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Sponsor / Company: Sanofi	**Study Identifiers:** NCT00343239
Drug substance(s): Taxotere / docetaxel / XRP6976	**Study code:** DOCET-L-00072/ NEO-TAX

Title of the study: Docetaxel, cisplatin and fluorouracil combination in neoadjuvant setting in the treatment of locally advanced gastric adenocarcinoma. A Phase 2 study (DOCET-L-00072/ NEO-TAX)

Study centers: 3 active centers in Turkey

Study period:

Date first patient enrolled: 05/Jun/2006

Date last patient completed: 28/Mar/2012

Phase of development: 2

Objectives:

Primary objective

To explore the efficacy of docetaxel, cisplatin and fluorouracil combination (DCF combination) in locally advanced gastric adenocarcinoma in neoadjuvant setting. After the completion of this treatment the percentage of patients who could undergo a R0 resection was the primary efficacy criteria.

Secondary objectives

Overall response rate to treatment, duration of disease free survival, overall survival, and pathological complete remission.

Methodology: Multicenter, single arm, open label study.

Number of patients:	Planned: 58
	Randomized: 59
	Treated: 59
Evaluated:	Efficacy: 59
	Safety: 59

Diagnosis and criteria for inclusion:

- Patients with a confirmed pathological diagnosis of gastric adenocarcinoma, from both genders and 18-70 years of age, inclusive;

- Selected Stage IIB (T3N0M0), Stage IIIA (T2aN2M0, T2bN2M0, T3N1M0, T4N0M0), Stage IIIB (T3N2M0) and selected Stage IV (T4N1-3M0, T1-4N3M0) patients. Clinical staging was performed according to AJCC 2002 by means of endoscopic ultrasonography (EUS) and computerized tomography (CT). Resectability of gastric tumor and peritoneal metastasis were expected to be verified by either laparotomy or laparoscopy;

- Eastern Cooperative Oncology Group (ECOG) performance status 0-2,

- Hematological evaluation: Neutrophils >1500/mm3, Platelets >100 000/mm3,Haemoglobin >9 g/100 mL),

- Sufficient renal, hepatic, pulmonary and cardiac functions,

- No previous chemotherapy due to gastric carcinoma and with a minimum life expectancy of 12 weeks,

- All patients must have informed consents signed before any study related procedures.

Study treatments

There were 3 investigational products used as combination chemotherapy on an adjuvant setting: docetaxel, cisplatin, and fluorouracil.

Study treatments were given as follows: docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 were infused on the first day of each cycle and stopped. Fluorouracil 750 mg/m^2/day were continued for 5 days and stopped. After 21 days from the first day of first cycle, a second or third cycle repeated. Third cycle was administered unless a disease progression was evaluated by means of CT and EUS planned to be performed after the second cycle or in cases of patient intolerability. No further tumor assessment was scheduled after the third cycle of treatment. However, if there was a disease progression defined by grading after second cycle, patient was forwarded to the surgery without third cycle administration. Chemotherapy regimen was ceased after 2 or 3 cycles, depending on toxicity evaluation and patients were operated and gastric cancer was removed.

Dosage of investigational medecinal products (IMPs) was reduced as shown in the table below according to protocol defined National Cancer Institut (NCI) toxicity criteria version 3.0:

Dose reduction scheme

IMP	Starting dose (mg/m²)		Dose Reduction 1 (mg/m²)		Dose Reduction 2 (mg/m²)
D	75	→	60	→	45
C	75	→	60	→	45
F	750 x 5 days	→	600 x 5 days	→	450 x 5 days

Investigational medicinal products:

Docetaxel	**Cisplatin**	**Fluorouracil**
Formulation: infusion solution	Formulation: infusion solution	Formulation: infusion solution
Route of administration: IV infusion on the first day of each 21-day cycle	Route of administration: IV infusion on the first day of each 21-day cycle	Route of administration: IV infusion on the first day of each 21-day cycle
Dose regimen: 75 mg/m^2	Dose regimen: 75 mg/m^2	Dose regimen: 750 mg/m^2/day

Non-investigational medicinal products:

Aprepitant (Emend®)	**Granocyte 34MU**	**Tropisetron (Navoban®) 5mg**	**Tropisetron (Navoban®) 5mg**
Formulation: 1 capsule (125mg), 2 capsules aprepitant (80mg)	Formulation: Lenograstim (rHuG-CSF) 33.6 (263) MIU (mcg) (powder for injectable solution)	Formulation: 5.64 mg tropisetron hydrochloride (capsules)	Formulation: 5.64 mg tropisetron hydrochloride (ampoule)
Route of administration: Oral	Route of administration: subcutaneous	Route of administration: Oral	Route of administration: intravenous
Dose regimen:	Dose regimen:	Dose regimen:	Dose regimen:
125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3	150 mcg/m^2/day	1 capsule/day for 5 days	1 ampoule/ day for 1 day

Duration of treatment: 63 days (with chemotherapeutic agent infusions on the first five days of each cycle).

