Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Progress Report

PRODIGE 59-DURIGAST trial: A randomised phase II study evaluating FOLFIRI + Durvalumab ± Tremelimumab in second-line of patients with advanced gastric cancer

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ARTICLE INFO

Article history:
Received 11 October 2020
Accepted 30 November 2020
Available online xxx

Keywords:
Adenocarcinoma
Chemotherapy
Gastric cancer
Immune checkpoint inhibitors

ABSTRACT

Gastric or gastro-oesophageal junction (GEJ) adenocarcinomas present poor overall survival (OS). First-line chemotherapy regimen for patients with HER2-negative tumours is based on a doublet or triplet of fluoropyrimidine plus platinum salt ± taxane. Second-line chemotherapy (Docetaxel or Irinotecan) improves OS which nonetheless remains poor (around 5 months). The first results of immune checkpoint inhibitors (anti-PD-1) combined with chemotherapy in metastatic gastric and GEJ cancers were discordant in recent phase III trials. Data on dual-blockade (anti-PD-L1 or anti-PD-1 plus anti-CTLA-4) plus chemotherapy are lacking.

DURIGAST is a randomised, multicenter, non-comparative, phase II study, evaluating safety and efficacy of FOLFIRI plus Durvalumab (anti-PD-L1) versus FOLFIRI plus Durvalumab and Tremelimumab (anti-CTLA-4) as second-line treatment of advanced gastric and GEJ adenocarcinoma. The primary objective is the rate of patients alive and without progression at 4 months. The main inclusion criteria are: patients with advanced gastric or GEJ adenocarcinoma, pre-treated with fluoropyrimidine + platinum salt ±

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https://doi.org/10.1016/j.dld.2020.11.036

taxane. Due to a lack of data on FOLFIRI, Durvalumab and Tremelimumab combination, a 2-step safety run-in phase has been performed before the randomised phase II. The safety run-in phase did not show any safety issue and the randomised phase II starts in September 2020.

1. Background

Despite therapeutic progress, the prognosis of gastric and gastro-oesophageal junction (GEJ) adenocarcinomas remains poor with overall survival (OS) ranging from 10% to 15% at 5-years [1]. Prognosis and treatment of these cancers at advanced stage depend on Human Epidermal Growth Factor Receptor-2 (HER2) status. In HER2 negative tumours, standard first-line chemotherapy is a doublet of fluoropyrimidine (5-Fluorouracil (5FU) or Capecitabine) plus platinum salt (Cisplatin or Oxaliplatin) [2]. The addition of Docetaxel to Cisplatin/Fluoropyrimidine regimen (DCF) increased OS but with higher toxicity, limiting its implementation in clinical routine practice [3,4]. Nevertheless using Granulocyte-macrophage colony-stimulating factor and new regimens like modified DCF (mDCF) or Docetaxel, Oxaliplatin and 5FU combination allow a significantly better tolerance [5–8]. Indeed, TFOX/FLOT regimens (Docetaxel-Oxaliplatin-5FU combination) were consequently developed with preliminary results showing significant efficacy with acceptable toxicities [9–11]. Based on these results some recommendations, like the French TNCD (*Thésaurus National de Cancérologie Digestive*), consider mDCF and FLOT/TFOX regimens as treatment option in fit patients with HER2 negative advanced/metastatic gastric cancers in first-line setting [10]. Indeed, in France, the ongoing GASTFOX phase III study compares TFOX versus FOLFOX as first-line chemotherapy of patients with advanced gastric or GEJ adenocarcinoma [11].

Second-line chemotherapy improves OS as compared to best supportive care (BSC) alone. Docetaxel, Paclitaxel, FOLFIRI or Irinotecan monotherapy allow significant longer OS (≈5 months) as compared with BSC alone (≈3 months) [12–14]. Ramucirumab alone or combined with Paclitaxel are also treatment options that have proven to be effective [15,16]. Currently, the standard second-line treatment for GC is mostly Paclitaxel plus Ramucirumab, based on the results from the RAINBOW trial, which showed higher OS compared to Paclitaxel alone [16]. Moreover, the FFCD 0307 trial, a phase III trial comparing FOLFIRI followed by ECX regimen (Epirubicine-Cisplatin-Capecitabine) to the reverse sequence (ECX-FOLFIRI), showed that both sequences are possible [17]. Consequently, Irinotecan monotherapy and FOLFIRI are one of the second-line treatment options [10]. Finally, if a triplet regimen (TFOX/FLOT) is more frequently used as first-line treatment, an Irinotecan-based regimen, which is a treatment option in second-line setting, will become the most used second-line regimen. Median OS and PFS of the Irinotecan/FOLFIRI regimen as second-line chemotherapy have ranged from 4.0 to 9.5 months and 2.5 to 5.3 months, respectively [18].

