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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00263354
		Study Code:	L_8915
Generic drug name:	Oxaliplatin	**Date:**	27/Mar/2008

Title of the study:	Oxaliplatin Phase II trial in association with 5FU and folinic acid in the treatment of advanced unresectable or metastatic gastric cancer L_8915		
Investigator(s):	German Calderillo Ruiz Av. San Fernando 22, Col. Seccion XVI, Tlalpan, Mexico D. F. Phone: (+52) 5628 04 00 Ext: 247 Fax: (+52) 5484 2466 Email: alogecaru@yahoo.com.mx		
Study center(s):	Country: Mexico Active centers: 2		
Publications (reference):	No publications have been done up to date		
Study period: Date first **patient/subject** enrolled: 13-oct-2003 Date last **patient/subject** completed: 13-jul-2006		**Phase of development:** Phase II	
Objectives:	<u>Primary:</u> • To determine the objective response to oxaliplatin/5FU/leucovorin combination chemotherapy in patients with advanced unresectable or metastatic gastric cancer <u>Secondary:</u> • To determine progression free survival, overall survival and quality of life		
Methodology:	This study is a non randomized, open label, multicentric, with Oxaliplatin 85 mg/m^2, Folinic acid 20 mg/m^2 that will be administered after discontinuation of the Oxaliplatin. The 5-Fluorouracil 500 mg /m^2 will be administered following the completion of the folinic acid, at day 1 and 15. At day 8, Folinic acid will be administered and 5-Fluorouracil will be administered following, at day 21 no treatment. Cycle length: 28 days, cycles to be repeated until progression or unacceptable toxicity (9 cycles max); 9 months active treatment, 25 months survival follow up of patients with diagnostic of advanced gastric cancer nor metastatic nor resectable		
Number of patients/subjects:	Planned: 20	Randomized:	Treated: 20
Evaluated:	Efficacy: 13	Safety: 20	
Diagnosis and criteria for inclusion:	Patients with diagnostic of advanced gastric cancer nor metastatic nor resectable, males and female older than 18 years old.		

Investigational product: Dose: Administration:	Oxaliplatin <u>Day 1 and 15:</u> Oxaliplatin 85mg/m² diluted in 250 mL glucose 5% administered as a 2-6h continuous IV infusion Folinic acid (FA): 20 mg/m² in 50 ml glucose 5 % as a 10 minutes intravenous infusion. The FA infusion will be administered after the discontinuation of the Oxaliplatin infusion. 5-Fluorouracil (5-FU) 500mg/m² as an IV bolus (less than 10 minutes) will be administered following the completion of the FA infusion. <u>Day 8:</u> Folinic acid (FA): 20 mg/m² in 50 ml glucose 5 % as 10 minutes intravenous infusion. 5-Fluorouracil (5-FU) 500mg/m² as an IV bolus (less than 10 minutes) will be administered following the completion of the FA infusion. Cycle length: 28 days (4 weeks). From day 1, day 28 will be day 1 of the following cycle. Cycles to be repeated until progression or unacceptable toxicity. (9 cycles max) Intravenous infusion
Duration of treatment: 9 months	**Duration of observation:** 25 months survival follow up
Reference therapy: Dose: Administration:	NA
Criteria for evaluation:	
Efficacy:	<u>Primary:</u> To evaluate response rate according to RECIST criteria <u>Secondary:</u> Progression free survival time Overall survival
Safety:	Adverse events reported by the investigator.
Statistical methods:	The statistical analysis is done according to the intent to treat. The missing data will be considered as failure or not response. Descriptive analysis for continuous and discrete variable was done, the descriptive analysis was done according to the nature of the variables: Mean standard deviation, minimum and maximum value and median. Frequency for the qualitative variables. Primary efficacy variable is evaluated through RECIST which is a response index, defined: all measured lesions identified in one dimensional form with a maximum of five lesions by organ, with total identification for 10 lesions, which must be representative for all compromised organs, as target lesions and should be registered and measured at baseline. Target lesions should be selected according to its size and ability for precise repeated measurements. A product for all target lesions for the biggest diameter will be obtained and reported as baseline biggest diameter. The initial product from every target lesion will be used as reference to characterize response of targeted objective. The Kaplan-Meyer method was used for survival time (without progression) it is calculated considering time to present progression or death and for overall survival. The frequency of the adverse events will be done.

