
- Tumor mutational burden
- Analyze of deficient MisMatch Repair (dMMR) DNA by IHC
- EBV status

For each included patient, a mandatory analysis of the primary tumor will be performed.

These analyzes will be carried out centrally.

Optional additional fresh primary tumor samples before treatment will be proposed (additional specific consent form), only at François Baclesse site (Caen) for tumor organoid cultures. The tissue samples will be sent directly to BioTICLA laboratory of INSERM unit U1086 (Caen), who will have been informed before of the patient's inclusion.

10.2 BLOOD SAMPLES

Blood samples will be collected at 5 times: inclusion before chemotherapy initiation, after pre-operative treatment, after surgery, after post-operative treatment and 3 months from the end of treatment. The samples will be frozen on site and will be repatriated at the end of the inclusions at the request of the promoter.

Translational further researches may be used to identify and monitor ctDNA during treatment.

Optional whole blood samples will be proposed only at François Baclesse site (additional specific consent form) before treatment, for preparation of PBMCs and storage for possible tumor organoid cultures.

10.3 SAMPLING SCHEDULE FOR BIOLOGICAL SAMPLES

	Type of sample	**Baseline**	**After pre-operative treatment**	**After surgery**	**After post-operative treatement**	**3 months from the end of treatment**
Tumor samples	Fresh or archival	1 FFPE tissue block				
	Fresh optional*	3-4 cores				
Blood samples	Plasma blood	✓	✓	✓	✓	✓
	PBMC*	✓				

* Optional samples only at François Baclesse site (Caen) for organoids research (additional specific consent form)

11 EFFICACY AND SAFETY CRITERIA

11.1 EFFICACY CRITERIA

Response to treatment will be evaluated according to pathologic response after pre-operative treatment and DFS and OS after post-operative treatment.

For the primary objective, the pathologic response after pre-operative treatment will be assessed by the local experienced pathologists. Tumour regression grade will be quantified using the Becker regression criteria [36], which are based on the estimation of the percentage of vital tumour cells in relation to the macroscopically identifiable tumour bed and include the following categories:

- TRG1a (equivalent to pathological complete regression; no residual tumour cells);
- TRG1b (subtotal regression; <10% residual tumour cells);
- TRG2 (partial regression; 10–50% residual tumour cells); and
- TRG3 (minor or no regression; >50% residual tumour cells).

11.2 SAFETY CRITERIA

The safety assessment will be done by evaluating the general condition (ECOG, weight) and clinical status of the patients, and by collecting the events during the trial (from the inform consent signature to 30 days after treatment discontinuation) will be listed on the eCRF. The intensity of the events will be estimated according to the NCI-CTCAE version 5.0 classification (grade 1 to 5 toxicity).

The intensity of adverse events not listed in this classification will be graded as follows:

- Grade 1: mild Discomfort noticed but no disruption of normal daily activity
- Grade 2: moderate Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
- Grade 3: severe Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk
- Grade 4: Life-threatening/disabling

  An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival
- Grade 5: Death AE resulting in death

12 SAFETY

12.1 GENERAL RULES - INSTRUCTIONS

Safety management will be conducted according to the French regulatory requirements (Law No. 2012-300 of 05/03/2012 as amended by Ordinance No. 2016-800 of 16 June 20161)

12.2 DEFINITIONS

12.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to it.

12.2.2 Adverse Reaction

All untoward medical occurrences in a patient or clinical investigation subject which participate to research involving the human person **related to the study procedure or to the experimental product.**

All untoward responses to an investigational medicinal product related to any dose administered.

12.2.3 Serious Adverse event

A serious adverse event (SAE) is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event*.

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Some “hospitalization/prolonged hospitalization” are not considered to be reported as SAE:

- Admission for administrative or social reasons
- Hospitalization predefined by the protocol
- Hospitalization for medical or surgical treatment planned before the beginning of the trial
- Passage to day hospital
- Hospitalizations for pre-existing signs and symptoms that have not been aggravated

12.2.4 Suspected Unexpected Adverse Reaction

Any serious adverse reaction for which the nature, severity, frequency or outcome is not consistent with the applicable product information (e.g investigator’s brochure for an unauthorized investigational product or summary of product characteristics for an authorised product).

