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FINAL STUDY REPORT

Full title of the trial:	Randomised Phase II study of biweekly versus fractionated triweekly combination Taxotere-Cisplatin-5FU in advanced gastric and gastro-esophageal junction cancer
Short title of the trial:	DoGE
EudraCT Number:	2008-000551-10
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1. TRIAL INFORMATION

PHASE	Phase II
STUDY DESIGN	Multicenter randomized phase II trial **Arm 1**: Fractionated Triweekly Regimen: One cycle is defined as a 3 weeks-period on treatment. All three drugs are administered day 1-day 8 every 3 weeks **Arm 2**: Biweekly regimen: The regimen will be administered every 2 weeks. A cycle is defined as a 2 weeks-period on treatment
STUDY RATIONALE	Despite a decreasing incidence in Europe and North America, gastric cancer (GC) remains worldwide the second cause of cancer-related death. Chemotherapy is nowadays the only palliative option able to moderately alleviate and delay the patients' grim outcome [1,2]. Cisplatin (C) combined with 5-Fluorouracil (F) is one of the most extensively studied regimens, associated with objective response rates ranking around 20% and median survival around 7.2 months [3]. Attempts at improving the treatment's efficiency often rely consensually although sometimes inadequately to incremental combinations. As an example, several guidelines have recommended the triplet combination epirubicin-cisplatin-5-fluorouracile (ECF) [4] over the simpler and safer doublet CF combination for gastric cancer in palliative [6,7] as well as adjuvant setting [8,9] because a perceived better response rate (RR) and improved median overall survival (mOS) [4,5] based on trials without any direct comparison. The ECF triplet turned however out recently not really beneficial as directly compared to a doublet combination despite adding significant toxicities [10]. Docetaxel has a definite activity in GC [11-14] and lacks cross-resistance with platinum compounds. Combined with cisplatin and 5FU in a triweekly fashion [15,16,17,18,19, 20], it has been shown to enhance the RR (37% versus 25%, p=0.01), the median time to progression (mTTP) (5.6 versus 3.7 months, HR 1.47, 95% CI 1.19 to 1.82, p<0.001) and the mOS (9.2 versus 8.6 months, HR 1.29, 95% CI 1.0 to 1.6; p=0.02), as compared to CF doublet. This efficiency advantage comes at the price of more severe adverse events, with 69% versus 59% grade III or IV adverse events including 29% febrile neutropenia versus 12% when triplet-treated patients are compared to doublet-treated patients. The triplet's toxicity profile has been a major reason for treatment withdrawal, has somehow prevented its incorporation into routine daily practice in advanced GC and in further adjuvant development. However, fractionated dosages of docetaxel and of cisplatin/5FU combination have been described in the breast and gastric cancer literature as less hematologically toxic and equivalently efficient [21-25]. Non-hematological toxicities, such as asthenia, nail changes, excessive lacrimation (tearing), and fluid retention, seem unaffected by the schedule change. Weekly cisplatin regimens with doses of 25mg/m² do not require any pre- and/or post-hydration and may therefore be administered on an outpatient basis. Using similar fractionated dose concept, in the search for more convenient DCF combinations, Chen and colleagues recommended in a phase I study a weekly 2 out of 3 weeks administration of D 40mg/m², 5FU 2000mg/m², Folinic Acid (FA) 300mg/m² and C

	30mg/m2,[26] associated with a 45% grade III-IV neutropenia rate, including 6.4% febrile neutropenia. A recently published non-randomized phase II trial [27] associated a biweekly administration of D 40 mg/m², C 40mg/m² along with a "modified De Gramond 5FU regimen" with an interesting 47% RR along with only 22% grade III-IV neutropenia and 5% febrile neutropenia. In this randomized phase II trial, the hypothesis that fractionated administration of the DCF combination (weekly and biweekly) would alleviate its hematological toxicity profile, making non-mandatory the use of hematological growth factors while retaining a comparable efficacy level was tested.
OBJECTIVES	**Primary objective**: To evaluate feasibility (i.e. absence of limiting toxicity –febrile neutropenia- and absence of progression) of a biweekly and a fractionated triweekly regimen of Taxotere-Cisplatin-5-FU in advanced gastric and oesogastric junction cancer. **Secondary objectives**: a) Evaluation of the efficacy in both regimens based on an outpatient administration. b) Evaluation of survival c) Evaluation of progression free survival d) Translational research.
ENDPOINTS	After 2 cycles of treatment: • Rate of non-progressive disease • Occurrence of at least one episode of febrile neutropenia.
INCLUSION CRITERIA	1. Histologically proven advanced adenocarcinoma of the stomach, esogastric junction, or esophagus, never treated before in advanced setting by chemotherapy and not fit for surgery. 2. Measurable and/or evaluable lesions 3. Previous adjuvant chemotherapy for gastric cancer is authorized if the tumour has not progressed during or 6 months after chemotherapy administration, provided it contains no docetaxel or more than 400 mg/m² (total dose) cisplatin. 4. Age ≥ 18 years 5. Performance status 0, 1 6. Hematological examination : Neutrophilic count ≥ 1.5 X 10^6/L, Platelets ≥ 100 X 10^6/L, 7. Hemoglobin ≥ 11 g / dL 8. ASAT/ALAT ≤ 1,5 X ULN , Alkaline Phosphatases < 2,5 ULN 9. Direct Bilirubin ≤ 1 X ULN 10. Written informed consent 11. Clearance creatinine ≥ 60 ml/min (calculated or evaluated by isotopic method)
EXCLUSION CRITERIA	1. Unwillingness to take anticonceptional means for women in procreating age 2. Ongoing pregnancy or lactation. 3. Uncontrolled central nervous system metastasis. 4. History of another concomitant malignant disease with the