Summary:	Decrease percentage of lesions is presents at least of 25%. Response according to RECIST index presents at least 55% of patients in complete or partial response. Survival time without progression presents a mean of 7.3 months according to Kaplan-Meyer analysis, and mean of 10 months in function with death survival. Four serious adverse events were reported. Tolerability to medication study is high, one patient presents hemoglobin stage III, one patient present platelet stage II, and one patient presents transaminases stage II.
Efficacy results:	**Primary efficacy** variable is evaluated through RECIST which is a response index. The initial product from every target lesion will be used as reference to characterize response of targeted objective. Mainly, stomach (60%) and lymphatic nodules (25%) are the main target organs selected. According to data, decrease percentage for diameter is calculated every 3 months and the results are:

Descriptive Statistics		N	Mean	Standard Deviation
Decrease Percentage	baseline – follow up 1	13	43.23	29.24
Decrease Percentage	baseline – follow up 2	7	66.83	26.31
Decrease Percentage	baseline – follow up 3	1	25.71	.

According to this percentages RECIST index is calculated:

Baseline RECIST Follow up 1	Frequency	Percentage	Valid Percentage	Cumulative Percentage
Complete Response (CR)	2	10	11.1	11.1
Partial Response (PR)	8	40	44.4	55.6
Stable Disease (SD)	3	15	16.7	72.2
Progressive Disease (PD)	5	25	27.8	100
Total	18	90	100	
Missing Data	2	10		
Total	20	100		

During the first 4 months of treatment (3 chemotherapy cycles) there are 56% of patients with some response (complete or partial)

Baseline RECIST Follow up 2	Frequency	Percentage	Valid Percentage	Cumulative Percentage
Complete Response (CR)	2	10	28.6	28.6
Partial Response (PR)	4	20	57.1	85.7
Stable Disease (SD)	1	5	14.3	100
Total	7	35	100	
Missing Data	13	65		
Total	20	100		

During the first 8 months of treatment (6 chemotherapy cycles) there are 86% of patients who continued until this time in the clinical study with some kind of response.

During the first 12 months of treatment (9 chemotherapy cycles) there is only one patient who presented progressive disease.

Secondary analysis using the Kaplan-Meyer method survival time (without progression), is calculated considering time to present progression or death.

Survival time without progression presents a mean of 7.3 months and a median of 5.9 months

Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
.47	End of treatment			0	19
.73	End of treatment			0	18
.97	End of treatment			0	17
1.07	End of treatment			0	16
1.27	Progression	0.9375	0.0605	1	15
2.70	Progression	0.8750	0.0827	2	14
3.07	Death	0.8125	0.0976	3	13
3.20	Progression	0.7500	0.1083	4	12
3.47	End of treatment			4	11
3.73	End of treatment			4	10
4.30	Death	0.6750	0.1206	5	9
5.13	End of treatment			5	8
5.28	Progression	0.5906	0.1318	6	7
5.40	End of treatment			6	6
5.40	End of treatment			6	5
5.60	End of treatment			6	4
5.90	Progression	0.4430	0.1616	7	3
8.00	End of treatment			7	2
8.10	End of treatment			7	1
11.23	End of treatment			7	0

Number of Cases: 20 Censored: 13 (65.00%) Events: 7

	Survival Time	Standard Error	95% Confidence Interval
Mean:	7.31	1.07	(5.20, 9.42)
Median:	5.90	0.77	(4.40, 7.40)

Using Kaplan Meyer analysis again for calculating global survival with a main event of patient death. According to data, there are only 2 cases of death and the calculated mean is 10.01 months.

Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
.47	Progression o interruption			0	19
.73	Progression o interruption			0	18
.97	Progression o interruption			0	17
1.07	Progression o interruption			0	16
1.27	Progression o interruption			0	15
1.79	Progression o interruption			0	14
3.07	Death	0.9286	0.0688	1	13
3.20	Progression o interruption			1	12
3.47	Progression o interruption			1	11
3.73	Progression o interruption			1	10
4.53	Death	0.8357	0.1077	2	9
4.13	Progression o interruption			2	8
5.20	Progression o interruption			2	7
5.40	Progression o interruption			2	6
5.60	Progression o interruption			2	5
5.80	Progression o interruption			2	4
6.93	Progression o interruption			2	3
8.00	Progression o interruption			2	2
9.10	Progression o interruption			2	1
11.23	Progression o interruption			2	0

Number of cases: 20 Censored: 18 (90.00%) Events: 2

	Survival Time	Standard Error	95% Confidence Interval	
Mean:	10.01	0.60	8.44,	11.57)
Median:	.	.	(. ,	.)

With available data, parameters for median are not possible to be calculated.

Safety results:	Four adverse events are reported as serious, 75% of these cases were reported as None relationship to study medication, and 25% of cases were reported as "Improbable". The detail for serious adverse events are in the following table:

PATIENT	DATE	REASON FOR SERIOUS ADVERSE EVENT	DIAGNOSTIC OR MAIN SYMPTON
5	21-Jan-2004	Hospitalization or Prolonged Hospitalization	Thrombosis
11	19-Oct-2004	Death	Progression of disease with death
17	28-Mar-2006	Death	Progression of disease (gastric cancer)
19	17-Nov-2005	Death	Progression of disease

The detailed for serious adverse events regarding toxicity and outcomes for serious adverse events are:

Patient	DATE	FIRST SYMPTOM DATE	TOXICITY GRADE	CYCLE OF STUDY MEDICATION APPLICATION	ACTION WITH STUDY MEDICATION	OUTCOME OF ADVERSE EVENT	DEATH DATE
5	21-Jan-2004	13-Jan-04	Grade 4	3	No change	Continue	
11	19-Oct-2004	13-Oct-04		2	Discontinued	Continue	13-Oct-04
17	28-Mar-2006	20-Feb-05	Grade 4	2	Discontinued	Death	04-Mar-05
19	17-Nov-2005	04-Oct-05	Grade 4	3	Discontinued	Death	04-Oct-05

Toxicity grade for laboratory test are the following:

- One patient presented hemoglobin toxicity grade 3 with the first chemotherapy cycle.

HEMOGLOBIN		GRADE					
		0	1	2	3	ND	Total
Baseline Hemoglobin	N	9	8	1	1	1	20
	%	45.00%	40.00%	5.00%	5.00%	5.00%	100.00%
Hemoglobin day 1 cycle 1	N	12	7			1	20
	%	60.00%	35.00%			5.00%	100.00%
Hemoglobin day 8 cycle 1	N	12	5	2		1	20
	%	60.00%	25.00%	10.00%		5.00%	100.00%
Hemoglobin day 15 cycle 1	N	9	5	2		4	20
	%	45.00%	25.00%	10.00%		20.00%	100.00%
Hemoglobin day 1 cycle 2	N	10	8				18
	%	55.60%	44.40%				100.00%
Hemoglobin day 8 cycle 2	N	6	4	1		6	17
	%	35.30%	23.50%	5.90%		35.30%	100.00%
Hemoglobin day 15 cycle 2	N	6	5			6	17
	%	35.30%	29.40%			35.30%	100.00%
Hemoglobin day 1 cycle 3	N	8	4	1			13
	%	61.50%	30.80%	7.70%			100.00%
Hemoglobin day 8 cycle 3	N	6	2	1		5	14
	%	42.90%	14.30%	7.10%		35.70%	100.00%
Hemoglobin day 15 cycle 3	N	4	3	1		5	13
	%	30.80%	23.10%	7.70%		38.50%	100.00%
Hemoglobin day 1 cycle 4	N	5	4	1		1	11
	%	45.50%	36.40%	9.10%		9.10%	100.00%
Hemoglobin day 8 cycle 4	N	3	4			4	11
	%	27.30%	36.40%			36.40%	100.00%
Hemoglobin day 15 cycle 4	N	2	5			4	11
	%	18.20%	45.50%			36.40%	100.00%
Hemoglobin day 1 cycle 5	N	5	3	1			9
	%	55.60%	33.30%	11.10%			100.00%
Hemoglobin day 8 cycle 5	N	1	4	1		3	9
	%	11.10%	44.40%	11.10%		33.30%	100.00%
Hemoglobin day 15 cycle 5	N	3	2	1		3	9
	%	33.30%	22.20%	11.10%		33.30%	100.00%
Hemoglobin day 1 cycle 6	N	5	3				8
	%	62.50%	37.50%				100.00%
Hemoglobin day 8 cycle 6	N	2	3			3	8
	%	25.00%	37.50%			37.50%	100.00%
Hemoglobin day 15 cycle 6	N	2	2			3	7
	%	28.60%	28.60%			42.90%	100.00%
Hemoglobin day 1 cycle 7	N					1	1
	%					100.00%	100.00%
Hemoglobin day 8 cycle 7	N					1	1
	%					100.00%	100.00%
Hemoglobin day 15 cycle 7	N					1	1
	%					100.00%	100.00%
Hemoglobin day 1 cycle 8	N	1					1
	%	100.00%					100.00%
Hemoglobin day 8 cycle 8	N					1	1
	%					100.00%	100.00%
Hemoglobin day 15 cycle 8	N					1	1
	%					100.00%	100.00%
Hemoglobin day 1 cycle 9	N	1					1
	%	100.00%					100.00%
Hemoglobin day 8 cycle 9	N					1	1
	%					100.00%	100.00%
Hemoglobin day 15 cycle 9	N					1	1
	%					100.00%	100.00%