The first results of anti-Program Death 1 (anti-PD1) and anti-Program Death-Ligand 1 (anti-PD-L1) monoclonal antibodies (mAbs), also called immune checkpoint inhibitors (ICIs), in chemorefractory metastatic gastric/GEJ cancers were promising in monotherapy versus BSC alone (Table 1) [19–21]. Nevertheless, recent phase III trials in second-line setting versus chemotherapy have been negative [22,23]. It is worth noting that in most of these trials, efficacy is higher in PD-L1-positive tumours, tumours with high tumour mutational burden (TMB), deficient MisMatch Repair (dMMR)/ Microsatellite Instability (MSI) tumours and Epstein-Barr Virus (EBV)-induced tumours [24].

KEYNOTE-062 a randomised, phase III trial, has compared Pembrolizumab alone or in combination with chemotherapy (platinum salt and 5FU or Capecitabine) versus chemotherapy alone as first-line treatment in patients with advanced gastric or GEJ adenocarcinoma with a PD-L1 Combined Positive Score (CPS) of 1 or higher [25]. There was no OS difference when adding Pembrolizumab to chemotherapy (12.5 months versus 11.1 months) and Pembrolizumab monotherapy was not inferior to chemotherapy alone (10.6 months versus 11.1 months). The absence of benefit of adding an anti-PD1 to chemotherapy is disappointing. Nevertheless, recently the phase III CheckMate-649 comparing Nivolumab plus chemotherapy (XELOX or FOLFOX) versus chemotherapy alone in first-line setting shown that Nivolumab plus chemotherapy is superior to chemotherapy alone in terms of OS (14.4 months versus 11.1 months) and PFS (7.7 months versus 6.0 months) in patients with a tumour with PD-L1 CPS $\geq$ 5 [26]. Finally, the phase I/II CheckMate-032 demonstrated promising results of Nivolumab (anti-PD1) plus Ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4) in advanced gastric cancer [27]. The phase III CheckMate-649 trial also evaluated the combination of Nivolumab plus Ipilimumab (anti-CTLA4) but results are not yet available.

Durvalumab is a human mAbs directed against PD-L1 and Tremelimumab is a human mAbs against CTLA-4, which is used in treatment of many cancers [28,29]. Durvalumab (anti-PD-L1) plus Tremelimumab combination showed a manageable safety profile, similar to others ICIs, in recent randomised phase III in lung and head and neck cancers [28–31]. A recently published phase Ib/II with Durvalumab and Tremelimumab alone or in combination in patients with advanced gastric and GEJ adenocarcinoma in second- and third-line settings demonstrated significant efficacy with a 6-month PFS of 20% and a 12-month OS of 38.8% in Durvalumab plus Tremelimumab arm [28]. Treatment-related grade 3/4 adverse events ranged from 4% to 42% according the combination used.

Since ICI combinations (anti-PD-L1/anti-PD-1 plus anti-CTLA-4) are promising and data on association with chemotherapy are lacking, especially in second-line setting and with FOLFIRI combination, DURIGAST trial is relevant. Few patients with advanced gastric or GEJ adenocarcinoma could benefit from a third-line treatment and a combination of FOLFIRI and ICI could be too toxic for a third-line treatment in patients with a poor performance status at this advanced stage of the disease. Indeed, DURIGAST study aimed to assess the efficacy and safety of FOLFIRI with Durvalumab or Durvalumab plus Tremelimumab as second-line treatment in patients with advanced gastric or GEJ adenocarcinoma.

2. Design

DURIGAST is a randomised, open-label, multicenter, non-comparative, phase II study conducted in France, designed to evaluate the safety and efficacy of FOLFIRI plus Durvalumab (arm A) and FOLFIRI plus Durvalumab plus Tremelimumab (arm B) in patients with advanced gastric or GEJ adenocarcinoma, pre-treated with fluoropyrimidine plus platinum salt +/- taxane. All French centres affiliate to the PRODIGE group ("*Partenariat de Recherche en Oncologie DIGEstive*") could participate to the study. Due to a lack of data concerning the combination of ICIs plus FOLFIRI, a safety run-in phase was performed before the randomised phase II.

Table 1
Main trials evaluating immunotherapy in metastatic gastric and GEJ adenocarcinoma.

