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Sponsor / Company : Sanofi **Drug Substance :** Docetaxel	**Study identifier :** NCT00816543 **Study Code :** DOCET_R_03761

Title of the study:

A single arm phase II feasibility study of neoadjuvant docetaxel, oxaliplatin and S-1 chemotherapy in potentially operable gastric or gastroesophageal adenocarcinoma

Study center(s): ASAN medical center

Study period:

Date first subject/patient enrolled: 11 Dec 2008
Date last subject/patient completed: 09 May 2012

Phase of development:

Phase 2

Objectives:

Primary objective

- The primary objective of this trial is to determine whether it is feasible in locally advanced gastric or gastroesophageal cancer to administer 3 cycles of docetaxel, oxaliplatin and S-1 as a chemotherapy scheme and also to determine what toxicities are involved.
- This regimen is considered safe (=has an acceptable toxicity profile), if at least 40% of patients have no grade 3-4 adverse event, as defined by the National Cancer Institute Common Toxicity Criteria (NCI CTC) v3.0, except for the absolute neutrophil count for which only a grade 4 Adverse Event (AE) will be taken into account and this for the whole treatment.
- Surgical R0 resection rates of 90% have been reported after neoadjuvant chemotherapy regimens for locally advanced gastric cancer. This experimental regimen is considered not worthy of further development if the surgical resection rate is ≤ 60%, which is clearly unacceptable and worthy of further evaluation if the R0 resection rate is ≥ 85%.
- The regimen is considered feasible if the regimen is safe and provides a high enough R0 resection rate.

Secondary objective

- To describe the disease free survival at one and two years in that subgroup of patients that has undergone a R0 resection. It is assessed by physical examination every 3 months, Computed Tomography (CT) of the abdomen every 6 months and gastrofiberscopy every 1 year after completion of the treatment for 2 years.
- To describe the downstaging after 3 cycles of chemotherapy, pathological Complete Response (pCR) in that subgroup of patients that has undergone a R0 resection and progression-free survival and overall survival at one and two years of the whole study population.

Methodology:

Phase II , single arm, single center, feasibility

Number of subjects/patients:
Planned: 41
Randomized: 41
Treated: 41

Evaluated:
Efficacy: 41
Safety: 41
Pharmacokinetics: N/A

Diagnosis and criteria for inclusion:

Inclusion criteria

- Patients with histologically confirmed, newly diagnosed, localized gastric or gastro-esophageal adenocarcinoma that is considered operable.
  - The bulk of disease must be localized in the stomach, although the gastroesophageal junction may be involved.
  - Patients with T3 or T4 carcinoma without (N0) and T2 or T3 or T4 with regional lymph node involvement assessed by Endoscopic UltraSound (EUS), no peritoneal seeding suspected on abdomen-pelvic CT or confirmed by laparoscopy.
- Age: 18–75 years
- Performance status 0 - 1 in Eastern Cooperative Oncology Group (ECOG) scale
- Adequate haematological function and liver and kidney function within 7 days prior to enrollment:
  - Absolute neutrophil count $\geq$ 1.5 x 10^9/L
  - Platelets $\geq$ 100 x 10^9/L
  - Haemoglobin > 10 g/dl
  - Calculated creatinine clearance $\geq$ 60 ml/min
  - Total bilirubin $\leq$ 3 x UNL
  - GOT and GPT $\leq$ 3 x UNL
- Signed and dated informed consent form

Exclusion criteria

- Previous surgery on primary tumor
- Prior palliative surgery (open and closure, passage operation)
- Any other type of tumor (e.g. leiomyosarcoma, lymphoma) or a secondary malignancy, excepting basal cell skin carcinoma or basal cell carcinoma in situ of the cervix which have already been successfully treated
- Distant metastases (M1) including distant nodal groups (Retropancreatic, para-aortic, portal, retroperitoneal, mesenteric node)
- Any previous palliative, adjuvant or neoadjuvant chemotherapy and/or radiotherapy
- Simultaneous therapy with other anti-tumor drugs
- Ileus, chronic inflammatory intestinal disease or extensive resection of the small intestine and other disorders which limit drug resorption. This includes gastric dumping syndrome, indications of accelerated passage through the small intestine, indications of resorption disorders after intestinal surgery

- Evidence of gastric outlet obstruction and /or severe tumor hemorrhage
- Other anamnestic reaction, serious illness or other medical conditions:
  - Unstable, persistent cardiac disease despite medicinal treatment, myocardial infarction within 6 months before the start of the trial
  - Chronic diarrhea
  - Neurological or psychological disorders including dementia and seizures
  - Active, non-controllable infection or sepsis
  - Actively disseminated intravascular coagulation