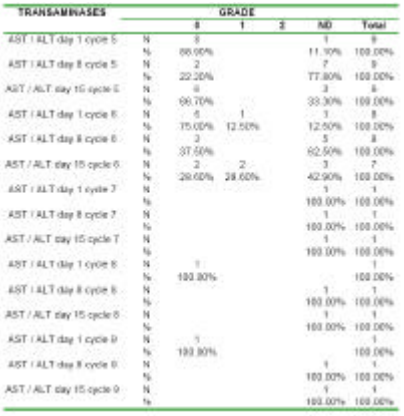
- One patient presented platelet toxicity grade 2 in the cycle 5.

PLATELET		GRADE			
		0	2	ND	Total
Baseline Platelet	N	19		1	20
	%	95.00%		5.00%	100.00%
Platelet day 1 cycle 1	N	19		1	20
	%	95.00%		5.00%	100.00%
Platelet day 8 cycle 1	N	19		1	20
	%	95.00%		5.00%	100.00%
Platelet day 15 cycle 1	N	16		4	20
	%	80.00%		20.00%	100.00%
Platelet day 1 cycle 2	N	18			18
	%	100.00%			100.00%
Platelet day 8 cycle 2	N	11		6	17
	%	64.70%		35.30%	100.00%
Platelet day 15 cycle 2	N	11		6	17
	%	64.70%		35.30%	100.00%
Platelet day 1 cycle 3	N	13			13
	%	100.00%			100.00%
Platelet day 8 cycle 3	N	9		5	14
	%	64.30%		35.70%	100.00%
Platelet day 15 cycle 3	N	8		5	13
	%	61.50%		38.50%	100.00%
Platelet day 1 cycle 4	N	10		1	11
	%	90.90%		9.10%	100.00%
Platelet day 8 cycle 4	N	7		4	11
	%	63.60%		36.40%	100.00%
Platelet day 15 cycle 4	N	7		4	11
	%	63.60%		36.40%	100.00%
Platelet day 1 cycle 5	N	8	1		9
	%	88.90%	11.10%		100.00%
Platelet day 8 cycle 5	N	6		3	9
	%	66.70%		33.30%	100.00%
Platelet day 15 cycle 5	N	6		3	9
	%	66.70%		33.30%	100.00%