Three cycles of neoadjuvant chemotherapy (DCF combination) was performed, unless a disease progression was observed at the tumor assessment scheduled after the second cycle or due to patient intolerability. Each cycle was planned as 21 days.

Duration of observation: 13 months after surgical intervention, with 4 regular hospital visits every 3 months (physical examination, safety laboratory evaluations and ECOG Performance Status (PS) at each follow-up visit, for a total of 12 months) and 1 additional face to face or telephone visit at the end of 13th month following surgery for the collection of survival data.

Criteria for evaluation:

Efficacy:

The primary efficacy criterion was the percentage of patients with R0 resectability after 3 cycles of neoadjuvant chemotherapy.

The secondary efficacy criteria were response rates to treatment, with disease free survival, overall survival and pathological complete remission rate.

Secondary efficacy evaluations were performed by means of employing EUS and/or CT, on the basis of evaluation criteria for solid tumors (RECIST).

Safety:

All adverse events (AE) reported by the patient/subject or noted by the Investigator were recorded according to NCI CTC (Version 3.0). For safety, a set of laboratory data including standard hematology and blood chemistry tests were collected and reported in the standard case report forms (CRF) format. Adverse event reporting started after initiation of the first dose of IMP and ended after 30 days after last dose of IMP. However, Investigators reported any serious adverse events (SAEs) related to IMP until the end of last visit.

Disease progression, secondary malignancies and death due to any reason are described as components of progression. These events were not reported as expedited cases unless they were related to IMP according to Investigator's decision. Similarly, for patients with progressive disease; AEs and SAEs emerging due to further chemotherapy or radiotherapy were not collected or reported.

Statistical methods:

Study protocol defined 3 analysis populations: A) Intent-to treat population (ITT): All patients who gave informed consent for the participation in the study and given a patient ID number. B) Treated population: Patients who received at least on dose of any study medication. All efficacy and safety analyses were primarily performed in this population C) Per-protocol population (PP): Patients who completed the study as described in the protocol without any violations.