Any serious adverse reaction for which the nature, severity, frequency or outcome is not consistent with the applicable product information, diagnostic or therapeutic study mandated procedure (non-invasive and/or invasive) evaluated in the protocol.

12.3 INVESTIGATOR’S RESPONSABILITIES

12.3.1 Detection and registration of adverse events

12.3.2 All AEs have to be searched, reported and recorded, processed and evaluated.

With the exception of serious adverse events (see section 12.3.3), all adverse events occurring, once the informed consent form has been signed, **during treatment and 45 days after the last study drug administration** must be recorded by the investigator.

The intensity of the events will be estimated according to the NCI-CTCAE version 5.0 classification (grade 1 to 5 toxicity). The intensity of adverse events not listed in this classification will be graded as follows:

- **Grade 1:** **mild** : Discomfort noticed but no disruption of normal daily activity
- **Grade 2:** **moderate** : Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
- **Grade 3:** **severe** : Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk
- **Grade 4:** **Life-threatening/disabling :** An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival
- **Grade 5:** **Death AE or resulting in death**

The investigator will specify for each event:

- ✓ The seriousness
- ✓ The date of start +/- the date of end of the event
- ✓ The duration
- ✓ The intensity
- ✓ The causality assessment
- ✓ The outcome

If a SAE occurs, the sponsor should be notified of the event awareness by the investigator without any delay. This will be done by mailing sponsor's Serious Adverse Event Report Form.

12.3.3 SAE reporting process

The investigator has to report the Sponsor of all serious adverse events occurring, once the informed consent form has been signed, **during treatment and 150 days after the last study drug administration**,

All late Serious Adverse Events and considered as reasonably related to the study treatment(s) or to the study procedure must be reported without delay limitation.

The investigator has to immediately report to the sponsor all serious adverse events with the exception of those that are identified as not requiring immediate reporting in the protocol or the investigator's brochure.

This will be done by mailing sponsor's Serious Adverse Event Report Form, and it will be following by some report, as needed, containing all available information concerning the SAE.

The investigator will specify for each event:

- ✓ The description as clear as possible according to the medical terminology,
- ✓ The intensity,
- ✓ The date of start and the date of end of the event,
- ✓ Measures taken and the necessity or not for a corrective treatment,
- ✓ If the treatment of the study was discontinued or if dose was modified
- ✓ The outcome: For a non-fatal event, the event should be followed until resolution or return to the initial status or to stabilization of potential sequels,
- ✓ The **causality assessment**: he has to assign a causality of "related to study treatment", if there is a "reasonable possibility" that the study treatment caused the event, or "not related to study treatment" if there is "no reasonable possibility" that the study treatment caused the event. The investigator must also assess whether the serious adverse event is "possibly related" to any study mandated procedure or activity, or others concomitants treatments, or under study or any others disease.

The investigator should also, when possible, attach to the serious adverse event report:

- ✓ A copy of the hospital report/hospitalization prolongation,
- ✓ A copy of the autopsy report,
- ✓ A copy of the results of all additional exams performed, including relevant negative results together with the range of normal laboratory values,
- ✓ Any other document judged useful and pertinent (including imaging)

All these documents should be **anonymized**.
Additional information may be requested by the sponsor.

The investigator should document the event as best as possible, provide medical diagnosis where possible and establish a causal link between the serious adverse event and the research, the study treatment, the associated drugs, an underlying pathology, progression of the disease or other cause.
The investigator shall promptly provide the sponsor with additional information regarding serious adverse events as he becomes aware of them.
The investigator should follow the patient who has had a serious adverse event until resolution, stabilization at a level acceptable to the investigator or return to the previous status, even if the patient withdraws from study and inform the sponsor of the serious adverse event outcome.