	exception of in situ cervix carcinoma or non-melanoma skin cancer 5. Participation to another clinical study within 4 weeks before inclusion in this study 6. Concomitant antineoplasic treatment. 7. Previous use in adjuvant setting of more than 400 mg/m² (total cumulated dose) cisplatin 8. Known deficiency in DPD or allergy to one or more drugs of the study 9. History of other uncontrolled life-threatening or severe disease 10. Uncontrolled infectious disease. 11. Impossibility to assure an adequate follow-up due to psychological, familial, social and/or geographic reasons 12. Liver tests: Direct Bilirubin > 1 x upper limit of normal (ULN), ASAT and/or ALAT >1.5 x ULN concomitant with alkaline Phosphatases > 2.5 x ULN. 13. Clearance creatinine < 60 ml/min 14. Uncontrolled angina pectoris or myocardial infarction < 6 weeks before beginning of the chemotherapy
INVESTIGATIONAL MEDICINAL PRODUCTS	***Arm 1: Fractionated Triweekly Regimen***: One cycle was defined as a 3 weeks-period on treatment. All three drugs are administered day 1-day 8 every 3 weeks. ***a) Docetaxel*****:** 40 mg/m² dose on day 1 and day 8. ***b) Cisplatin:*** following docetaxel at 35 mg/m² dose Day 1 and Day 8. **c) *Folinic Acid and 5-FluoroUracil (5FU):*** were administered last. Folinic Acid was administered in 1 hour infusion at the dose of 400 mg/m² (or 200 mg/m² levogyre form). 5FU was administered by protracted IV infusion of 1800 mg/m² over 24 hours. ***Arm 2: Biweekly regimen:*** The regimen was administered every 2 weeks. A cycle was defined as a 2 weeks-period on treatment. a) **Docetaxel**: 50 mg/m² dose. b) **Cisplatin**: following docetaxel at a 50 mg/m² dose. c) 400 mg/m² **Folinic Acid** IV in 1 hour (or 200mg/m² Levogyre form) followed by 48 hours perfusion of 2.0 g/m² **5FU**
INDICATION OF USE	Advanced adenocarcinoma of the stomach, esogastric junction, or esophagus
TARGETED POPULATION	Subjects never treated before in advanced setting by chemotherapy and not fit for surgery
PARTICIPATING COUNTRY	Belgium
PARTICIPATING SITES NUMBER	15
LENGTH OF THE STUDY	• Actual start date of recruitment to the protocol: 02/10/2008 • Actual date stop date of recruitment to the protocol: 03/10/2013 • No long term follow-up planned
INDEPENDENT DATA MONITORING COMMITTEE	No

2. SUBJECT INFORMATION

2.1. General information

In the DoGE trial, 53 subjects were included in both arms.

The actual number of subjects enrolled in each age range for the whole trial is specified in the table 1.

Table 1: Age range for the whole trial

Age categorical characteristic	Number of subjects	
	Arm 1	Arm 2
In Utero	0	0
Preterm newborn-gestational age>37 week	0	0
Newborns (0-27 days)	0	0
Infants and toddlers (28 days – 23 months)	0	0
Children (2 – 11 years)	0	0
Adolescents (12 – 17 years)	0	0
Between 18 and 65 years	37	30
From 66 years to 84 years	15	23
85 years and over	1	0
TOTAL	53	53

In Arm 1:

The median of subjects' age is 61 years (full range 33-85).

Amongst the 53 subjects included in Arm 1, 16 were female and 37 were male.

In Arm 2:

The median of subjects' age is 64 years (full range 40-83).

Amongst the 53 subjects included in Arm 2, 14 were female and 39 were male.

The following measures were put in place to protect trial subjects: recommendations for treatment adaptation according to occurrence of AEs were formulated in the protocol.

2.2. Subject disposition

In Arm 1, 53 subjects were enrolled in the trial, 52 subjects completed the trial and 1 subject did not complete the trial.

In Arm 2, 53 subjects were enrolled in the trial, 51 subjects completed the trial and 2 subjects did not complete the trial.

The reasons why some subjects did not complete the trial with the corresponding subjects' number are specified in the table 2.

Table 2: Non-completion reasons with corresponding subjects' number.

Non-completion reasons	**Number of subjects**	
	Arm 1	**Arm 2**
Adverse event, not serious	/	/
Concurrent illness preventing further protocol treatment	/	2
Consent withdrawn by subject	1	/
No treatment (in eligible patients)	1	2
Physician decision	/	/
Progression before treatment	/	/
Protocol violation	/	/

3. STATISTICAL ANALYSIS

3.1. Sample size calculation

The primary objective was to evaluate the limiting acute hematological toxicity of both weekly- and biweekly-fractionated regimen of DCF in advanced gastric and GEJ adenocarcinomas by capturing the occurrence of at least one episode of febrile neutropenia within the first 6 weeks of treatment (i.e. two cycles in arm 1 and three cycles in arm 2). In order to exclude insufficiently active regimen, the rate of non-progressive disease after 6 weeks of treatment was also assessed. In each arm, a Briant and Day design allowing early stopping both for futility or excessive toxicity was used according to the following assumptions: a non-progressive disease rate below 70% was considered as unacceptable while a non-progressive disease rate above 85% was worth to be detected. The probability of accepting falsely a regimen with a poor activity has been set to 10%. A rate of febrile neutropenia less than 10% should lead to the acceptation of the regimen. A rate of febrile neutropenia above 25% was considered unacceptable. The probability of accepting falsely a regimen with unacceptable toxicity has been set to 15%. Overall, in case of interesting activity and favourable toxicity profile, the regimen should be considered as interesting with a probability of 90%. With these assumptions, 28 evaluable patients needed to be registered and assessed in a first step in each arm. In case of strictly less

than 21 patients with non-progressive disease or strictly more than 7 patients with at least one febrile neutropenic episode, the corresponding arm would be closed prematurely.

