PRODIGE 59 - DURIGAST trial: A randomised phase II study evaluating FOLFIRI plus Durvalumab and FOLFIRI plus Durvalumab plus Tremelimumab in second-line treatment of patients with advanced gastric or gastro-oesophageal junction adenocarcinoma.

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INTRODUCTION

- Immune checkpoint inhibitors (ICI) have demonstrated their efficacy as first-line treatment of in advanced gastric/gastro-oesphageal junction (GEJ) with PD-L1 combined positive score (CPS) ≥5.
- Efficacy of 2nd line chemotherapy in advanced gastric/GEJ adenocarcinoma remains limited based on paclitaxel, ramucirumab, irinotecan alone or combined with 5FU.
- **No study up until now has evaluated the efficacy of ICIs combined with chemotherapy as 2nd line treatment of advanced gastric/GEJ adenocarcinoma.**

PATIENTS AND METHODS

DURIGAST PRODIGE 59 is a randomized, multicenter, phase II study designed to assess the efficacy and safety of the combination of **FOLFIRI plus durvalumab** (anti-PD-L1) (FD) versus **FOLFIRI plus durvalumab and tremelimumab** (anti-CTLA-4) (FDT).

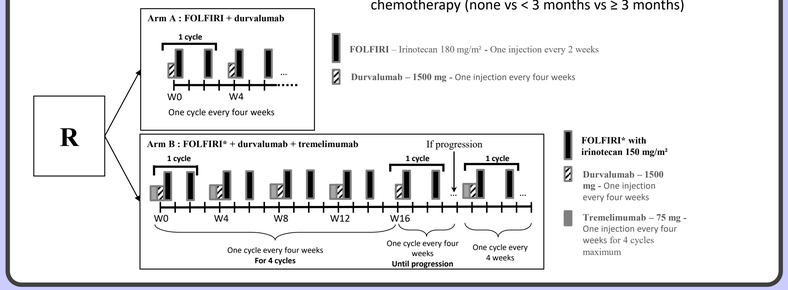
Key eligibility criteria were:
- **advanced gastric/GEJ adenocarcinoma**
- **platinum-based first-line chemotherapy**
- **ECOG performance status (PS) 0 or 1**

The primary endpoint is progression-free survival (PFS) at 4 months, which was expected to be 70% (H_0:50%). With an α risk of 5%, a power of 85% and 5% of non-evaluable patients, 47 evaluable patients were needed by arm. Secondary endpoints included safety, overall survival (OS) and quality of life.

STUDY DESIGN

Figure 1. Study design

The following factors were considered for the stratification:
- Center
- Duration of disease control with previous first-line chemotherapy (none vs < 3 months vs ≥ 3 months)



SAFETY RUN-IN PHASE

- To assess the safety of the combination of FOLFIRI + Durvalumab + Tremelimumab combination in 11 patients
- **63.6% experienced at least one grade 3-4 adverse events related to the treatment**, most frequently neutropenia (36.4%).
- **Only one immune-related adverse event** (grade 2 hyperthyroidism).
- One seizure epilepsy related to a brain metastasis was observed but was not related by the investigator to the treatment (Independent Data Monitoring Committee recommended brain imaging at inclusion for the randomised phase II).

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CHARACTERISTICS

- 48 patients were randomized in each arm.
- Primary endpoint was analysed on the modified intent-to-treat population (patients with at least one dose of treatment): 47 in arm A and 45 in arm B.

Table 1. Patients characteristics

Variables	All patients n=92	Folfiri + Durvalumab n=47	Folfiri + Durvalumab + Tremelimumab n=45
Age (years, range)	60.0 [24.7-83.3]	59.9 [28.2-83.3]	60.2 [24.7-82.6]
Female (n, %)	28 (30.4%)	14 (29.8%)	14 (31.1%)
ECOG performance status (n, %)***			
0	31 (33.7%)	11 (23.4%)	20 (44.4%)
1	61 (66.3%)	36 (76.6%)	25 (55.6%)
Body Mass Index (kg/m², range)	27.1 [16.6-48.4]	25.5 [17.8-39.1]	27.6 [16.6-48.4]
Primary tumour site (n, %)			
Gastro-esophageal junction	**49 (53.3%)**	**27 (57.4%)**	**22 (48.9%)**
Stomach	43 (46.7%)	20 (42.6%)	23 (51.1%)
Tumour subtype (Lauren classification) (n, %)			
Intestinal type	46 (50.0%)	22 (46.8%)	24 (53.3%)
Diffuse type	36 (39.1%)	20 (42.6%)	16 (35.6%)
Others/Unknown	10	5	5
Microsatellite instability			
Deficient	4 (4.3%)	3 (6.4%)	1 (2.2%)
Proficient	84 (91.3%)	40 (85.1%)	44 (97.8%)
Unknown	4	4	0
Delay of metastatic disease (n, %)			
Metachronous	32 (34.8%)	17 (36.2%)	15 (33.3%)
Synchronous	**60 (65.2%)**	**30 (63.8%)**	**30 (66.7%)**
Resection of primary tumour (n, %)			
No	67 (72.8%)	34 (72.3%)	33 (73.3%)
Yes	25 (27.2%)	13 (27.7%)	12 (26.7%)
Site of metastases (n, %)			
Liver	**37 (40.2%)**	**19 (40.4%)**	**18 (40.0%)**
Lung	18 (19.6%)	9 (19.1%)	9 (20.0%)
Peritoneal carcinomatosis	33 (35.9%)	16 (34.0%)	16 (34.0%)
Lymph nodes	36 (39.1%)	19 (40.4%)	17 (37.8%)
Prior first-line chemotherapy regimen (n, %)			
Doublet regimen	**47 (63.5%)**	**28 (73.7%)**	**19 (52.8%)**
Triplet regimen	25 (33.8%)	9 (23.7%)	16 (44.4%)