Study treatments

Investigational medicinal product(s): Docetaxel, Oxaliplatin, S-1

Formulation: Infusional (docetaxel and oxaliplatin) and oral tablet (S-1)

Route(s) of administration: IV and oral

Dose regimen:

NEOADJUVANT CHEMOTHERAPY REGIMEN:

- Docetaxel 50 mg/ m² IV. will be given as a 1 hour infusion on day 1 for each period of 3 weeks
- Oxaliplatin 100 mg/m² on day 1 will be given as a two-hour IV. infusion for each period of 3 weeks
- S-1 40mg/ m² p.o. bid days 1-14 every 3 weeks

A total of 3 cycles was given

ADJUVANT CHEMOTHERPY REGIMEN:

The patients who have undergone curative resection for stage II, III or IV (M0) gastric cancer received adjuvant chemotherapy with S-1 for 1 year (two oral doses of 40 mg /m^2/day of S-1 for 4 weeks, followed by 2 weeks rest).

Duration of treatment:

- Before Surgery: Cycle 1, Cycle 2, Cycle 3 (1 Cycle = 21 days)
- After Surgery: S-1 for 1 year (every 6 weeks)

Duration of observation:

- Before Neo-Chemotherapy: Day -21, and Day -7
- During Neo-Chemotherapy: Cycle 1, Cycle 2, Cycle 3
- Before surgery
- After Surgery: Every 3 months for 2 years

Criteria for evaluation:

Efficacy:

- Remission rate
- Resectability
- Local recurrence and metastasis rate
- 1 and 2-year overall survival rates
- 1 and 2-year Progression Free Survival (PFS)
- 1 and 2-year Disease Free Survival (DFS)

Safety/tolerability:

- Safety: adverse events observed by the investigators and reported by the patients
- Laboratory data, including hematological test and blood chemistry tests
- Other special examinations performed and recorded by the investigators

Statistical methods:

The type I and type II error rates for this trial was both set to 10%

1. False positive error: if the true safety is 20% or if the R0 resection rate is 60%, then the probability of recommending the regimen for further investigation, is no more than 0.10 (type I error, α).
2. Power: if the true safety rate is 40% and the true resection rate is 85%, then the probability of recommending the regimen for further investigation, is at least 0.90 (1 minus type II error, 1-β).

With these parameters, the design suggested to enter 17 patients in the first stage, once the patients had finished treatment, assess the results and

- if 10 or less can be resected, the trial is terminated
- if 3 or fewer are without toxicity, the trial is terminated
- Otherwise (if 11 or more can be resected and 4 or more are non toxic), continue accruing until 41 patients
- if 11 or fewer are without toxicity or if 28 or less can be resected, the experiment terminates at the phase II
- if 12 or more are without toxicity and 29 or more can be resected, recommendation to test in phase III is warranted.

With these settings, the probability to terminate the trial early if the regimen is too toxic and does not allow enough resectability is 79.8% and the expected sample size was 22 patients, the probability to terminate the trial early if the regimen is too toxic or does not allow enough is 55-57% with an expected sample size of 27-28 patients. The probability of erroneously concluding that the regimen is feasible is below 9% and the actual power to conclude that the regimen is safe and allows R0 resectability if the true safety rate is 40% and the true resectability rate is 85%

Summary:

Patients who completed the trial were 33 patients (80.49%) and 8 patients discontinued (4 patients due to progressive disease, 2 patients due to withdrew consent and 2 patient due to other reasons)

Table 1. Treatment completion and discontinuation

Treatment completion and discontinuation		N=41 n(%)
Completed treatment		33(80.49)
Discontinued		8(19.51)
Primary reason for discontinuation of study medication	Progressive disease	4(9.76)
	Adverse event	0(0.00)
	Patient no longer wants to receive study medication	0(0.00)
	Protocol violation	0(0.00)
	Death	0(0.00)
	Lost to follow up	0(0.00)
	Withdrew consent	2(4.88)
	Other	2(4.88)

Population characteristics:

More men than women enrolled in this trial and median age was 56.27±9.87 yrs. (Table 2)