If at least 21 patients did not progress and no more than 7 patients developed febrile neutropenia, accrual would have been pursued until 63 evaluable patients. The treatment would be considered as interesting at the end of this second step if at least 49 patients benefited from a non-progressive disease at 6 weeks treatment and less than 13 patients experienced at least one febrile neutropenic episode within 6 weeks treatment.

At the end of the patients' recruitment, we had 53 patients per arm (instead of the planned 63 patients). Accordingly, treatment would be considered as interesting if at least 42 patients had non progressive disease at 6 weeks treatment, and less than 9 patients experienced febrile neutropenia within 6 weeks of treatment (numbers obtained by approximation, no design obtained with exactly 53 patients in each arm). Early study closure due to slow accrual led to a reduced 80% power instead of the planned 90%.

The same design was used for the 2 arms of the study but no formal comparison was planned between them. Randomization was performed at the data centre of Institut Jules Bordet using the minimization technique with the use of institution as stratification factor. Patients were also stratified according to their Performance status (PS) (0 or 1).

The study was not powered to allow comparison between arms.

3.2. Statistical methods

Confidence intervals for binary variables were calculated using the Wilson method.

Time to significant event (TTSE) was defined as time from randomization to toxicity of grade > 2, progression or death, whatever occurred first. Progression-free survival (PFS) was defined as time from randomization to progression or death, whatever occurred first. Patients alive and without progression at last follow-up were censored. Overall survival (OS) was defined as time to death, whatever the cause of death. Patients alive at last follow-up were censored. TTSE, PFS, OS were assessed with Kaplan-Meier curves. The median survival time was calculated with 95% confidence limits.

3.3. Results

3.3.1. Study population

Between October 2008 and October 2013, 106 patients were recruited in 15 Belgian centers. Both treatment arms were balanced for age, sex, performance status, tumor location, and differentiation. Among the 106 patients included, 103 effectively received the treatment assigned (52 in arm 1 and 51 in arm 2), one patient withdrew his consent 5 days after inclusion, one developed an intestinal occlusion, and a third one died the 13th day after inclusion from progressive disease without having received any treatment.

3.3.2. Efficacy

Forty-five patients in each arm had at least 6 weeks of treatment (2 cycles in arm 1 and 3 cycles in arm 2). Best responses are summarized in table 3: response in 50% in both arms 1 and 2.

Table 3. Best Responses

	Arm 1 Three weekly regimen At least 2 chemo cycles (N = 45)	Arm 2 Biweekly regimen At least 3 chemo cycles (N = 45)
Complete response	2	2
Partial response	20	18
Stable disease	16	16
Progression	6	4
Not evaluable	1	5

Time to significant event (TTSE) was defined as the time to toxicity greater than grade II, progression, or death, whatever occurred first. Median TTSE was 0.51 month (95% CI, 0.39 to 1.51) and 0.75 month (95% CI, 0.46 to 1.25) in arms 1 and 2 respectively.

Median overall survival was 8.2 months (95% CI, 6.0 to 14.5) and 11.9 months (95% CI, 7.4 to 15.9) respectively. OS rate at 6 months was 63.1% (±7.0%) and 70.5% (±6.4%). Median PFS was 5.1 months (95% CI, 3.2 to 6.5) and 5.2 months (95% CI, 3.0 to 6.9) respectively.

The 6 weeks-DCR (disease control rate) was 83% (95% CI 71-91) in arm 1 and 79% (95% CI 67-88) in arm 2.

3.4. Discussion

Incremental improvements aiming at increasing the response rates hence the patients' survival are commonly found in solid tumors therapeutic developments. Sometimes they miss the point because of insufficient added efficiency [30] or because unacceptable additive toxicity [20]. However, the need for improvement in the treatment of both locally advanced and metastatic GC is huge and largely justifies attempts to make a more efficient drug regimen more tolerable for the patients. The DCF regimen, despite being incontestably superior to doublet cisplatin/5FU in terms of response rate, OS and PFS, is so toxic that it remains often reluctantly used for patients with advanced gastric or gastro-esophageal junction cancer, even combined with a prophylactic use of hematological growth factors [20].

Attempts to improve the toxicity pattern of this triple association are reported in the literature: Inal and colleagues retrospectively reviewed 107 advanced GC patients whose initial treatment was DCF or simplified triweekly DCF (D and C given both at 60 mg/m² on day 1 and F 600 mg/m² continuous infusion days 1–5, every 3 weeks) and suggested less grade III-IV neutropenia for the simplified triweekly DCF: 13.6% versus 48.2% for patients treated according to the original DCF (p=0.003). [28]

Shah and colleagues described a randomized phase II trial studying a modified biweekly DCF (mDCF) (D 40mg/m2, C 40 mg/m2, F 2000 mg/m2) to the classical DCF supported by hematological growth factors. The study was prematurely closed after an interim analysis showing significantly less grade III-IV toxicities and febrile neutropenia for mDCF as compared to standard DCF within the 3 first months of treatment (respectively 54% versus 71% and 9% versus 16%). [29]

The DoGE study described in this manuscript was designed to assess a weekly- and a biweekly-fractionated DCF version given without any prophylactic hematological growth factors support. Due to the study's design, as is the case for the Shah et al report, our data do not allow any direct comparison between arms. The weekly mDCF was associated with

42% (95%CI: 30-56%) grade III-IV hematological toxicities including 9% febrile neutropenia. The biweekly mDCF arm was associated with 65% (95%CI: 51-76%) grade III-IV hematological toxicities with only 5% febrile neutropenia.