12.3.4 Special cases

ADVERSE EVENT OF SPECIAL INTEREST

An adverse event of special interest (AESI) is a serious or non-serious adverse event that requires special attention and will be specifically searched. AESIs should be notified and followed as serious adverse events.
As part of this research, the following events are considered as AESI:

- Immune related diseases:
  - Endocrine disorders (i.e. hypothyroidism, hyperthyroidism, diabetes, hypophysitis, hypopituitarism, adrenal insufficiency)
  - Pneumonitis
  - Colitis
  - Immune mediated liver injury
  - Nephritis
  - Other immune-mediated events

Others:

- Infusion reactions to spartalizumab
- Skin reactions: grade 3/4 , Stevens-Johnson syndrome and toxic epidermal necrolysis

REPORTING EXCEPTIONS

Serious adverse event not to be notified immediately

Any event that is part of the natural history of the disease (progression of the disease or hospitalization for progression of the disease) should not be notified to pharmacovigilance on the SAE form but has to be reported into the e-CRF.

Warning: disease progression resulting in death has to be notified

Some "hospitalization/prolongation of hospitalization" are not considered as serious adverse events and do not require notification to pharmacovigilance (see last paragraph "Serious adverse event ").

PREGNANCY

If a woman starts a pregnancy as part of the study or in some cases if her partner participates in the study (drug that can reach the seminal line of the man), the investigator has to report pregnancy to the sponsor.

The investigator informs the sponsor who will send him a "PREGNANCY NOTIFICATION FORM".

The investigator has to follow the patient until the end of the pregnancy or its interruption and notify the outcome to the sponsor. If the outcome of pregnancy falls within the definition of serious adverse events (spontaneous abortion with hospitalization, fetal death, congenital anomaly, ...) the investigator has to complete a SAE form and has to follow the complete SAE reporting process.

If it's a paternal exposure, the investigator has to obtain the parturient consent to report pregnancy data.

13 STATISTICAL CONSIDERATIONS

13.1 NUMBER OF SUBJECTS

We used an optimal Simon's two stage phase II design to estimate the sample size.

According to Al-Batran S-E et al outcomes, patients rate achieving pathological complete regression with FLOT regimen was 16% [95%CI: 10-23] (n=128). To assess efficacy of FLOT regimen combined with spartalizumab, we assume a histological complete response rate p<10% as unacceptable (corresponding to the lower CI limit of response rate in Al-Batran), and a response rate p>23% as demonstrating efficacy of the treatment combination (corresponding to the upper CI limit). With an alpha level of 5% and statistical power of 80%, 58 assessable patients are required, including 20 in the first stage.

Taking into account that 15% of patients will be lost or non assessable, we plan to include a total of 67 patients in the trial (23 in the first stage and 44 in the second).

13.2 STATISTICAL ANALYSIS

All enrolled patients who receive at least one dose of study medication will be evaluable for the efficacy analysis as well as included in the safety analysis.

Safety analysis

A safety analysis was planned one month's follow-up after the surgery of 10th patient. Enrolment was halted during this safety analysis.

This analysis included analyses of safety data, of the delays in performing surgery and of the perioperative complications.

A substantial amendment was submitted to the ANSM for authorization with:

- A summary of data from this analysis of the safety data of the first 10 patients
- The opinion of the IDMC concerning these safety data, with an analysis of the impact of neoadjuvant treatment on the time frame for the surgery, the reasons for postponing the surgery, and the consequences for the continuation of the clinical trial.

  Safety analysis of FLOT plus immunotherapy in neoadjuvant treatment on 10 patients, including toxicities and dose reductions, showed tolerance observations consistent with the safety profile of similar association in this setting. No safety signal that may have compromised the pursuit of the trial was noticed. In particular, the grade 3 immune-mediated encephalitis that occurred in one patient was rapidly reversible after the prompt implementation of a specific and adapted management.

  Similarly, the type and frequency of toxicities observed during the peri-operative period (up to one month post-surgery) were in line with events usually observed in this setting and compatible with the pursuit of the trial. No death was observed.