PLATELET		GRADE			
		0	2	ND	Total
Platelet day 1 cycle 6	N	8			8
	%	100.00%			100.00%
Platelet day 8 cycle 6	N	5		3	8
	%	62.50%		37.50%	100.00%
Platelet day 15 cycle 6	N	4		3	7
	%	57.10%		42.90%	100.00%
Platelet day 1 cycle 7	N			1	1
	%			100.00%	100.00%
Platelet day 8 cycle 7	N			1	1
	%			100.00%	100.00%
Platelet day 15 cycle 7	N			1	1
	%			100.00%	100.00%
Platelet day 1 cycle 8	N	1			1
	%	100.00%			100.00%
Platelet day 8 cycle 8	N			1	1
	%			100.00%	100.00%
Platelet day 15 cycle 8	N			1	1
	%			100.00%	100.00%
Platelet day 1 cycle 9	N	1			1
	%	100.00%			100.00%
Platelet day 8 cycle 9	N			1	1
	%			100.00%	100.00%
Platelet day 15 cycle 9	N			1	1
	%			100.00%	100.00%

- All neutrophile data are normal.
- One patient presented transaminases toxicity grade 2 in cycle 2.

TRANSAMINASES		GRADE				
		0	1	2	ND	Total
Baseline SGPT	N	16	1		1	20
	%	80.00%	5.00%		5.00%	100.00%
AST / ALT day 1 cycle 1	N	14	1		5	20
	%	70.00%	5.00%		25.00%	100.00%
AST / ALT day 8 cycle 1	N	9			11	20
	%	45.00%			55.00%	100.00%
AST / ALT day 15 cycle 1	N	10	1		9	20
	%	50.00%	5.00%		45.00%	100.00%
AST / ALT day 1 cycle 2	N	14		1	3	18
	%	77.80%		5.60%	16.70%	100.00%
AST / ALT day 8 cycle 2	N	7			10	17
	%	41.20%			58.80%	100.00%
AST / ALT day 15 cycle 2	N	7	1		9	17
	%	41.20%	5.90%		52.90%	100.00%
AST / ALT day 1 cycle 3	N	12	1			13
	%	92.30%	7.70%			100.00%
AST / ALT day 8 cycle 3	N	4			10	14
	%	28.60%			71.40%	100.00%
AST / ALT day 15 cycle 3	N	4			9	13
	%	30.80%			69.20%	100.00%
AST / ALT day 1 cycle 4	N	9			2	11
	%	81.80%			18.20%	100.00%
AST / ALT day 8 cycle 4	N	4			7	11
	%	36.40%			63.60%	100.00%
AST / ALT day 15 cycle 4	N	7			4	11
	%	63.60%			36.40%	100.00%

	 • For the bilirubin and creatinine value there are many missing data, but available data are in laboratory limits.
Date of report:	20-Mar-2008

TRANSAMINASES		GRADE				
		0	1	2	ND	Total
AST / ALT day 1 cycle 5	N	8			1	9
	%	88.89%			11.11%	100.00%
AST / ALT day 8 cycle 5	N	2			7	9
	%	22.22%			77.78%	100.00%
AST / ALT day 15 cycle 5	N	6			3	9
	%	66.67%			33.33%	100.00%
AST / ALT day 1 cycle 6	N	6	1		1	8
	%	75.00%	12.50%		12.50%	100.00%
AST / ALT day 8 cycle 6	N	3			5	8
	%	37.50%			62.50%	100.00%
AST / ALT day 15 cycle 6	N	3	2		3	7
	%	28.60%	28.60%		42.90%	100.00%
AST / ALT day 1 cycle 7	N				1	1
	%				100.00%	100.00%
AST / ALT day 8 cycle 7	N				1	1
	%				100.00%	100.00%
AST / ALT day 15 cycle 7	N				1	1
	%				100.00%	100.00%
AST / ALT day 1 cycle 8	N	1				1
	%	100.00%				100.00%
AST / ALT day 8 cycle 8	N				1	1
	%				100.00%	100.00%
AST / ALT day 15 cycle 8	N				1	1
	%				100.00%	100.00%
AST / ALT day 1 cycle 9	N	1				1
	%	100.00%				100.00%
AST / ALT day 8 cycle 9	N				1	1
	%				100.00%	100.00%
AST / ALT day 15 cycle 9	N				1	1
	%				100.00%	100.00%