Moreover, the study did observe a rate of non-hematological toxicities far below those described with original DCF regimen: 60% and 45% grade III-IV non-hematological toxicities including 30 % and 21% gastrointestinal grade III-IV toxicities respectively for weekly mDCF and biweekly mDCF. Historical data associated the classical DCF with a 49% risk of gastrointestinal toxicities. The rate of nausea, vomiting, and diarrhea, were particularly lower than expected for DCF.

It is obviously impossible, in the absence of direct comparison with the original DCF regimen, to demonstrate a superiority or even a non-inferiority for both weekly and biweekly modified DCF as compared to the historical DCF regimen. Nevertheless, there is absolutely no hint that the improved safety profile of weekly and biweekly regimen comes with a concession on efficacy: the patients included in the DoGE study experienced a mOS of 8.2 months (95% CI, 6.0-14.5) for the weekly regimen and 11.9 months (95% CI, 7.4-15.9) for the biweekly regimen, seemingly favorably matching the 9.2 months mOS reported in the V325 trial for historical DCF. Similarly a mPFS of 5.1 months (95% CI, 3.2-6.5) for the weekly regimen and of 5.2 months (95% CI, 3.0-6.9) in the biweekly regimen were achieved, comparable to the 5.6 months reported in the V325 trial. As such, with a better toxicity profile, the lack of requirement for hematological prophylactic support, and comparable efficacy, both weekly and biweekly modified DCF regimens appear as viable alternatives for first line treatment in metastatic GC setting, and plausible candidate regimen for future trials in adjuvant/neoadjuvant setting minimizing the risk of toxicities delaying curative surgery.

3.5. Conclusion

Fractionated weekly and biweekly regimen of docetaxel/cisplatin and 5FU both improve the toxicity profile of this triple combination without compromising its efficacy as compared to the standard triweekly combination. They represent valuable and more convenient alternatives with the additional advantage of avoiding the systematic use of prophylactic hematological growth factor.

4. SAFETY ANALYSIS

4.1. General information

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the first administration of study treatments until 30 days after the last dose of study treatments.

In Arm 1:

52 subjects were exposed to the investigational medicinal products.

35 subjects were affected by serious adverse events.

52 subjects were affected by non-serious adverse events.

In Arm 2:

51 subjects were exposed to the investigational medicinal products.

27 subjects were affected by serious adverse events.

Notes:

1. The adverse event and serious adverse event assessment method was systematic.

2. The MedDRA version used was the version 20.1.

4.2. Serious Adverse Events overview

The tables 4 and 5 present all serious adverse events sorted by MedDRA System Organ Class (SOC), MedDRA Preferred Terms (PT) in Arm 1 and Arm 2, respectively.

Table 4: All serious adverse events sorted by MedDRA SOC and MedDRA PT in Arm 1

MedDRA SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAE occurrences causally related to IMPs**
Blood and lymphatic system disorders			
Anaemia	1	1	
Aplastic anaemia	1	1	1
Febrile neutropenia	6	6	6
Neutropenia	1	1	1
Thrombocytopenia	1	1	1
Gastrointestinal disorders			
Abdominal pain	1	1	1
Colitis	1	1	1
Diarrhoea	9	9	9
Duodenitis	1	1	1
Dysphagia	1	1	1
Enterocolitis	1	1	1
Gastrointestinal disorder	1	1	1
Gastrointestinal haemorrhage	1	1	
Gastrointestinal obstruction	1	1	
Gastrointestinal toxicity	1	1	1
Ileus paralytic	1	1	1
Intestinal obstruction	1	1	
Nausea	4	4	3
Oesophagitis	1	1	1
Pancreatitis acute	1	1	
Vomiting	10	11	9
General disorders and administration site conditions			

MedDRA SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAE occurrences causally related to IMPs**
Asthenia	2	2	2
Fatigue	2	2	2
General physical health deterioration	7	7	4
Pyrexia	1	1	
Hepatobiliary disorders			
Hepatic function abnormal	1	1	
Hepatic haemorrhage	1	1	
Infections and infestations			
Bacteraemia	1	1	1
Device related infection	1	1	
Infection	1	1	1
Lung infection	1	1	1
Pneumonia	2	2	1
Sepsis	1	1	1
Septic shock	2	2	2
Investigations			
Alanine aminotransferase increased	1	1	
Aspartate aminotransferase increased	1	1	
Gamma-glutamyltransferase increased	1	1	
Weight decreased	3	3	3
Metabolism and nutrition disorders			
Decreased appetite	5	6	5
Dehydration	1	1	1
Electrolyte imbalance	1	1	1
Hyperglycaemia	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression	1	1	
Renal and urinary disorders			
Renal impairment	1	1	1
Respiratory, thoracic and			

MedDRA SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAE occurrences causally related to IMPs**
mediastinal disorders			
Dyspnoea	1	1	
Lung disorder	1	2	
Pulmonary embolism	1	1	
Vascular disorder			
Thrombophlebitis	1	1	
Thrombosis	1	1	