Trials	Line of treatment	Evaluated treatments	Population	Number of patients	Objective response rate (%)	Duration of response (months)	PFS (months)	OS (months)	p values for OS[a]
	Metastatic chemoresistance setting								
KEYNOTE-059 (NCT02335411) (15) phase II	3rd line or more	Pembrolizumab (anti-PD-1)	All-comers	259	12%	8.4 m	–	5.6 m	–
ATTRACTION-2 (NCT02267343) (14) phase III	3rd line or more	Nivolumab (anti-PD-1)	All-comers	330	11%	9.5 m	1.6 m	5.3 m	< 0.001
		Placebo		163	0%	–	1.5 m	4.1 m	
JAVELIN Gastric 300 (NCT02625623) (17) phase III	2nd line	Avelumab (anti-PD-L1)	All-comers	185	2.2%	Not reached	1.4 m	4.6 m	0.810
		Chemotherapy (Paclitaxel or Irinotecan)		186	4.3%	5.5 m	2.7 m	5.0 m	
KEYNOTE-061 (NCT02370498) (16) phase III	2nd line	Pembrolizumab (anti-PD-1)	PD-L1 positive with CPS ≥1	196	16%	18.0 m	1.5 m	9.1 m	0.042
		Paclitaxel		199	14%	5.2 m	4.1 m	8.3 m	
CheckMate-032 (NCT03959293) (20) phase I/II	3rd line or more	Nivolumab 3 mg/kg	All-comers	59	12%	7.1 m	1.4 m	6.2 m	–
		Nivolumab 1 mg/kg + Ipilimumab (anti-CTLA-4) 3 mg/kg		49	24%	7.9 m	1.4 m	6.9 m	
		Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg		52	8%	Not reached	1.6 m	4.8 m	
Kelly RJ et al. (NCT03959293) (22) phase I/II	2nd line	Durvalumab (anti-PD-L1) and Tremelimumab (anti-CTLA-4)	All-comers	27	7.4%	–	1.8 m	9.2 m	–
		Durvalumab		24	0%	–	1.6 m	3.4 m	
		Tremelimumab		12	8.3%	20.1 m	1.7 m	7.7 m	
	Maintenance after metastatic first-line chemotherapy								
JAVELIN (NCT01772004) (30) phase Ib	Maintenance after 1st line	Avelumab (anti-PD-L1)	All-comers	90	6.7%	21.4 m	2.8 m	11.1 m	–
Bang YJ et al. (31) phase II	Maintenan-ce after 1st line	Ipilimumab	All-comers	57	1.8%	–	2.7 m	12.7 m	–
		Placebo		57	7%	–	4.9 m	12.1 m	
	Immunotherapy and chemotherapy combination								
KEYNOTE-062 (NCT02494583) (19) phase III	1st line	Pembrolizumab	PD-L1 positive with CPS ≥1	256	14.8%	13.7 m	2.0 m	10.6 m	0.16[b]
		5FU cisplatin		250	37.2%	6.8 m	6.4 m	11.1 m	0.04[c]
		5FU cisplatin plus Pembrolizumab		257	48.6%	6.8 m	6.9 m	12.5 m	
CheckMate-649 (21) phase III	1st line	Nivolumab plus chemotherapy vs. chemotherapy[d]	All-comers	789	–	–	7.7 m[e]	14.4 m[e]	< 0.0001
				792	–	–	6.0 m	11.1 m	
Attraction-4 (32) phase III	1st line	Nivolumab plus chemotherapy vs. Chemotherapy[f]	All-comers	362	57.5%	–	10.5 m	17.5 m	0.257
				362	47.8%	–	8.3 m	17.2 m	

OS: overall survival; PFS: progression-free survival; m: months; CPS: combined positive score.
[a] for randomised trials.
[b] for Pembrolizumab versus chemotherapy.
[c] for Pembrolizumab and chemotherapy versus chemotherapy.
[d] Xelox or Folfox.
[e] results in PD-L1 CPS ≥ 5.
[f] S-1 plus oxaliplatin or Xelox.

2.1. Study objectives and endpoints

The objective of the safety lead-in phase was to validate the good tolerability of FOLFIRI plus Durvalumab plus Tremelimumab combination. There were no pre-defined criteria to evaluate tolerability of the safety lead-in phase but will be based on opinion both of an Independent Data Monitoring Committee (IDMC) and French authorities (ANSM, "*Agence nationale de sécurité du médicament*").

The primary endpoint of the randomised phase II is the percentage of patients alive and without progression at 4 months with FOLFIRI plus Durvalumab or FOLFIRI plus Durvalumab plus Tremelimumab based on the RECIST 1.1 score evaluated by the investigator. PFS is a standard primary endpoint in several randomised trial evaluating second-line treatment in advanced gastric cancer [17,18,22].