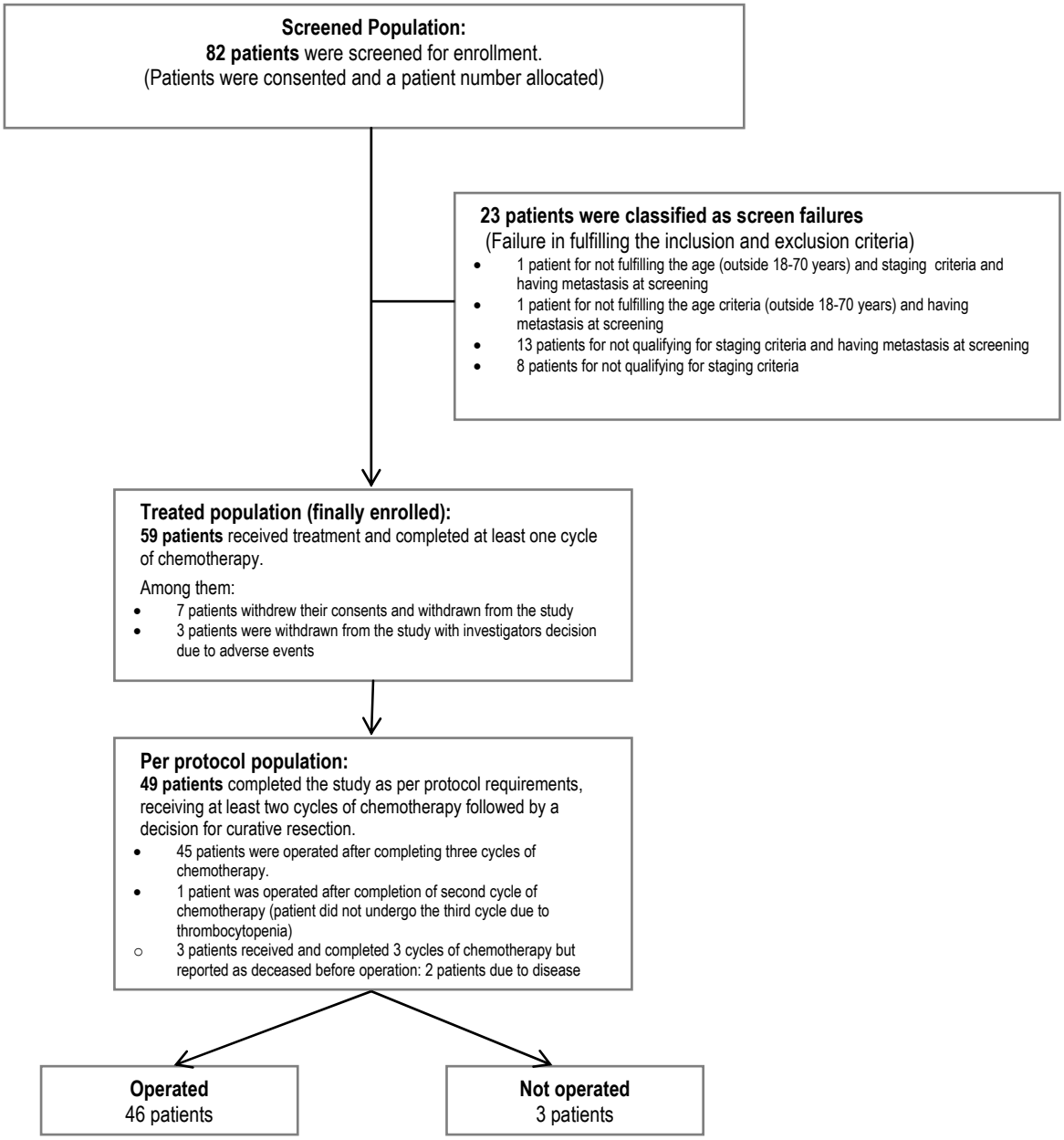
Descriptive statistical methods were employed for the demographic and patient/disease characteristics and percentage of patients with R0 resectability as the primary response criteria as per protocol definition. Secondary efficacy criteria were also evaluated by means of descriptive statistical method for treatment response rate and disease free survival on the basis of CT (with the RECIST criteria) and EUS results, and overall survival and pathologic complete remission rates. Survival rates were calculated with Kaplan-Meier survival method with differences tested by using log-rank test (%95 CI). Treatment response rate was calculated by using Wilcoxon Signed Ranks Test (%95 CI).

On June 14, 2011 an interim analysis was performed on patient screening visit data (baseline characteristics data) using descriptive statistical methods. An abstract was sent to ESMO 2011 congress as a late breaking abstract but rejected.

Summary:

Population characteristics:

Schematic diagram for complete set of study population



Patient demographics:

Patients presenting with gastric adenocarcinoma were mostly male, in both ITT (81.7%) and treated (81.4%) population. The median age of patients was 59.0 (32-70) years in the treated population. Median time elapsed from the first symptoms until diagnosis was 88.5 (8-394) days. All patients had undergone a biopsy for reaching the final diagnosis. No patients received any anti-cancer treatment prior to enrollment. Primary location of gastric adenocarcinoma cases (65 locations were recorded in 59 cases) were as follows:

Primary tumor localization at baseline (Treated population). 65 localization was reported in 59 patients

Tumor localization	N	%
Antrum	18	30.5
Corpus	19	32.2
Cardia	26	44.1
Total gastric	2	3.4

ECOG Performance Scores of patients at baseline (Treated population) (N=59)

ECOG PS	N	%
0	14	23.7
1	39	66.1
2	6	10.2
3	-	-

Disease Stage in Treated Population (N=59)

Stage Baseline (Visit 1)	N	%
IIA	3	5,4
IIB	7	12,5
IIIA	29	51,8
IIIB	8	14,3
IV	9	16,1
Not reported	***3***	
Total	**59**	**100**

Efficacy results:

The primary efficacy criterion was the R0 resectability rate after 3 cycles of neoadjuvant chemotherapy and gastric surgery. Clinical evaluation of resectability was done only during baseline (prior to treatment) in line with available medical information. However, firm decision of surgery was taken after radiological evaluations before 3rd cycle of chemotherapy. Among the treated population (59 patients), 46 patients were operated (1 patient after the completion of 2nd cycle of chemotherapy). Out of 46 operated patients, 1 patient had a not resectable tumor and in another patient resectability evaluation could not be concluded. A total of 13 patients were not operated (10 patients due to previously specified reasons and 3 patients due to death despite a planned surgery). In 80.4% of operated patients total gastrectomy was performed. The percent of patients with R0 resection was 64.4%. A summary of surgical resections is given below:

Surgical resection rates (Treated population)

Surgical resection (Treated population, N= 59)	**N**	**%**
Not operated	**13**	**22.0**
Operated*	46	78.0
R0	*38*	*64.4*
R1	*4*	*6.8*
R2	*2*	*3.4*
Tumor was not resectable	**1**	**1.7**
Unknown**	**1**	**1.7**
Total	**59**	**100.0**

* 1 patient was operated after completion of 2nd chemotherapy cycle due to thrombocytopenia, others received all 3 cycles.
** 1 patient's resectability was not evaluated.

Secondary efficacy criteria were response rates to treatment, with disease free survival, overall survival and pathological complete remission rate.

Response rates and disease free survival evaluations were performed by means of employing computerized tomography (CT), on the basis of Evaluation Criteria for Solid Tumors (RECIST guidelines, 2000):

A total of 38 patients were also evaluated by endosonography at baseline and after cycle 2. Endosonographic evaluation of both primary tumor and lymph nodes showed that staging improved in 15 patients, no staging improvement was shown in 18 patients with 5 disease staging progression.

Response status according to RECIST criteria (Treated population)

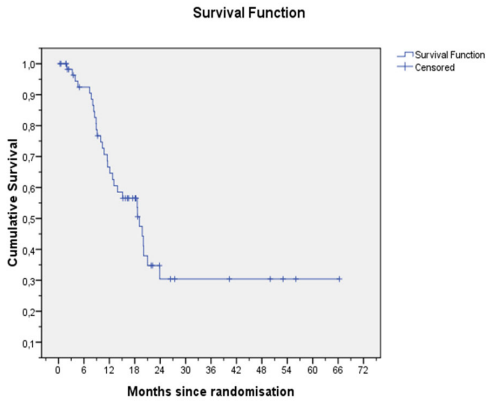
RESPONSE STATUS	**N**	**%**
Partial Response	16	27.1
Progressive Disease	4	6.8
Stable Disease	27	45.8
Stable	*1*	*3.7*
Progression 3-6%	*3*	*11.1*
Response 4-29%	*23*	*85.2*
Not Evaluable	12	20.3

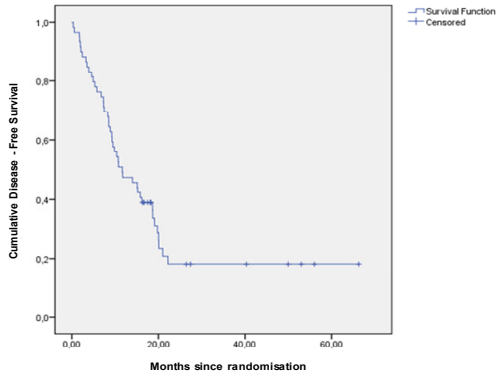
Survival evaluations were performed on 59 patients (treated population). Survival analyses were performed with Kaplan-Meier survival tests and median overall survival was found as 19.1 months (CI: 13.5-24.7 months). On the other hand, median disease free survival was (11.6 months, CI: 5.9-17.4).

At the time of telephone visits conducted after the completion of follow-up period, disease free survival was recorded in 30.6 % of patients, based on patient's declaration.

Survival estimates (Treated population)

OVERALL SURVIVAL[1] (N=59) Means and Medians for survival (in months) and 95 % CI's				
	Estimate	**SE**	**Lower bound**	**Upper bound**
Mean survival	29,5	4,1	21,5	37,5
Median survival	19,1	2,9	13,5	24,7
DISEASE FREE SURVIVAL[2] (N=59) Means and Medians for survival (in months) and 95 % CI's				
	Estimate	**SE**	**Lower bound**	**Upper bound**
Mean survival	20,9	3,2	14,6	27,2
Median survival	11,6	2,9	5,9	17,4