Table 5: All serious adverse events sorted by MedDRA SOC and MedDRA PT in Arm 2

MedDRA SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAE occurrences causally related to IMP**
Blood and lymphatic system disorders			
Febrile neutropenia	3	3	3
Leukocytosis	1	1	
Neutropenia	2	2	2
Thrombocytopenia	1	1	1
Cardiac disorders			
Cardiac arrest	1	1	
Cardiac tamponade	1	1	1
Pericardial effusion	1	1	
Ear and labyrinth disorders			
Vertigo	1	1	1
Gastrointestinal disorders			
Constipation	1	1	
Diarrhoea	2	2	1
Intestinal obstruction	1	1	
Intestinal perforation	1	1	
Nausea	1	1	1
Oesophageal stenosis	1	1	
Stomatitis	1	1	
Vomiting	4	4	3
General disorders and administration site conditions			
Asthenia	2	3	3
Death	1	1	
Fatigue	3	3	3
General physical health deterioration	4	4	3
Malaise	1	1	1
Pyrexia	4	4	1
Systemic inflammatory response syndrome	1	1	
Hepatobiliary disorders			
Liver disorder	1	1	
Infections and infestations			
Bronchitis	1	1	
Pneumonia	1	1	

MedDRA SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAE occurrences causally related to IMP**
Sepsis	1	1	
Septic shock	2	2	1
Skin infection	1	1	
Investigations			
C-reactive protein increased	1	1	
Weight decreased	1	1	1
Metabolism and nutrition disorders			
Cell death	1	1	
Decreased appetite	5	6	4
Dehydration	2	2	
Malnutrition	1	1	
Metabolic acidosis	1	1	
Renal and urinary disorders			
Oliguria	1	1	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	1	1	
Pneumothorax	1	1	
Skin and subcutaneous tissue disorders			
Pruritus	1	1	1
Surgical and medical procedures			
Cytoreductive surgery	1	1	
Gastrectomy	1	1	
Intraperitoneal hyperthermic chemotherapy	1	1	
Tumour excision	1	1	
Vascular disorders			
Hypotension	1	1	1

4.3. Non-Serious Adverse Events overview

The frequency threshold for reporting non-serious adverse events is 0 %.

The table 6 and 7 present all non-serious adverse events sorted by MedDRA System Organ Class (SOC), MedDRA Preferred Terms (PT).

Table 6: All non-serious adverse events sorted by MedDRA SOC and MedDRA PT in Arm 1.

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs
Blood and lymphatic system disorders			
Anaemia	28	39	34
Febrile neutropenia	3	3	3
Leukopenia	2	2	2
Lymphopenia	1	1	1
Blood and lymphatic system disorders			
Neutropenia	21	47	46
Thrombocytopenia	15	24	22
Cardiac disorders			
Palpitations	1	1	1
Tachycardia	3	3	2
Ear and labyrinth disorders			
Vertigo	1	1	1
Eye disorders			
Blindness	1	1	
Diplopia	1	1	
Dry eye	1	1	1
Lacrimation increased	2	2	1
Vision blurred	1	1	
Gastrointestinal disorders			
Abdominal pain	5	9	6
Abdominal pain upper	1	1	1
Anal ulcer	1	1	1
Ascites	1	1	
Constipation	7	8	8
Diarrhoea	33	63	60
Dry mouth	1	1	1
Dyspepsia	1	2	1
Dysphagia	3	4	2
Flatulence	1	2	1
Gastric ulcer	1	1	
Gastrointestinal pain	1	1	1

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs
Melaena	1	1	
Mouth ulceration	1	1	1
Nausea	31	52	50
Stomatitis	9	12	12
Vomiting	24	39	36
General disorders and administration site conditions			
Asthenia	1	1	1
Chest pain	1	1	
Chills	1	1	1
Fatigue	37	54	52
General physical health deterioration	2	2	1
Mucosal inflammation	6	7	7
Oedema	1	1	1
Oedema peripheral	6	7	2
Pain	1	1	
Pyrexia	2	2	
Hepatobiliary disorders			
Hepatic function abnormal	4	4	4
Immune system disorders			
Hypersensitivity	2	3	3
Infections and infestations			
Bronchitis	4	5	1
Conjunctivitis	1	1	
Fungal oesophagitis	1	2	
Gastroenteritis	1	1	
Gastrointestinal fungal infection	1	1	1
Lung infection	1	1	1
Oral fungal infection	2	2	1
Pharyngitis	1	1	
Pneumonia	3	3	1
Respiratory tract infection	1	1	
Rhinitis	1	1	
Injury, poisoning and procedural complications			
Skin injury	1	1	1

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs
Investigations			
Alanine aminotransferase increased	1	3	
Aspartate aminotransferase increased	2	2	
Blood alkaline phosphatase increased	2	3	
Blood creatinine increased	1	1	1
Gamma-glutamyltransferase increased	1	1	
Weight decreased	12	15	10
White blood cell count decreased	1	1	1
Metabolism and nutrition disorders			
Decreased appetite	33	43	37
Hypoalbuminaemia	2	2	1
Hypocalcaemia	4	6	2
Hypokalaemia	7	10	7
Hypomagnesaemia	8	11	9
Hyponatraemia	2	4	
Hypophosphataemia	3	5	1
Metabolic disorder	7	8	2
Musculoskeletal and connective tissue disorders			
Back pain	3	5	
Bone pain	1	1	
Muscle spasms	3	3	2
Muscular weakness	1	1	
Musculoskeletal pain	2	3	
Musculoskeletal stiffness	2	1	1
Myalgia	1	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage	1	2	
Nervous system disorders			
Concentration loss	1	1	1
Dysgeusia	8	13	12
Head discomfort	1	1	
Headache	3	4	1
Paraesthesia	3	3	3
Peripheral motor neuropathy	2	2	1