Secondary endpoints are: percentage of patients alive and without progression at 4 months according to centralized review, OS, time to failure of strategy, safety profile (according to Common Terminology Criteria for Adverse Event v 4.0 (CTCAE)), health-related quality of life (QoL), time to progression (TTP), median PFS, best objective response rate (BRR) and disease control rate (DCR) according to the investigator and centralized review (according to RECIST 1.1 and iRECIST criteria) and efficacy endpoints (OS, PFS, TTP, BRR and DCR) according to the expression of PD-L1 and other biomarkers (see ancillary studies).

Table 2
Main inclusion and exclusion criteria.

Inclusion criteria
- Age ≥ 18 years. - Known MSS/MSI status or tumour tissue available (paraffin-embedded, primary tumours or metastases) to allow determination of MSS/MSI status. - Failure of platinum-based 1st line therapy with or without trastuzumab or early recurrent disease after surgery with neoadjuvant and/or adjuvant platinum-based chemotherapy (within 6 months of the end of chemotherapy) or progression during neoadjuvant and/or adjuvant platinum-based chemotherapy. - Measurable or non-measurable lesion according to RECIST 1.1 critera. - Adequate organ function: absolute neutrophil count ≥ 1.5×10^9/L, haemoglobin ≥ 9 g/dL, platelets ≥ 100×10^9/L, AST/ALT ≤ 3 x Upper Limit of Normal (ULN) (≤ 5 x ULN in case of liver metastase(s)), GGT ≤ 3 x ULN (≤ 5 x ULN in case of liver metastase(s)), bilirubin ≤ 1.5 x ULN, creatinine clearance > 40 mL/min (MDRD, Modification of diet in renal disease).
Exclusion criteria
- History of chronic inflammatory bowel disease (IBD). - Any unresolved significant toxicity National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 ≥ grade 2 from previous anticancer therapy (except for alopecia and neuropathy). - Major surgical procedure (e.g. exploratory laparoscopy is not considered as a major surgical procedure) within 28 days prior to the first dose of treatment. - Prior allogeneic bone marrow transplantation or prior solid organ transplantation. - Active or prior documented autoimmune or inflammatory disorders (patients with alopecia, vitiligo, controlled hypo or hyperthyroidism, any chronic skin condition not requiring immunosuppressant therapy are eligible). Patients without active disease in the last 5 years may be included. - Uncontrolled intercurrent illness. - History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT-scan. - History of leptomeningeal carcinomatosis. - Positive test for HIV, active hepatitis B or hepatitis C, active tuberculosis. - Current or prior use of immunosuppressive/steroid medication within 14 days before the first dose of study drugs. - Known Uridine Diphosphate Glucuronyltransferase (UGT1A1) or Dihydropyrimidine Dehydrogenase (DPD) enzyme deficiencies. - Active infection requiring intravenous antibiotics at the time of Day 1 of Cycle 1. - Other malignancy within 5 years prior to study enrolment, except for localized cancer in situ, basal or squamous cell skin cancer.

2.2. Ancillary studies

Blood, stool and tumour samples will be collected in order to identify predictive factors of treatment response, prognostic factors and/or biomarkers of treatment toxicity. Biomarkers analyses on the tumour (immunohistochemistry (IHC) and/or tumour DNA) will include MMR IHC/MSI testing, immune response/immune scores (CD3, CD8 and other immune markers), tumour mutational burden (TMB), gastric molecular sub-groups and PD-L1 expression with no pre-defined cut-off.

Stool samples will be collected prospectively in all patients (before treatment and at week 8 before the first evaluation of treatment efficacy) to analyse microbiota (16S rRNA sequencing). Blood samples will be collected just before the first treatment course, before the third course and at progression to determine the level of circulating tumour DNA.

2.3. Population and patient selection

Inclusion and non-inclusion criteria are the same for the safety run-in phase and for the randomised phase II. The main inclusion criteria are patients with histologically proven advanced unresectable (locally advanced or metastatic) gastric adenocarcinoma/GEJ (Siewert II or III) adenocarcinoma, progression or intolerance after first-line chemotherapy with fluoropyrimidine + platinum salt ± taxane, Eastern Cooperative Oncology Group (ECOG) - Performance Status (PS) 0 or 1 and adequate organ function (Table 2).