Various survival factors were analyzed in treated population (N=59) by using Log-rank test. There were no difference in survival rates of age groups, however, when patients were grouped on the basis of median age as older and younger (median age=59 years), older patients survived longer (p=0.017). Patients with ECOG performance status of 1 at diagnosis had better overall survival (p=0.019). However, 30% of patients with PS 0 were in stage IV, while this rate was only 10.1% for PS 1 patients. In addition, surgery was performed in 92% of PS 1 patients, compared to 28.6% of PS 0 patients. Among treated population, patients who had an operation (N=46) after 3 cycles of neoadjuvant chemotherapy with DCF combination had a significantly higher overall survival compared to not operated patients (N=13) (Median survival were 19.8 months for operated patiens vs. 9.1 months for not operated patients; p=0.01). R0 resection was achieved for 83% of operated patients and median survival for these patients was 20.1 months from baseline (%95 CI: 18.0-22.2).

Safety results:

A total of 528 AEs were reported in 56 patients. In 23 cases the AEs were rated as SAEs in 15 patients. Three patients never reported AEs. The most frequent all grades AEs regardless of any relationship with study treatment were leucopenia (78.0%). neutropenia (66.1%), nausea (61.0%) and diarrhea (50.8%). Treatment exposure was 94% in treated population. IMP dose was reduced according to protocol in 16 patients (27%). IMP dose was delayed between 1 to 6 days in 3 patients (5%) for 6 times.

In PP population, 2 patients died 30 days after the last IMP administration due to disease progression. One patient died due to an unknown reason (death-NOS) within 30 days after last IMP administration.

Most frequent adverse events by grade, regardless of IMP relationship (Treated population)

Adverse events	Total		Grade 1		Grade 2		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%	N	%
Leucopoenia	**46**	**78,0**	3	5,1	20	33,9	20	33,9	3	5,1
Neutropenia	**39**	**66,1**			8	13,6	19	32,2	12	20,3
Nausea	**36**	**61,0**	20	33,9	13	22,0	2	3,4	1	1,7
Diarrhoea	**30**	**50,8**	11	18,6	13	22,0	5	8,5	1	1,7
Anaemia	**28**	**47,5**	4	6,8	24	40,7				
Vomiting	**23**	**39,0**	12	20,3	9	15,3	2	3,4		
Appetite decreased	**14**	**23,7**	9	15,3	4	6,8	1	1,7		
Thrombocytopenia	**14**	**23,7**	10	16,9	3	5,1	1	1,7		
Alopecia	**13**	**22,0**	8	13,6	2	3,4			3	5,1
Asthenia	**12**	**20,3**	3	5,1	7	11,9	1	1,7	1	1,7
Mucositis oral	**10**	**16,9**	7	11,9	3	5,1				
Weight decreased	**7**	**11,9**	2	3,4	5	8,5				
Fever	**3**	**5,1**	2	3,4	1	1,7				
Constipation	**3**	**5,1**	3	5,1						
Esophagitis	**3**	**5,1**	3	5,1						

The most frequent SAE was febrile neutropenia.

Reported SAEs by relationship with IMP and by grade (Treated population)

SAE term (investigator reported)	MedDRA preferred term	Relationship with IMP	Grade	N
Neutropenic fever	Febrile neutropenia			7
		Yes	3	4
		Yes	4	3
Neutropenia	Neutropenia	Yes	2	1
Epigastric pain	Abdominal pain upper	No	3	1
Hypotension	Hypotension	No	3	1
Gastrointestinal bleeding	Gastrointestinal hemorrhage	Yes	4	1
Hypercreatinemia	Hypercreatinemia	Yes	2	1
Fever chills, neutropenia	Pyrexia, neutropenia	Yes	1	1
Pneumonia	Pneumonia	Yes	4	1
Unconsciousness	Loss of consciousness	Yes	4	1
Acute coronary syndrome	Acute coronary syndrome	Yes	4	1
Deep vein thrombosis	Deep vein thrombosis	Yes	2	1
Oral mucosit/dehydration	Stomatitis	Yes	2	1
Hyponatremia	Hyponatraemia	No	1	1
Pulmonary thromboembolism	Pulmonary embolism	No	3	1
Splenectomy which required hospitalization	Splenectomy	No	4	1
Convulsions	Convulsion	Yes	3	1
Death (NOS) *	Death (NOS)	No	4	1
Total				** 23

* Patient died 4 days after the last IMP administration.
** One case was reported as death as a component of disease progression, which then downgraded. One patient died more than 30 days after the last IMP administration.

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