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs
Peripheral sensory neuropathy	11	16	15
Presyncope	2	2	1
Tremor	2	2	2
Psychiatric disorders			
Anxiety	2	3	1
Insomnia	1	1	
Renal and urinary disorders			
Bladder discomfort	1	1	1
Dysuria	1	1	1
Renal impairment	5	6	6
Respiratory, thoracic and mediastinal disorders			
Cough	7	7	1
Dyspnoea	3	4	3
Epistaxis	4	4	4
Hiccups	2	3	2
Lung disorder	1	2	2
Oropharyngeal pain	1	1	1
Pulmonary embolism	1	1	
Rhinorrhoea	1	2	
Skin and subcutaneous tissue disorders			
Alopecia	14	14	14
Dry skin	2	3	3
Erythema	1	1	1
Rash	1	1	
Rash erythematous	2	2	2
Vascular disorders			
Deep vein thrombosis	1	1	1
Embolism	2	2	1
Haematoma	1	1	
Haemorrhage	1	1	
Hypotension	2	2	2
Vena cava thrombosis	1	1	

Table 7: All non-serious adverse events sorted by MedDRA SOC and MedDRA PT in Arm 2.

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs
Blood and lymphatic system disorders			
Anaemia	31	40	34
Febrile neutropenia	4	4	3
Leukopenia	3	4	4
Lymphopenia	1	1	
Neutropenia	35	87	85
Thrombocytopenia	10	19	19
Cardiac disorders			
Atrial fibrillation	1	1	
Palpitations	1	1	1
Ear and labyrinth disorders			
Hypoacusis	1	2	2
Vertigo	2	2	1
Eye disorders			
Blepharitis	1	1	1
Cataract	1	1	1
Dry eye	1	1	1
Lacrimation increased	1	1	1
Vision blurred	1	1	1
Gastrointestinal disorders			
Abdominal pain	8	11	5
Aphthous ulcer	1	1	
Ascites	1	2	1
Constipation	12	12	5
Diarrhoea	24	38	35
Dyspepsia	3	4	3
Dysphagia	9	12	5
Eructation	1	1	
Flatulence	1	9	9
Nausea	28	65	65
Odynophagia	1	1	1
Oesophageal pain	2	2	
Oesophagitis	2	2	2
Pneumoperitoneum	1	1	
Salivary hypersecretion	1	1	1
Stomatitis	17	24	24
Vomiting	21	39	37

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs
General disorders and administration site conditions			
Asthenia	2	2	2
Chest pain	1	1	
Chills	1	1	
Fatigue	39	57	54
General physical health deterioration	2	3	3
Influenza like illness	1	1	
Malaise	1	1	
Mucosal inflammation	8	10	10
Oedema peripheral	5	5	2
Pain	3	3	2
Pyrexia	3	3	2
Visceral oedema	1	1	1
Hepatobiliary disorders			
Hepatic function abnormal	4	4	4
Immune system disorders			
Hypersensitivity	1	1	
Infections and infestations			
Bronchitis	3	3	1
Conjunctivitis	4	4	4
Herpes zoster	1	1	1
Infection	2	2	
Lip infection	1	1	1
Rhinitis	1	1	
Sepsis	1	1	
Sinusitis	2	2	
Tonsillitis	1	1	1
Upper respiratory tract infection	1	1	
Urinary tract infection	1	1	
Viral upper respiratory tract infection	1	1	
Injury, poisoning and procedural complications			
Humerus fracture	1	1	
Nasal injury	1	1	
Rib fracture	1	1	
Investigations			
Alanine aminotransferase increased	1	1	

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs
Amylase increased	1	1	1
Aspartate aminotransferase increased	1	1	
Blood alkaline phosphatase increased	3	3	1
Blood creatinine increased	1	1	1
Creatinine renal clearance increased	1	2	2
Gamma-glutamyltransferase increased	1	1	
Lipase increased	2	2	2
Weight decreased	17	20	18
Metabolism and nutrition disorders			
Decreased appetite	21	32	28
Dehydration	2	2	1
Hypermagnesaemia	1	2	1
Hypoalbuminaemia	3	3	
Hypocalcaemia	2	2	
Hypokalaemia	3	3	3
Hypomagnesaemia	5	8	8
Hyponatraemia	2	2	
Hypophosphataemia	1	1	
Metabolic disorder	10	13	9
Vitamin D deficiency		1	
Musculoskeletal and connective tissue disorders			
Arthralgia	1	1	
Back pain	1	1	
Groin pain	1	1	
Musculoskeletal chest pain	1	1	
Musculoskeletal pain	1	2	2
Neck pain	1	1	
Pain in extremity	2	2	
Nervous system disorders			
Ageusia	1	1	1
Dizziness	1	1	1
Dysgeusia	8	9	9
Headache	1	1	
Peripheral motor neuropathy	2	2	2
Peripheral sensory neuropathy	16	17	17
Radial nerve palsy	1	1	
Restless legs syndrome	1	1	
Syncope	1	1	

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AE occurrences causally related to IMPs
Psychiatric disorders			
Insomnia	2	2	2
Renal and urinary disorders			
Acute kidney injury	1	1	
Dysuria	1	2	2
Renal impairment	5	5	
Reproductive system and breast disorders			
Rectocele	1	1	
Vaginal prolapse	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough	2	2	1
Dyspnoea	8	9	2
Epistaxis	1	2	
Nasal dryness	1	1	1
Productive cough	1	1	
Rhinorrhoea	2	3	
Skin and subcutaneous tissue disorders			
Alopecia	25	25	25
Dermatitis acneiform	1	1	1
Dry skin	2	2	2
Nail toxicity	1	1	1
Skin reaction	1	1	1
Vascular disorders			
Deep vein thrombosis	1	1	1
Embolism	1	1	
Flushing	1	1	1
Haematoma	1	1	
Hypertension	1	1	1
Hypotension	5	8	8

The table 8 and 9 present the non-serious adverse reactions (all grades), i.e. related to the study medications, experienced by the subjects in DoGE trial sorted by MedDRA SOC, frequency and MedDRA Preferred Terms (PT) in arm 1 and arm 2 respectively. Multiple

occurrences of a specific adverse reaction for a subject through cycle have been counted only once.