2.4. Study treatments

Patients will receive FOLFIRI regimen with folinic acid 400 mg/m^2 by 2-hour intra-venous (IV) infusion, 5FU bolus 400 mg/m^2 by 10-minute IV infusion, continuous 5FU 2400 mg/m^2 by 46-hour IV infusion and Irinotecan at 150 mg/m^2 in the safety run-in phase or 180 mg/m^2 in the randomised phase II, by 2-hour IV infusion every 2 weeks.

Accordingly, treatment arm Tremelimumab will be administered at a dose of 75 mg in 1-hour IV infusion before Durvalumab at a dose of 1500 mg in 1-hour IV infusion every 4 weeks.

2.5. Safety run-in phases

A total of 11 patients were included in the 2 steps of the safety run-in phase in five expert centers, before starting the phase II part of the study (Fig. 1).

The first safety run-in phase enroled 5 patients treated with FOLFIRI (Irinotecan at 180 mg/m^2) and Durvalumab and did not show any safety issue. The second safety run-in phase has randomized 6 patients between FOLFIRI (Irinotecan at 180 mg/m^2) and Durvalumab versus FOLFIRI (Irinotecan at 150 mg/m^2), Durvalumab and Tremelimumab (3 patients per arm) and also confirmed the good tolerance of these combinations.

The safety analysis was carried out when all patients have received at least 2 cycles of treatment. Safety was evaluated by an IDMC and ANSM in August 2020 that authorized to start the randomised phase II. Phase II has began in September 2020, 103 centers will participate and 6 patients have been already included.

2.6. Randomised phase II

Randomization, in order to have comparable patients between the 2 arms of treatment, is carried out using the minimization technique according to the 1:1 ratio to receive FOLFIRI plus Durvalumab (Arm A) or FOLFIRI plus Durvalumab and Tremelimumab (Arm B) (Fig. 1b). The following factors are considered for the stratification: centre and duration of disease control in previous first-line chemotherapy (no disease control versus < 3 months versus ≥ 3 months).

In arm B, Tremelimumab is administered for only 4 cycles and the patient will then continue to receive FOLFIRI plus Durvalumab. Treatment is repeated every 2 weeks until disease progression, unacceptable toxicity, withdrawal of consent or patient refusal. In