  Overall, the IDMC recommends the Sponsor to pursue the study without modification but to plan a second formal safety analysis after the inclusion of the 30th patient : this safety analysis

will notably focus on grade 3 and 4 toxicities, spartalizumab-related toxicities, as well as all SAE (severe adverse events) and AESI (adverse events of special interest) notified to pharmacovigilance.

- The inclusions must only be restarted after authorization from the ANSM.

Interim analysis:

According to the optimal Simon's two stage phase II design used in this trial, an interim analysis after the 23th inclusion was planned, without halting inclusions. A minimum of 3 complete responses out of 20 assessable patients in the first stage will allow pursuing the study in the second stage. Otherwise, the study will stop for insufficient efficacy.

To be noticed, data concerning surgical pathologic response were available for 9 patients included in the first safety analysis, and reported in the file presented to the IDMC. The number of complete pathological responses observed among of these 9 assessable patients fulfilled the futility criterion of the Simon design. In this context, the IDMC indicated the planned interim analysis will have no more decisional impact on the pursuit of the study. It therefore recommended not to realise the planned interim analysis but to include available efficacy data in the second safety report, to assess the benefit/risk ratio of the combination.

Final analysis:

On the 58 assessable patients considered for the final analysis, the study will conclude to efficacy if at least 10 complete responses are observed. Besides this such obtained efficacy criterion, the response rate will be estimated with a 95%CI confidence interval.

General considerations:

The number of patients who were not evaluable, who died or withdrew before treatment began will be specified. Categorical variables will be summarized using numbers and proportions. Quantitative variables will be summarized using quartiles and range (mean and standard error for Gaussian-like variables). Chi-squared test and T-Student test will be used to measure association of, respectively, qualitative and quantitative variables with pCR response.

Time-to-event variables will be summarized by the Kaplan-Meier estimator. Association of time-to-event variables with factors of interest will be measured by a Cox model and the log-rank test.

Adverse events of the Spartalizumab + FLOT regimen combination will be described according to NCI CTCAE criteria v5.0 and tabulated by grade and frequence, based on time of occurrence and relationship to treatment. Will be excluded events unrelated or not likely related to treatment, but included events for which the relationship with treatment is not assessable. Tolerability will be summarized by duration of treatment, reasons of discontinuation, dose reduction rates and reasons for dose reductions.

14 QUALITY CONTROL

14.1 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An IDMC will be set-up to ensure the protection of patients, to ensure the ethical conduct of the study, to evaluate the benefit/risk ratio of the study and to insure an independent review of the scientific outcomes during and at completion of the study.

The Independent Committee exercises a consultative role for the promoter who takes the final decision for implementing the recommendations proposed by the committee.

The committee will include a statistician, a pharmacologist and a clinical physician.

This committee will be consulted:

- **Before the trial initiation**
- **At safety analysis (after the surgery of 10th patient)**
- **At safety analysis (after the inclusion of the 30th patient)**
- **At the final analysis**

Dealing with safety, the committee will be informed of regular reviewing of safety data and advice. The Sponsor will sent the annual safety reports and eventually SAEs and / or SUSARS according to the conditions provided for during the first meeting, The committee should propose to stop inclusions in case of unacceptable toxicities (in terms of severity and/or frequency).
For this purpose, regular teleconferences will be planned and will contain two parts: the first one with the Sponsor introducing the teleconference with a safety review, and the second one with only IDMC members who will independently deliberate. A tracking form for Grade ≥ 3 AEs and the relationship to the study treatments will be distributed ahead of time and jointly reviewed at each teleconferences. The statistician of the Sponsor will be in charge of reporting all safety concerns to the IDMC, in terms of grade and timing along with treatment protocol adherence.
All the decisions will be documented in writing and communicated to all the investigators.
If needed, ad hoc teleconferences may be organized for any safety alert.

14.2 QUALITY ASSURANCE

In order to ensure the authenticity and credibility data in accordance to Good Clinical Practices (GCP), the sponsor will implement a quality assurance system that includes:

- the management of the test according to the procedures of the Clinical Research Unit
- the quality control of the data of the investigator site by the monitor whose role is to check the concordance and the coherence of the data of case report form of observation compared to the documents-source
- the provision if the funding provides for dedicated staff in the service to assist the investigator in the logistics of the study and the collection of data in the case report form.