Table 2. Demography

Characteristic		Mean±SD, Median(Min-Max) N=41
Gender		n(%)
	Male	28(68.29)
	Female	13(31.71)
Age(years)		56.27±9.87, 57(29-73)
Height(cm)		163.88±8.97, 164(148-183)
Weight(kg)		63.73±12.16, 64(40-94)
BSA(m^2)		1.70±0.20, 1.72(1.34-2.19)
Neurological symptoms (NCI CTCAE v.3 grade)		n(%)
	0	41(100.00)
	1-5	0(0.00)

The median duration of gastric cancer was 0.53±0.25 month ranged from 0.07 to 1.21 month. Gastric cancer was mostly diagnosed by EUS of upper gastrointestinal tract, Gastrofiberscopy and CT scan (92.68%), followed by EUS of upper gastrointestinal tract, Gastrofiberscopy, CT scan and Laparoscopy (7.32%). Tumor site was of 82.93% in localized gastric and 17.07% in gastro-esophageal. The most common type of cancer was adenocarcinoma (87.80%), followed by signet ring cell carcinoma (12.20%). Tumor staging by AJCC (American Joint Committee on Cancer) grade showed that T3 of primary tumor (82.93%), N1 of regional lymph nodes (63.41%), M0 of distant metastasis (100.00%) was the mostly graded. (Table 3)

Table 3. Current gastric cancer diagnosis

Current gastric cancer diagnosis			N=41n(%)
Duration of gastric cancer (month)	Mean±SD		0.53±0.25
	Median		0.52
	Min-Max		0.07-1.21
Diagnostic tools	Clinical		0(0.00)
	EUS of upper gastrointestinal tract + Gastrofiberscopy + CT scan		38(92.68)
	EUS of upper gastrointestinal tract + Gastrofiberscopy + CT scan + Laparoscopy		3(7.32)
	Others		0(0.00)
Site	Localised gastric		34(82.93)
	Gastro-esophageal		7(17.07)
Type of cancer	Adenocarcinoma		36(87.80)
	Lymphomas		0(0.00)
	Gastric stromal tumours		0(0.00)
	Carcinoid tumours		0(0.00)
	Adenocanthomas		0(0.00)
	Squamous cell carcinoma		0(0.00)
	Others-signet ring cell carcinoma		5(12.20)
Tumor staging -AJCC grade	Primary Tumor	T0	0(0.00)
		T1	0(0.00)
		T2	5(12.20)
		T3	34(82.93)
		T4	2(4.88)
		TX	0(0.00)
	Regional Lymph Nodes	N0	2(4.88)
		N1	26(63.41)
		N2	12(29.27)
		N3	1(2.44)
		NX	0(0.00)
	Distant Metastasis	M0	41(100.00)
		M1	0(0.00)
		MX	0(0.00)
Number of lymph nodes examined	Mean±SD		2.68±1.66
	Median		2
	Min-Max		0-6
Histological grade -AJCC grade	G1+G2		13(31.71)
	G3+G4		24(58.54)
	NA		4(9.76)
ECOG status	0		9(21.95)
	1		32(78.05)

Efficacy results

Primary end-point

Primary variables were defined as the R0 resection rate and the toxicity rate of grade 3-4 Adverse Event (except for the absolute neutrophil count for which only a grade 4 AE will be taken into account).

In the first stage, when 12 patients entered 12 patients could be R0 resected and 4 patients were nontoxic, so that the trial continued accruing until 41 patients. In the second stage, total 41 patients entered, 40 patients (97.56%) could be R0 resected and 13 patients (31.71%) were nontoxic. This experimental regimen was considered feasible and recommendation to test in phase III was warranted as 12 or more were nontoxic (13 patients) and 29 or more (40 patients) could be R0 resected. (Table 4)

Table 4. Resection rate and safety rate

Resection rate and safety rate	N=41 n(%)
R0 resection rate [95% CI]	40(97.56) [87.14, 99.94]
Safety rate [95% CI]	13(31.71) [18.08, 48.09]

Resection rate

The respectability was assessed by both the number of patients undergoing surgery and the number of patients with R0, R1, R2 resection. R0 resection rate was 97.56% (40/41 patients) and R1 was 2.44% (1/41 patients). There was no patient with R2 resection. (Table 5)

Table 5. resection rate

Resection rate	N=41 n(%)
R0	40(97.56)
R1	1(2.44)
R2	0(0.00)

Remission rate

The remission rate was assessed by means of the number of patients who react to the treatment (pathological partial and completed remission) under the 95% confidence interval. Remission rate was 51.22% (Complete reponse: 0.00%, Partial response: 51.22%) and its 95% confidence interval was 35.13 - 67.12%. (Table 6)

Table 6. Remission rate

Remission rate		N=41 n(%)
	Remission rate [95% CI]	21(51.22) [35.13, 67.12]
	Complete response	0(0.00)
	Partial response	21(51.22)
	Stable disease	20(48.78)
	Disease progression	0(0.00)
	Not evaluable	0(0.00)

Secondary end-point

1) disease free survival

Local recurrence and metastasis rate was 9.76% (4 patients), and the 1-year disease-free survival (DFS) was 94.92% and the 2-year DFS was 89.65%. Median FU duration is 27.22 months (95% CI:26.89, 27.75).