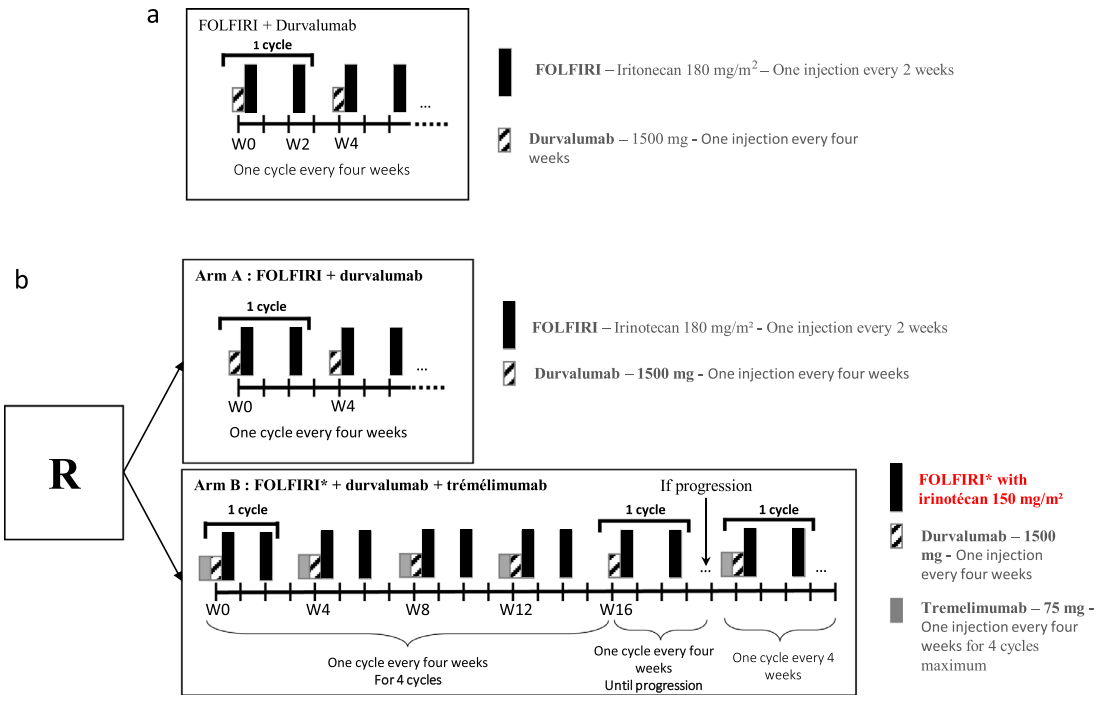

Fig. 1. Design of safety run-in phase and randomised phase II.
(a) First safety run-in phase with FOLFIRI plus Durvalumab ($n = 5$)
Folinic acid 400 mg/m^2 by 2-hour intra-venous (IV) perfusion
5FU bolus 400 mg/m^2 by 10-minute IV perfusion
Continuous 5FU 2400 mg/m^2 by 46-hour IV perfusion
Irinotecan 180 mg/m^2 by 2-hour IV perfusion
every 2 weeks
Durvalumab 1500 mg every 4 weeks
(b) Second safety run-in phase with FOLFIRI plus Durvalumab versus FOLFIRI plus Durvalumab and Tremelimumab ($n = 6$) and randomised phase II ($n = 94$)
Folinic acid 400 mg/m^2 by 2-hour intra-venous (IV) perfusion, for 2 arms
5FU bolus 400 mg/m^2 by 10-minute IV perfusion, for 2 arms
Continuous 5FU 2400 mg/m^2 by 46-hour IV perfusion, for 2 arms
Irinotecan 180 mg/m^2 by 2-hour IV perfusion in Arm A of second safety run-in phase, 150 mg/m^2 in Arm B of second safety run-in phase and 180 mg/m^2 in both arms of randomised phase II
every 2 weeks
Durvalumab 1500 mg, for 2 arms every 4 weeks
Tremelimumab 75 mg, only for Arm B every 4 weeks.
* Irinotecan 150 mg/m^2 in Arm B of second safety run-in phase, and 180 mg/m^2 in randomised phase II.

case of progression on FOLFIRI plus Durvalumab after a previous disease control, Tremelimumab can be re-introduced once at investigator discretion for 4 courses.

Patients is evaluated every 8 weeks for clinical examination, laboratory assessment and morphological assessment (Table 3). Briefly, clinical examination includes ECOG PS, QoL (EORTC QLQ-C30 and STO-22) and safety evaluation. Morphological assessment is based on thoracic-abdominal-pelvic CT according to RECIST 1.1 criteria. At the physician's discretion, it is possible to continue treatment after progression and to perform a new CT-scan 4 to 8 weeks later to confirm progression.

2.7. Data management

For each patient enroled in the study, all required data must be entered in electronic case report form (eCRF), which is accessible only by authorized persons via secured web connection. The investigator has the responsibility for its completion and its approval. Once completed, eCRF will be locked and monitored by a clinical research assistant mandated by *Fédération Francophone de Cancérologie Digestive* (FFCD).

2.8. Statistical considerations

Median PFS with FOLFIRI as second-line chemotherapy in gastric/GEJ adenocarcinoma is between 2 and 4 months [13,17,18,32,33]. PFS is a surrogate marker of OS and a primary endpoint commonly used in phase II trials. Indeed, in order to use binomial exact method for sample size calculation, the hypotheses are:

H0. 50% of patients alive and without progression at 4 months is not acceptable.

H1. 70% of patients alive and without progression at 4 months is expected.

With a risk α (one-sided) of 5%, a power of 85% and according to the binomial exact method, 44 evaluable patients (i.e. patients randomised and with at least one dose of products received) are needed by arm [34]. Assuming 5% of non-evaluable or lost to follow-up patients, 47 patients will be included by arm for the randomised phase II (94 patients in total).

Rules for selection to be applied to each arm (on the 44 evaluable patients) stipulate that if 28 or more patients are alive without progression at 4 months, the arm will be considered as efficient. In the event that both arms show efficacy, safety data will be analysed to determine whether one arm has a better safety profile. This non-comparative design permits to have first indication on efficacy and safety of combinations without exposing a high number of patients before potentially initiating a comparative study of the best regimen in a phase III versus FOLFIRI.

Table 3
Main examination and follow-up schedule.