15 ETHICS AND REGULATORY CONSIDERATIONS

The study will be conduct in accordance with the French Public Health Law, specially relating to research involving the biomedical human person of the Public Health Code, articles L1121-1 and following (Law No. 2012-300 of 05/03/2012 as amended by Ordinance No. 2016-800 of 16 June 2016), the Bioethics Law, the law related to the protection of physical persons for the treatments of personal data and related to information technology, database and liberties, the Helsinki declaration and the Good Clinical Practices.

15.1 CLINICAL TRIAL AUTHORISATION

An authorization request will be sent by the sponsor to the French regulatory authorities before the study initiation:

- Ethics Committee (Committee for the Protection of Persons, CPP)
- Competent Health Authority (ANSM)

Information will be given to the Competent Authority (ANSM), with transmission of the synopsis of the study and the favorable opinion of the CPP.

This study is under of the "Reference Methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the law of 6 January 1978 as amended relating to data processing, files and freedoms. This change was approved by decision of 5 January 2006.

The François Baclesse Center respects the regulations in force, in particular the rights of the persons being treated according to the EU regulation 2016/679 on the protection of data ("RGPD").

Any substantial modification in the protocol about objectives, design, population, evaluation, significant administrative modifications will need the coordinator approval, the sponsor approval, CPP approval and the competent authority authorization.

15.2 INFORMATION OF PATIENTS INVOLVED IN THE RESEARCH

Patients will be completely and faithfully informed with understandable words on the objectives and constraints of the research, potential risks, required measures for monitoring and safety, of their right to decline the participation in the study or the possibility to withdraw from the study at any time.

All these information are included in the informed consents form given to the patient: one for the main study, other for ancillary studies. The investigator, or the physician who represents him, will collect the signed written informed consent(s) before the definitive inclusion in the study. A copy of the information and consent form signed by the two parties will be given to the patient; the investigator will keep the second copy.

For any significant modification of the protocol related to the objectives of the research, its design, the population, the exams or significant administrative aspects, a new consent from each person participating to the research will be collected if needed.

15.3 INVESTIGATOR RESPONSIBILITIES

The Principal Investigator of each participating center is committed to conduct the clinical trial in accordance with the trial protocol and with the regulations in force, notably the decision of 24 November 2006 related to Good Clinical Practices.

The Principal Investigator is responsible for:

- ✓ Giving to Sponsor his/her curriculum vitae and that of co-investigators
- ✓ Identifying persons involved in the research in his/her team and defining their responsibilities
- ✓ Initiating the inclusion of patients after Sponsor authorization
- ✓ Making the maximum effort to include the required number of patients within the established recruitment period.

Each Investigator is responsible for:

- ✓ Obtaining the signed and dated informed consent and personally signing this consent for each participating patient before any procedure specific to the trial
- ✓ Regularly completing the CRF for each patient included in the trial and to allow to CRAs mandated by the Sponsor a direct access to source data in order to validate the data entered in the CRF
- ✓ Dating, correcting and signing any correction in the CRFs and data clarification forms (DCF)
- ✓ Accepting the regular monitoring visits of the monitor and eventual auditors mandated by the Sponsor or inspectors of supervisory authorities

Source documents, defined as any document or original item that allow to prove the existence or accuracy of a data or a fact recorded during the study, will be kept during 15 years by the investigator or the hospital if the source is a hospital medical record.

The archiving of the data will be the responsibility of the investigator and according to the legislation. The patient should keep the data and a patient identification list for a minimum of 15 years after the end of the study.

15.4 DATA CONFIDENTIALITY

The investigator will ensure the confidentiality of all information concerning the project for himself and for all persons involved in the conduct of the trial until the publication of the test results. This confidentiality obligation will not apply to information that the investigator will be required to provide to patients in the context of their participation in the trial or to information already published. The investigator will ensure not to publish, disclose or use, in any way, directly or indirectly, scientific or technical informations of the trial.

