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Progress Report

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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 ± 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.

Keywords: gastric cancer; adenocarcinoma; chemotherapy; immune checkpoint inhibitors.

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 Digestiv*e), 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 tumor with PD-L1 CPS $\geqslant$ 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.

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.

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).

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), tumor 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.

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).

Study treatments

Patients will receive FOLFIRI regimen with folinic acid 400 mg/m^2 by 2-hour intravenous (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/m² in the safety run-in phase or 180 mg/m² 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.

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 (Figure 1).

The first safety run-in phase enrolled 5 patients treated with FOLFIRI (Irinotecan at 180 mg/m²) 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/m²) and Durvalumab versus FOLFIRI (Irinotecan at 150 mg/m²), 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.

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) (Figure 1b). The following factors are considered for the stratification: center 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 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.

Data management

For each patient enrolled 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).

Statistical considerations

Median PFS with FOLFIRI as second-line chemotherapy in gastric/GEJ adenocarcinoma is between 2 to 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:

- H_0: 50% of patients alive and without progression at 4 months is not acceptable.
- H_1: 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.

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, 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 neo-adjuvant 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.

Conflicts of interest

None declared.

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Figure Legends

Figure 1. Design of safety run-in phase and randomised phase II.

1a. 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/m² by 2-hour IV perfusion

every 2 weeks

Durvalumab 1500 mg every 4 weeks

1b. 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/m² 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/m² 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