	BEFORE TREATMENT	DURING TREATMENT	DURING TREATMENT	AFTER TREATMENT END
	During the 14 days preceding the start of treatment	Before each course of treatment	Every 8 weeks (at each evaluation)	Every 2–3 months up to death
Clinical and biological informed consent	X			
Biopsies or tumour block, fixed in paraffin	**X**[a]			
CLINICAL EXAMINATION				
ECOG Performance status	X	X	X	
Evaluation of toxicities NCI-CTCAE Version 4.0		X	X (and 30 days after end of treatment)	X (until 12 months after the end of treatment)
QLQ-C30 and STO-22 questionnaires	X		X	
BIOLOGICAL ASSESSMENT				
Laboratory assessment	X[b]	X[c]	X[b]	
CEA and CA19.9 markers	X		X	
DPD status	X			
PARACLINICAL REVIEWS				
Thoraco-abdominal-pelvic CT scan or MRI	X		X	X
ANCILLARY STUDY				
Blood samples (2 tubes)	X		X[d]	
Stools	X (before treatment)		X (only at week 8)	

NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; QLQC30 and STO-22: Quality of Life Questionnaire - Core Questionnaire; MRI: Magnetic resonance imaging; DPD: Dihydropyrimidine Dehydrogenase.
[a] The investigator needs to ensure that tumour tissues are available and sends them after patient randomization.
[b] CBC, platelets, liver panel (bilirubin (total and conjugated), ALT, AST, ALP, GGT, LDH), serum creatinine, MDRD creatinine clearance, TSH, blood protein, albumin, prealbumin, CRP, coagulation (PT, PTT), serum electrolytes (sodium, potassium, calcium, magnesium), lipase, glucose, urea, urinalysis (urine strip – check of the protein level, if more than 2 crosses then check the proteinurea on 24 h).
[c] CBC, platelets, urea, liver panel (bilirubin (total and conjugated), ALT, AST, ALP, GGT), bilirubin (total and conjugated), serum electrolytes (sodium, potassium, calcium, magnesium), serum creatinine, MDRD creatinine clearance.
[d] Blood sample at 4 weeks for ancillary studies.

3. Discussion

Patients with unresectable GEJ/gastric cancers have a poor prognosis and it is a challenge to find a better treatment than chemotherapy alone. In a second-line setting, Docetaxel, Paclitaxel, Ramucirumab and Irinotecan/FOLFIRI are proposed to patients in good general condition [10]. Nevertheless, OS remains inferior to 6 months [12,13,15].

Several studies have shown low efficacy of anti-PD1/anti-PD-L1 as monotherapy in all-comers GEJ/gastric cancers. Possible strategies to improve the outcome are a combination of ICIs together (i.e. anti-PD1/anti-PD-L1 plus anti-CTLA-4) and/or with chemotherapy. In addition, the identification of predictive biomarkers to better select patients for ICI treatment (dMMR/MSI status, PD-L1 overexpression, high TMB and/or EBV-induced tumours) can be of interest. Indeed, even though in the DURIGAST trial we decided to combine FOLFIRI plus anti-PD-L1 ± anti-CTLA-4 as second-line treatment in all-comers gastric/GEJ adenocarcinoma and all known biomarkers of response to ICI will be analysed.

It is worth noting that DURIGAST is the first study of anti-PD-L1 and anti-CTLA-4 combination with chemotherapy versus anti-PD-L1 and chemotherapy for patients with gastric/GEJ adenocarcinoma pre-treated with fluoropyrimidine + platinum salt ± taxane. The KEYNOTE-062 study combined cisplatin-based chemotherapy and anti-PD1 in first line setting with no significant results for this combination [25]. By contrast the CheckMate-649 and ATTRACTION-4 studies recently show a survival increase with Nivolumab plus oxaliplatin-based chemotherapy as compared to chemotherapy alone [26,35]. In non-metastatic setting promising results with ICI are expected as neoadjuvant treatment in dMMR/MSI tumours [36].

Finally, the results of DURIGAST trial will help to define the best combination to evaluate in a phase III trial in second-line setting (FOLFIRI versus FOLFIRI plus anti-PD-(L)1 or FOLFIRI versus FOLFIRI plus anti-PD-(L)1 and anti-CTLA-4) and also to determine whether this combination should be evaluated in all-comers or sub-groups of patients with relevant biomarkers identified in the DURIGAST trial.

Conflict of interest

None declared.

Financial support

This study was supported in part by Astra Zeneca. Fédération Francophone de Cancérologie Digestive (FFCD) is funding the biobank and molecular analysis.

Acknowledgements

We thank all physicians who are participating in the DURIGAST trial. We also thank all the cooperative PRODIGE group (FFCD – UNICANCER GI – GERCOR) for their contribution and participation to the present trial, especially Lila Gaba the FFCD DURIGAST project managers. Finally, we thank Astra Zeneca and the “Ligue nationale contre le cancer” for their support.