Table 8: Non-serious adverse reactions sorted by MedDRA SOC, frequency and MedDRA PT in Arm 1(N=52).

MedDRA SOC *Frequency* MedDRA PT	**Number of subject (%)**
Blood and lymphatic system disorders	
Very common	
Anaemia	25 (48.1%)
Neutropenia	21 (40.4%)
Thrombocytopenia	15 (28.8%)
Common	
Febrile neutropenia	3 (5.8%)
Leukopenia	2 (3.8%)
Lymphopenia	1 (1,9%)
Cardiac disorders	
Common	
Tachycardia	2 (3.8%)
Palpitations	1 (1.9%)
Ear and labyrinth disorders	
Common	
Vertigo	1 (1.9%)
Eye disorders	
Common	
Dry eye	1 (1.9%)
Lacrimation increased	1 (1.9%)
Gastrointestinal disorders	
Very common	
Diarrhea	32 (61.5%)
Nausea	29 (55.8%)
Vomiting	22 (42.3%)
Constipation	7 (13.5%)
Stomatitis	9 (17.3%)
Abdominal pain	4 (7.7%)
Common	
Dysphagia	2 (3.8%)
Anal ulcer	1 (1.9%)
Dry mouth	1 (1.9%)

MedDRA SOC *Frequency* MedDRA PT	**Number of subject (%)**
Dyspepsia	1 (1.9%)
Flatulence	1 (1.9%)
Gastrointestinal pain	1 (1.9%)
Mouth ulceration	1 (1.9%)
General disorders and administration site conditions	
Very common	
Fatigue	34 (65.4%)
Mucosal inflammation	6 (11.5%)
Common	
Oedema peripheral	2 (3.8%)
Chills	1 (1.9%)
Asthenia	1 (1.9%)
General physical health deterioration	1 (1.9%)
Oedema	1 (1.9%)
Hepatobiliary disorders	
Common	
Hepatic function abnormal	4 (7.7%)
Immune system disorders	
Common	
Hypersensitivity	2 (3.8%)
Infections and infestations	
Common	
Bronchitis	1 (1.9%)
Gastrointestinal fungal infection	1 (1.9%)
Lung infection	1 (1.9%)
Oral fungal infection	1 (1.9%)
Pneumonia	1 (1.9%)
Injury, poisoning and procedural complications	
Common	
Skin injury	1 (1.9%)
Investigations	
Very common	
Weight decreased	8 (15.4%)
Common	
Blood creatinine increased	1 (1.9%)

MedDRA SOC *Frequency* MedDRA PT	**Number of subject (%)**
White blood cell count decreased	1 (1.9%)
Metabolism and nutrition disorders	
Very common	
Decreased appetite	27 (51.9%)
Hypomagnesaemia	7 (13.5%)
Hypokalaemia	6 (11.5%)
Common	
Hypocalcaemia	2 (3.8%)
Metabolic disorder	2 (3.8%)
Hypoalbuminaemia	1 (1.9%)
Hypophosphataemia	1 (1.9%)
Musculoskeletal and connective tissue disorders	
Common	
Muscle spasms	2 (3.8%)
Myalgia	2 (3.8%)
Musculoskeletal stiffness	1 (1.9%)
Nervous system disorders	
Very common	
Peripheral sensory neuropathy	10 (19.2%)
Dysgeusia	7 (13.5%)
Common	
Paraesthesia	3 (5.8%)
Tremor	2 (3.8%)
Concentration loss	1 (1.9%)
Headache	1 (1.9%)
Peripheral motor neuropathy	1 (1.9%)
Presyncope	1 (1.9%)
Psychiatric disorders	
Common	
Anxiety	1 (1.9%)
Renal and urinary disorders	
Common	
Renal impairment	5 (9.6%)
Bladder discomfort	1 (1.9%)
Dysuria	1 (1.9%)

MedDRA SOC *Frequency* MedDRA PT	**Number of subject (%)**
Respiratory, thoracic and mediastinal disorders	
Common	
Epistaxis	4 (7.7%)
Dyspnoea	2 (3.8%)
Cough	1 (1.9%)
Hiccups	1 (1.9%)
Lung disorder	1 (1.9%)
Oropharyngeal pain	1 (1.9%)
Skin and subcutaneous tissue disorders	
Very common	
Alopecia	14 (26.9%)
Common	
Dry skin	2 (3.8%)
Erythema	1 (1.9%)
Rash erythematous	2 (3.8%)
Vascular disorders	
Common	
Hypotension	2 (3.9%)
Deep vein thrombosis	1 (1.9%)
Embolism	1 (1.9%)

N=number of patients who received the investigational medicinal products.

Frequencies are defined as= very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000).