Figure 1a

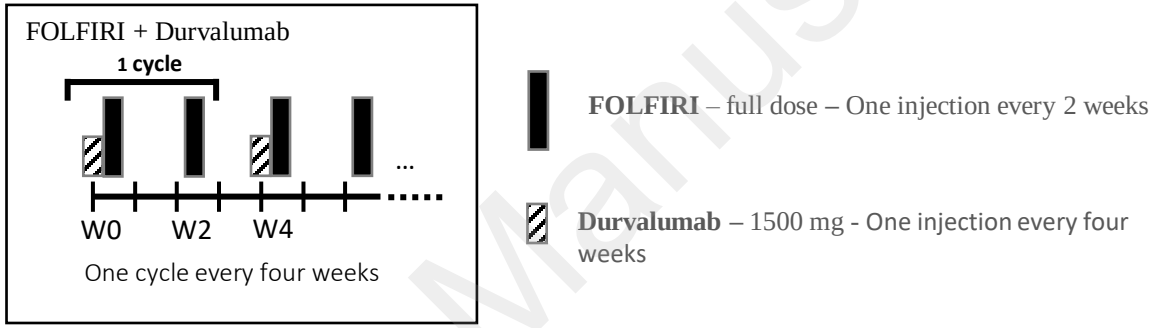


Figure 1b

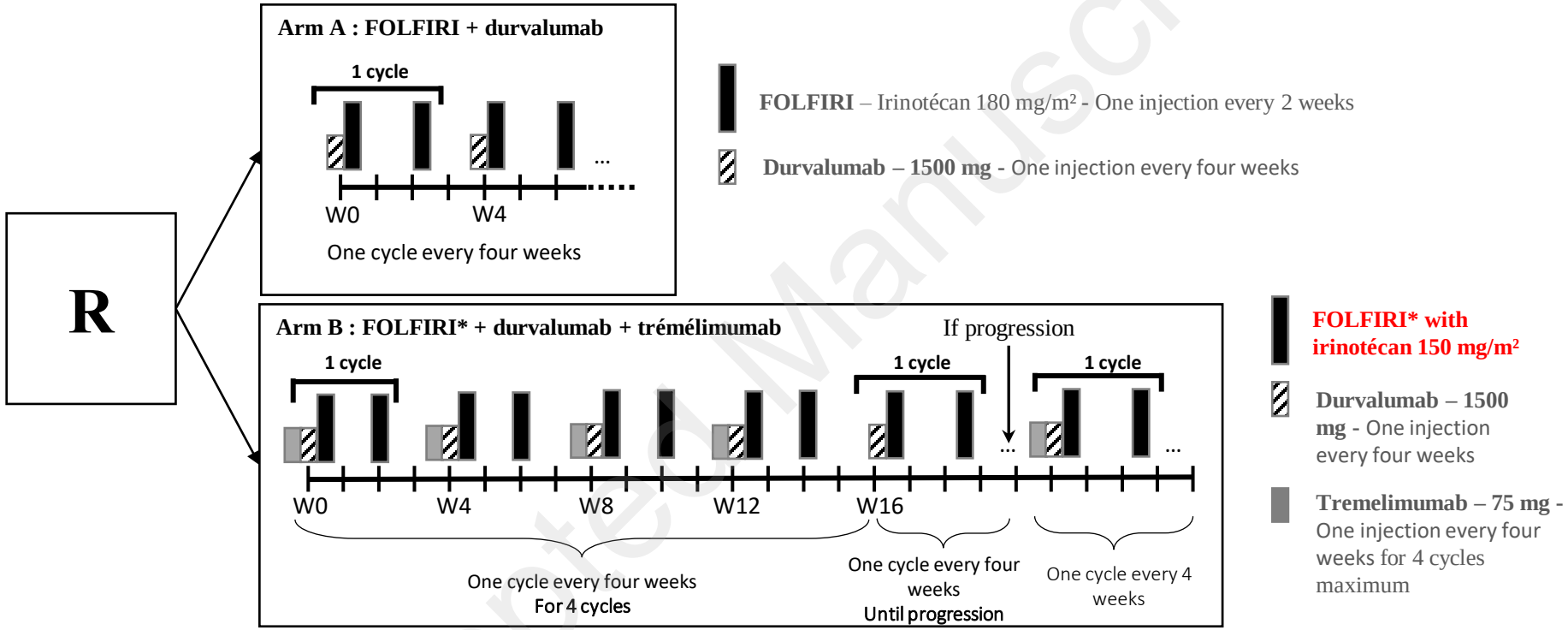
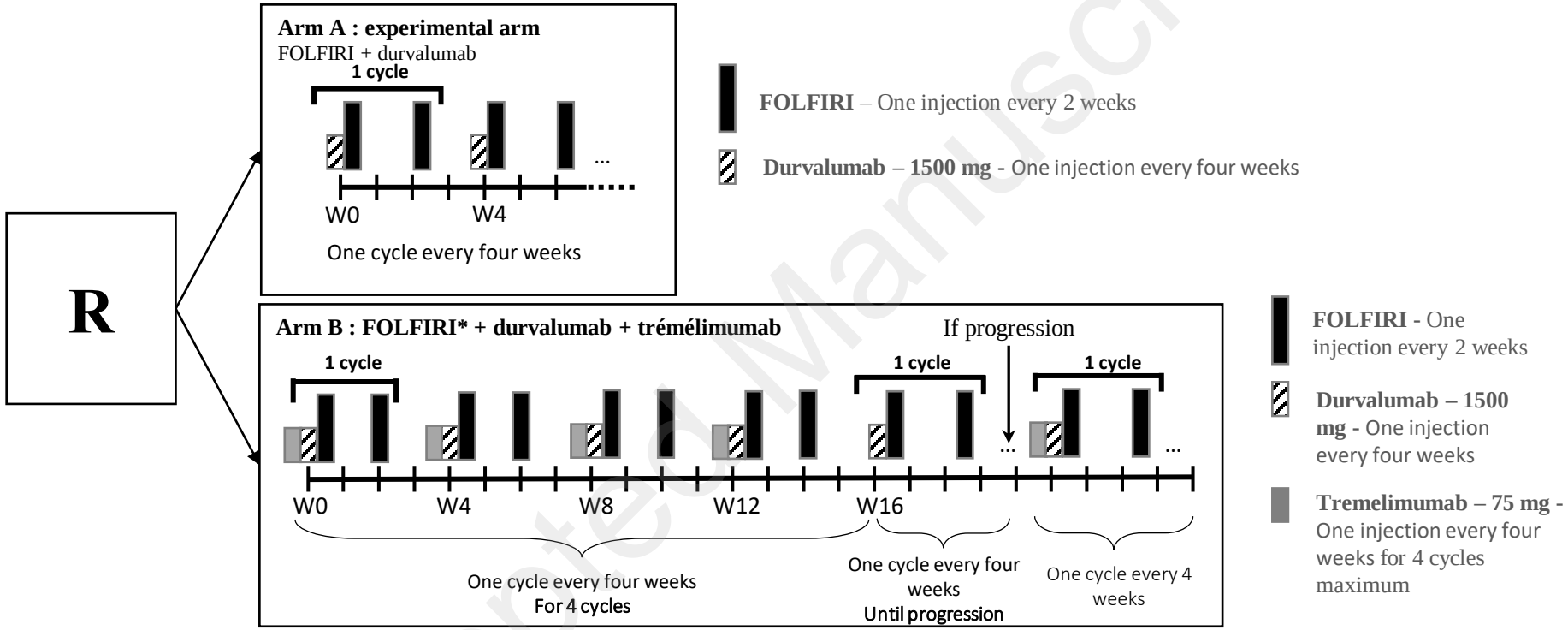