References

[1] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[2] Kang Y-K, Kang W-K, Shin D-B, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III non inferiority trial. Ann Oncol 2009;20:666–73.
[3] Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the v325 study group. J Clin Oncol 2006;24:4991–7.
[4] Wang J, Xu R, Li J, et al. Randomized multicenter phase III study of a modified docetaxel and cisplatin plus fluorouracil regimen compared with cisplatin and fluorouracil as first-line therapy for advanced or locally recurrent gastric cancer. Gastric Cancer 2016;19:234–44.

[5] Shah MA, Janjigian Y-Y, Stoller R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric cancer consortium. J Clin Oncol 2015;33:3874–9.
[6] Lorenzen S, Hentrich M, Haberl C, et al. Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. Ann Oncol 2007;18:1673–9.
[7] Al-Batran S-E, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008;19:1882–7.
[8] Tebbutt NC, Cummins MM, Sourjina T, et al. Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial. Br J Cancer 2010;102:475–81.
[9] Van Cutsem E, Boni C, Tabernero J, et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. Ann Oncol 2015;26:149–56.
[10] Zaanan A, Bouché O, Benhaim L, et al. Gastric cancer: french intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). Dig Liver Dis 2018;50:768–79.
[11] Zaanan A, Samalin E, Aparicio T, et al. Phase III randomized trial comparing 5-fluorouracil and oxaliplatin with or without docetaxel in first-line advanced gastric cancer chemotherapy (GASTFOX study). Dig Liver Dis 2018;50:408–10.
[12] Ford H, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014;15:78–86.
[13] Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47:2306–14.
[14] Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 2013;31:4438–44.
[15] Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicenter, placebo-controlled, phase 3 trial. Lancet 2014;383:31–9.
[16] Wilke H, Muro K, Cutsem EV, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224–35.
[17] Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (fédération francophone de cancérologie digestive, fédération nationale des centres de lutte contre le cancer, and groupe coopérateur multidisciplinaire en oncologie) study. J Clin Oncol 2014;32:3520–6.
[18] Maugeri-Saccà M, Pizzuti L, Sergi D, et al. FOLFIRI as a second-line therapy in patients with docetaxel-pretreated gastric cancer: a historical cohort. J Exp Clin Cancer Res 2013;32:67.
[19] Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1–10.
[20] Kang Y-K, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:2461–71.
[21] Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 2018;4:e180013 -e180013.
[22] Shitara K, Özgüroğlu M, Bang Y-J, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 2018;392:123–33.
[23] Bang Y-J, Ruiz EY, Van Cutsem E, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol 2018;29:2052–60.
[24] Kim ST, Cristescu R, Bass AJ, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. Nat Med 2018;24:1449–58.
[25] Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer the KEYNOTE-062 phase 3 randomized clinical trial. JAMA oncol 2020;6:1–10.
[26] Moehler MH, Shitara K, Garrido M, et al. Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): first results of the CheckMate 649 study. Annals of Oncology 2020;31(suppl_4):S1142–215.
[27] Janjigian YY, Bendell J, Calvo E, et al. CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. J Clin Oncol 2018;36:2836–44.
[28] Kelly RJ, Lee J, Bang Y-J, et al. Safety and efficacy of durvalumab and tremelimumab alone or in combination in patients with advanced gastric and gastroesophageal junction adenocarcinoma. Clin Cancer Res 2020;26:846–54.
[29] Ferris RL, Haddad R, Even C, et al. Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study. Ann Oncol 2020;31:942–50.
[30] Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. The Lancet 2019;394:1929–39.
[31] Rizvi NA, Cho BC, Reinmuth N, et al. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non–small cell lung cancer: the MYSTIC phase 3 randomized clinical trial. JAMA Oncol 2020;6:661–74.
[32] Samalin E, Afchain P, Thézenas S, et al. Efficacy of irinotecan in combination with 5-fluorouracil (FOLFIRI) for metastatic gastric or gastroesophageal junction adenocarcinomas (MGA) treatment. Clin Res Hepatol Gastroenterol 2011;35:48–54.
[33] Kim SH, Lee G-W, Go SI, et al. A phase II study of irinotecan, continuous 5-fluorouracil, and leucovorin (FOLFIRI) combination chemotherapy for patients with recurrent or metastatic gastric cancer previously treated with a fluoropyrimidine-based regimen. Am J Clin Oncol 2010;33:572–6.
[34] A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med 2001;20:859–66.
[35] Boku N, Ryu M-H, Kato K, et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). Ann Oncol 2019;30(2):250–8.
[36] Cohen R, Pudlarz T, Garcia-Larnicol ML, et al. Localized MSI/dMMR gastric cancer patients, perioperative immunotherapy instead of chemotherapy: the GERCOR NEONIPIGA phase II study is opened to recruitment. Bull Cancer 2020;107:438–46.