The study may not be the subject of any written or oral commentary without the agreement of the sponsor; all the information communicated or obtained during the realization of the test belonging in full right to the sponsor who can freely dispose of it.

16 DATA AND DOCUMENTS KEEPING

16.1 DATA EBTRY AND HANDLING

Data management will be performed by the Data Processing Center (CTD) of the North West Cancéropôle (Centre de Traitement des Données du Cancéropôle Nord-Ouest). The CTD provides a database management software dedicated to clinical research: Ennov Clinical (version 7.5.10, ENNOV / CLINSIGHT, 33155 Cenon, France).

This software package, which is based on an Oracle database architecture, is designed for the overall management of clinical and epidemiological studies, meets the regulatory requirements related to this type of study. The CTD Ennov Clinical instance is validated in its computing environment. A data validation plan will be developed jointly by the Clinical Research Unit and the Data Processing Center and will describe in detail the controls to be performed for each variable.

A database specific to the study will be created, tested and validated before the start of the study. All information required by the protocol must be recorded on the paper observation books - or on the electronic observation booklet - under the responsibility of the principal investigator and an explanation must be provided for each missing data item. The data will have to be entered in these notebooks as they are obtained, and the sponsor will take over the monitoring.

The data will then be checked by the CTD in accordance with the data validation plan.

The database will be frozen after final quality control and then exported to the adequate format for statistical analysis according to an automated and validated procedure.

16.2 ARCHIVING

The sponsor must ensure the archiving of essential documents on the conduct of the study in conditions ensuring their safety, for the minimum duration provided by BPC, 15 years after the end of the research.

These documents are the protocol and annexes, including any amendments, original signed information forms and consents, questionnaires, case report forms, follow-up documents, statistical analyzes, the final report of the study.

16.3 PUBLICATION POLICY

The results of this study, property of the Sponsor (Centre François Baclesse), will be published under scientific articles. Publications relating to or resulting from this research will be communicated and submitted for review by the study coordinators to all investigators.

The authors include investigators that have included most patients, the biostatistician who has performed the data analysis, the clinical researcher monitor and the participants who provided substantial contribution to the development of the study, the analysis and interpretation of results and / or the writing of the manuscript.

Acknowledgement to IDMC members will be indicated in final publication.

No publication or presentation of the results will be allowed without the agreement of all the parties. Each investigator will be author in the order determined by the number of eligible patients included. No publication or communication will be performed without the agreement of the coordinating investigator and the Sponsor with the obligation to mention the name of the Sponsor, the organism which financially supported the conduct of the trial and thanking to Laboratories Novartis that provided Spartalizumab. Each publication will indicate the following sentence: “This study was supported by a grant from the French Cancer Institute INCa and the ARC French Foundation for Cancer Research *(reference CLIPPNo 19-022, INCa_14824)**”.***

Some dedicated publications for ancillary studies will be also performed.

This work will be the property of all authors and will be at their disposal for transversal communications and publications.

Publications related to the results of potential ancillary studies need prior approval of the coordinating investigator and methodologist and will be done after the publication of the main study, which should be cited as reference.

17 FUNDING AND INSURANCE

17.1 FUNDING

Any additional costs referred to the Code of Public Health are being negotiated between the CFB and the representative of the institution, taking into account the financial resources available to the CFB in the frame of its public promotion activities.

However, the CFB will ensure the study implementation and supply of the following material (protocol, CRF, investigator file) needed to the conduct of the study.

In the case of equipment or treatments are provided by other partners, the conditions must be specified in the study agreement.

17.2 INSURANCE

The sponsor has subscribed for the duration of the study an insurance covering his own liability and that of any physician involved in the realization of the study. It will also ensure full compensation for the harmful consequences to search for the person undergoing it and assigns, unless evidence against him that the damage is not attributable to its fault or that of any intervener, without that can be opposite the act of a third party or the voluntary withdrawal of the person who had originally agreed to participating to research. (Article L 1121-10)

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