Table 9: Non-serious adverse reactions sorted by MedDRA SOC, frequency and MedDRA PT in Arm 2 (N=51)

MedDRA SOC *Frequency* MedDRA PT	**Number of subjects (%)**
Blood and lymphatic system disorders	
Very common	
Neutropenia	34 (66.7%)
Anaemia	29 (56.9%)
Thrombocytopenia	10 (19.6%)
Common	
Febrile neutropenia	3 (5.9%)
Leukopenia	2 (3.9%)
Cardiac disorders	

MedDRA SOC *Frequency* MedDRA PT	**Number of subjects (%)**
Common	
Palpitations	1 (1.9%)
Ear and labyrinth disorders	
Common	
Hypoacusis	1 (1.9%)
Vertigo	1 (1.9%)
Eye disorders	
Common	
Blepharitis	1 (1.9%)
Cataract	1 (1.9%)
Dry eye	1 (1.9%)
Lacrimation increased	1 (1.9%)
Vision blurred	1 (1.9%)
Gastrointestinal disorders	
Very common	
Nausea	28 (54.9%)
Diarrhea	23 (41.2%)
Vomiting	19 (37.3%)
Stomatitis	17 (33.3%)
Common	
Constipation	5 (9.8%)
Dysphagia	4 (7.8%)
Abdominal pain	3 (5.9%)
Dyspepsia	2 (3.8%)
Oesophagitis	2 (3.8%)
Ascites	1 (1.9%)
Flatulence	1 (1.9%)
Odynophagia	1 (1.9%)
Salivary hypersecretion	1 (1.9%)
General disorders and administration site conditions	
Very common	
Fatigue	37 (72.5%)
Mucosal inflammation	8 (15.7%)
Common	
Asthenia	2 (3.8%)
General physical health deterioration	2 (3.8%)
Oedema peripheral	2 (3.8%)

MedDRA SOC *Frequency* MedDRA PT	**Number of subjects (%)**
Pain	2 (3.8%)
Pyrexia	2 (3.8%)
Visceral oedema	1 (1.9%)
Hepatobiliary disorders	
Common	
Hepatic function abnormal	4 (7.8%)
Infections and infestations	
Common	
Conjunctivitis	4 (7.8%)
Bronchitis	1 (1.9%)
Herpes zoster	1 (1.9%)
Lip infection	1 (1.9%)
Tonsillitis	1 (1.9%)
Viral upper respiratory tract infection	1 (1.9%)
Injury, poisoning and procedural complications	
Common	
Nasal injury	1 (1.9%)
Investigations	
Very common	
Weight decreased	15 (29.4%)
Common	
Lipase increased	2 (3.8%)
Amylase increased	1 (1.9%)
Blood alkaline phosphatase increased	1 (1.9%)
Blood creatinine increased	1 (1.9%)
Creatinine renal clearance increased	1 (1.9%)
Metabolism and nutrition disorders	
Very Common	
Decreased appetite	18 (35.3%)
Metabolic disorder	8 (15.7%)
Common	
Hypomagnesaemia	5 (9.8%)
Dehydration	1 (1.9%)
Hypermagnesaemia	1 (1.9%)
Hypokalaemia	3 (5.9%)

MedDRA SOC *Frequency* MedDRA PT	**Number of subjects (%)**
Musculoskeletal and connective tissue disorders	
Common	
Musculoskeletal pain	1 (1.9%)
Nervous system disorders	
Very common	
Peripheral sensory neuropathy	16 (31.3%)
Dysgeusia	7 (13.7%)
Common	
Peripheral motor neuropathy	2 (3.8%)
Ageusia	1 (1.9%)
Dizziness	1 (1.9%)
Radial nerve palsy	1 (1.9%)
Psychiatric disorders	
Common	
Insomnia	2 (2.9%)
Renal and urinary disorders	
Common	
Renal impairment	4 (7.8%)
Dysuria	1 (1.9%)
Respiratory, thoracic and mediastinal disorders	
Common	
Dyspnoea	2 (3.8%)
Cough	1 (1.9%)
Nasal dryness	1 (1.9%)
Skin and subcutaneous tissue disorders	
Very common	
Alopecia	25 (49.0%)
Common	
Dry skin	2 (3.8%)
Dermatitis acneiform	1 (1.9%)
Nail toxicity	1 (1.9%)
Vascular disorders	
Common	
Hypotension	5 (9.8%)
Deep vein thrombosis	1 (1.9%)

MedDRA SOC *Frequency* MedDRA PT	**Number of subjects (%)**
Flushing	1 (1.9%)
Hypertension	1 (1.9%)

N=number of patients who received the investigational medicinal products.

Frequencies are defined as= very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000).

The most frequent adverse reactions observed present in both arms are listed in the below table.

Table 10: The most frequent adverse reactions in common.

Most frequent adverse reactions	**Arm 1**	**Arm 2**
Anaemia	48.1%	56.9%
Neutropenia	40.4%	66.7%
Thrombocytopenia	28.8%	19.6%
Diarrhea	61.5%	41.2%
Nausea	55.8%	54.9%
Vomiting	42.3%	37.3%
Stomatitis	17.3%	33.30%
Fatigue	65.4%	72.50%
Mucosal inflammation	11.5%	15.70%
Weight decreased	15.4%	29.40%
Anorexia	51.9%	35.30%
Peripheral sensory neuropathy	19.2%	31.30%
Dysgeusia	13.5%	13.70%
Alopecia	26.9%	49.00%

The most frequent adverse reaction observed in both arms is fatigue, 65.4% in arm 1 and 72.5% in arm 2.

In arm 1, the most frequent adverse reactions observed are diarrhea (61.5%), nausea (55.8%), anorexia (51.9%), anaemia (48.1%) and neutropenia (40.4%) while in arm 2 the most frequent adverse reactions observed are neutropenia (66.7%), anaemia (56.9%), nausea (54.9%), alopecia (49.0%) and diarrhea (41.2%).

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APPENDIX 1: List of participating investigators

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