Figure 2



Tables

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) Placebo	All-comers	330 163	11% 0%	9.5 m -	1.6 m 1.5 m	5.3 m 4.1 m	< 0.001
JAVELIN Gastric 300 (NCT02625623) (17) phase III	2nd line	Avelumab (anti-PD-L1) Chemotherapy (Paclitaxel or Irinotecan)	All-comers	185 186	2.2% 4.3%	Not reached 5.5 m	1.4 m 2.7 m	4.6 m 5.0 m	0.810
KEYNOTE-061 (NCT02370498) (16) phase III	2nd line	Pembrolizumab (anti-PD-1) Paclitaxel	PD-L1 positive with CPS ≥1	196 199	16% 14%	18.0 m 5.2 m	1.5 m 4.1 m	9.1 m 8.3 m	0.042
CheckMate-032 (NCT03959293) (20) phase I/II	3rd line or more	Nivolumab 3mg/kg Nivolumab 1mg/kg + Ipilimumab (anti-CTLA-4) 3mg/kg Nivolumab 3mg/kg + Ipilimumab	All-comers	59 49 52	12% 24% 8%	7.1 m 7.9 m Not reached	1.4 m 1.4 m 1.6 m	6.2 m 6.9 m 4.8 m	-

		1mg/kg							
Kelly RJ *et al.* (NCT03959293) (22) phase I/II	2nd line	Durvalumab (anti-PD-L1) and Tremelimumab (anti-CTLA-4) Durvalumab Tremelimumab	All-comers	27 24 12	7.4% 0% 8.3%	- - 20.1 m	1.8 m 1.6 m 1.7 m	9.2 m 3.4 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	Maintenance after 1st line	Ipilimumab Placebo	All-comers	57 57	1.8% 7%	- -	2.7 m 4.9 m	12.7 m 12.1 m	-
	Immunotherapy and chemotherapy combination								
KEYNOTE-062 (NCT02494583) (19) phase III	1st line	Pembrolizumab 5FU cisplatin 5FU cisplatin plus Pembrolizumab	PD-L1 positive with CPS ≥1	256 250 257	14.8% 37.2% 48.6%	13.7 m 6.8 m 6.8 m	2.0 m 6.4 m 6.9 m	10.6 m 11.1 m 12.5 m	0.16[b] 0.04[c]
CheckMate 649 (21) Phase III	1st line	Nivolumab plus chemotherapy vs. chemotherapy[d]	All-comers	789 792	- -	- -	7.7 m[e] 6.0 m	14.4 m[e] 11.1 m	< 0.0001
ATTRACTION-4 (32) Phase III	1st line	Nivolumab plus chemotherapy vs. Chemotherapy[f]	All-comers	362 362	57.5% 47.8%	- -	10.5 m 8.3 m	17.5 m 17.2 m	0.257

[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
OS: overall survival
PFS: Progression-free survival
m: months
CPS: combined positive score

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 neo-adjuvant and/or adjuvant platinum-based chemotherapy (within 6 months of the end of chemotherapy) or progression during neo-adjuvant and/or adjuvant platinum-based chemotherapy.
- Measurable or non-measurable lesion according to RECIST 1.1.
- Adequate organ function: absolute neutrophil count ≥ 1.5 x 10^9/L, haemoglobin ≥ 9 g/dL, platelets ≥ 100 x 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.

Table 3. Main examination and follow-up schedule

	BEFORE 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)	

[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 24h)
[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

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