DISEASE-FREE AND OVERALL SURVIVAL

	Folfiri + Durvalumab	FOLFIRI + durvalumab + tremelimumab
PFS at 4 months [90% CI]	44.7% [32.2-57.7]	55.6% [42.3-68.3]
Median PFS [95%CI]	3.8 [3.0-7.4] months	5.4 [2.9-6.4] months
Disease contol rate	67.4%	68.9%
Duration of response	5.1 months	4.3 months
Median OS [95%CI]	13.3 [6.6-15.6] months	9.5 [7.1-11.3] months

Figure 2. Progression-free survival.

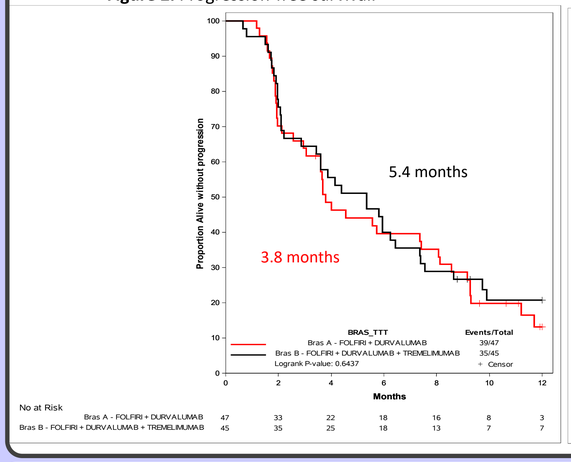

Figure 3. Overall survival.

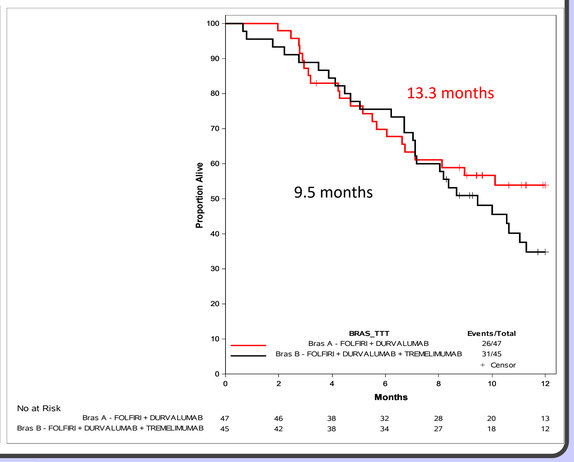

Table 2. Safety

Variables	Folfiri + Durvalumab n=47		Folfiri + Durvalumab + Tremelimumab n=45	
	Grade 1-2	Grade 3-4-5	Grade 1-2	Grade 3-4-5
Patients with at least one adverse event	**43 (93.5%)**	**22 (47.8%)**	**42 (91.3%)**	**22 (47.8%)**
Endocrine disorders	**4 (8.7%)**		**10 (21.7%)**	
Hyperthyroidism	1 (2.2%)	-	1 (2.2%)	-
Hypothyroidism	3 (6.5%)		3 (6.5%)	
Gastrointestinal disorders	**37 (80.4%)**	**5 (10.9%)**	**40 (87.0%)**	**11 (23.9%)**
Diarrhea	23 (50.0%)	1 (2.2%)	30 (65.2%)	5 (10.9%)
Colitis	-	2 (4.3%)	-	-
Vomiting	12 (26.1%)	3 (6.5%)	14 (30.4%)	1 (2.2%)
Investigations	**30 (65.2%)**	**10 (21.7%)**	**29 (63.0%)**	**14 (30.4%)**
AST/ALT increase	6 (13.0%)	-	7 (15.2%)	-
Neutrophil decrease	14 (30.4%)	7 (15.2%)	9 (19.6%)	11 (23.9%)
Lymphocyte decrease	10 (21.7%)	1 (2.2%)	14 (30.4%)	2 (4.3%)
General disorder	**25 (54.3%)**	**9 (19.6%)**	**27 (58.7%)**	**11 (23.9%)**
Fatigue	25 (54.3%)	8 (17.4%)	25 (54.3%)	11 (23.9%)

CONCLUSION

- Acceptable safety profile of immune checkpoint inhibitors plus FOLFIRI in 2nd line treatment for advanced gastric/GEJ adenocarcinoma.
- **Primary endpoint was not meet but both arms demonstrated a clinically relevant efficacy never before achieved.**
- Ancillary studies are ongoing to identify predictive biomarkers of efficacy (PD-L1 status, immune scores, tumor mutation burden and microbiota).

Trial registration: NCT03959293

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