2) progression free survival

In this study, no patient progressed and no patient died, so PFS and OS could not be confirmed.

Safety

During the treatment period, all patients experienced AEs and AEs possibly related to treatment. When a patient experienced adverse events with different grades, adverse event with the highest grade was counted for the number (%) of patients with adverse events. Non-hematological AEs of grade 1, 2, 3 and 4 were reported in 4.88%, 48.78%, 43.90% and 2.44%, respectively. There were AEs possibly related to treatment with grade 4 in non-hematological treatment-emergent AEs. Hematological AEs of grade 1, 2, 3 and 4 were reported in 7.32%, 21.95%, 39.02% and 31.71%, respectively. Serious adverse events and serious adverse events possibly related to treatment were reported in 29.27% and 17.07%. There were no AEs which caused death or permanent discontinuation of treatment. (Table 5)

Table 7. Summary of treatment-emergent adverse events

		N=41 n(%)	
		Adverse event	Adverse drug reaction
All period			
Patients with AEs		**41(100.00)**	**41(100.00)**
Non-hematological AEs of	grade 1	2(4.88)	10(24.39)
	grade 2	20(48.78)	21(51.22)
	grade 3	18(43.90)	10(24.39)
	grade 4	1(2.44)	0(0.00)
Hematological AEs of	grade 1	3(7.32)	2(4.88)
	grade 2	9(21.95)	9(21.95)
	grade 3	16(39.02)	16(39.02)
	grade 4	13(31.71)	13(31.71)
Patients with SAEs		**12(29.27)**	**7(17.07)**
SAEs of	grade 1	0(0.00)	0(0.00)
	grade 2	3(7.32)	2(4.88)
	grade 3	8(19.51)	5(12.20)
	grade 4	1(2.44)	0(0.00)
Patients who died due to AEs		**0(0.00)**	**0(0.00)**
Patients discontinued due to AEs		**0(0.00)**	**0(0.00)**

On-neoadjuvant treatment			
Patients with AEs		**41(100.00)**	**41(100.00)**
Non-hematological AEs of	grade 1	10(24.39)	14(34.15)
	grade 2	21(51.22)	19(46.34)
	grade 3	10(24.39)	8(19.51)
	grade 4	0(0.00)	0(0.00)
Hematological AEs of	grade 1	2(4.88)	2(4.88)
	grade 2	11(26.83)	11(26.83)
	grade 3	14(34.15)	14(34.15)
	grade 4	13(31.71)	13(31.71)
Patients with SAEs		**8(19.51)**	**7(17.07)**
SAEs of	grade 1	0(0.00)	0(0.00)
	grade 2	2(4.88)	2(4.88)
	grade 3	6(14.63)	5(12.20)
	grade 4	0(0.00)	0(0.00)
Patients who died due to AEs		**0(0.00)**	**0(0.00)**
Patients discontinued due to AEs		**0(0.00)**	**0(0.00)**
On-adjuvant treatment			
Patients with AEs		**40(97.56)**	**38(92.68)**
Non-hematological AEs of	grade 1	2(4.88)	20(48.78)
	grade 2	24(58.54)	15(36.59)
	grade 3	13(31.71)	3(7.32)
	grade 4	1(2.44)	0(0.00)
Hematological AEs of	grade 1	8(19.51)	11(26.83)
	grade 2	21(51.22)	16(39.02)
	grade 3	10(24.39)	9(21.95)
	grade 4	1(2.44)	1(2.44)
Patients with SAEs		**5(12.20)**	**0(0.00)**
SAEs of	grade 1	1(2.44)	0(0.00)
	grade 2	1(2.44)	0(0.00)
	grade 3	2(4.88)	0(0.00)
	grade 4	1(2.44)	0(0.00)
Patients who died due to AEs		**0(0.00)**	**0(0.00)**
Patients discontinued due to AEs		**0(0.00)**	**0(0.00)**

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