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Sponsor/Company: sanofi-aventis **Drug substance**: Oxaliplatin (SR96669)	**Study Identifier**: NCT00094965 **Study code**: POP5347

Title of the study:
Phase 2 trial of oxaliplatin in combination with bolus/infusional 5-FU/LV (FOLFOX4) in patients with advanced gastrointestinal (GI) cancers with varying degrees of renal impairment.

Study centers:
Multicenter with a total of 11 centers in the United States.

Study period:

Date first patient enrolled: 24-Sep-2004
Date last patient completed: 13-Aug-2007

Phase of development: Phase 2

Objectives:
The primary objective was to evaluate the safety of oxaliplatin in combination with bolus/infusional 5 fluorouracil/leucovorin, (FOLFOX4 regimen) in adult patients with advanced gastrointestinal (GI) cancer with normal renal function and mild, moderate, and severe renal impairment.

The secondary objectives were to evaluate pharmacokinetics (PK) of oxaliplatin.

Methodology:
Multicenter, open label, Phase 2 study with 4 cohorts of at leats 10 evaluable patients with normal and impaired renal function defined as creatinine clearance, normal: >80mL/min, mild: 50 to 80mL/mim, moderate: 30 to 49mL/min, and severe: <30mL/min.

Number of patients:

		Normal	Mild	Moderate	Severe
Number of Patients:	Planned	10	10	10	10
	Treated	12	13	11	5
Evaluated:	Efficacy	12	13	11	5
	Safety	12	13	11	5
	Pharmacokinetics	11	13	10	4

Diagnosis and criteria for inclusion:

Male and female patients, ≥18 years with histologically or cytologically confirmed locally advanced or metastatic GI malignancy, no prior oxaliplatin, cisplatin,or other nephrotoxic anticancer agent, Karnofsky Performance Status (KPS) (Eastern cooperative Oncology Group Performance Status) ≥70%; for patients with normal renal function and patients with mild renal impairment, KPS ≥50% for patients with moderate and severe renal impairment.

Investigational product: Oxaliplatin (SR96669)

Administration: FOLFOX4
Day 1:
Oxaliplatin intravenous (IV) 85 mg/m^2 over 2 hours simultaneously with Leucovorin 200 mg/m^2 IV over 2 hours, followed by 5-FU 400 mg/m^2 IV bolus, then 5-FU 600 mg/m^2 IV over 22 hours.

Day 2:
Leucovorin 200 mg/m^2 IV over 2 hours, followed by 5-FU 400 mg/m^2 IV bolus, then 5-FU 600 mg/m^2 IV over 22 hours. Treatment cycle repeated every 2 weeks.

Patients in the severe cohort had a starting dose 65 mg/m^2 oxaliplatin with the option to escalate based on tolerability.

Reference therapy: None

Duration of treatment: 2-week treatment regimen for a maximum of 12 cycles

Duration of observation: Up to 1 year to follow neurotoxicity recovery

Criteria for evaluation:

Safety:
Safety measurements included Adverse events (AEs) graded using Common Terminology Criteria for Adverse Events, Version 3.0, oxaliplatin-specific neurotoxicity scale for paresthesia, chemistry, hematology, and 24-urine collection.

Pharmacokinetics:
Blood samples were collected at selected times during cycles 1 and 2 and urine samples were collected during cycle 1 only. Plasma, plasma ultrafiltrate and urine samples were analyzed for platinum concentrations using validated methods.

Efficacy:
Efficacy measure was tumor response based on RECIST (Response Evaluation Criteria in Solid Tumors) criteria.

Statistical methods:

Safety:

Safety was evaluated in all patients who received study treatment. Regression analysis included all patients treated for at least 2 cycles. All adverse events (AEs) and laboratory results were summarized for each cohort by All Grades and Grade 3, 4 within 30 days of last dose of oxaliplatin.

Protocol pre-specified incidence of toxicities in the GI system, peripheral nervous system, and renal/urinary system, as well as for hematologic parameters (granulocytopenia, febrile neutropenia, thrombocytopenia) were analyzed to investigate a potential relationship with baseline 24-hour creatinine clearance by using a logistic regression model with one-sided testing at the 0.05 level. Patients with severe renal impairment were not included in the regression analysis because they were treated with a reduced dose of oxaliplatin (65 mg/m^2).

Pharmacokinetics:

Patients who received at least 2 cycles of treatment were evaluated for PK analysis. Plasma and plasma ultrafiltrate PK parameters along with the urinary excretion and renal plasma ultrafiltrate platinum clearance were listed by patient and summarized using descriptive statistics by cohort.

Efficacy:

Best overall response to treatment was listed for all treated patients.

Summary:

Baseline characteristics:

Mean age ± standard deviation (SD) was similar between the 4 groups of patients: 66.2 ±11.3 for normal, 68.8 ± 10.8 for mild, 68.2 ± 10.0 for moderate and 77.0 ± 9.3 for severe impaired renal function. The majority of patients was male and Caucasian, and had a KPS in the range of 80 to 100% (see Table 1).

Table 1 - Summary of demographic and baseline characteristics of treated patients

Parameter	Normal (N=13)		Mild (N=14)		Moderate (N=11)		Severe (N=5)	
Age (years)								
Mean (SD)	66.2 (11.31)		68.8 (10.80)		68.2 (10.03)		77.0 (9.27	
Min - Max	45 - 83		48 - 82		48 - 83		63 - 87	
Gender [n (%)]								
Male	9	(69.2)	10	(71.4)	8	(72.7)	2	(40.0)
Female	4	(30.8)	4	(28.6)	3	(27.3)	3	(60.0)
Caucasian/white	8	(61.5)	11	(78.6)	7	(63.6)	5	(100)
KPS [n (%)]								
70-100	12	(92.3)	13	(92.9)	11	(100.0)	5	(100.0)
60	0	(0)	1	(7.1)	0	(0)	0	(0)
Missing	1	(7.7)	0	(0)	0	(0)	0	(0)

Mean ± SD creatinine clearance at baseline was 102.8 ± 22.4 for normal, 62.0 ± 7.4 for mild, 39.5 ± 6.4 for moderate, and 23.4 ± 5.6 for severe impaired renal function (see Table 2).

Table 2 – Summary of baseline creatinine clearance (mL/min)

Parameter	Normal (N=13)	Mild (N=14)	Moderate (N=11)	Severe (N=5)
Mean (SD)	102.8 (22.35)	62.0 (7.36)	39.5 (6.38)	23.4 (5.59)
Median	101.0	64.0	39.0	25.0
Min - Max	82.0 - 170.0	51.0 - 72.0	30.0 - 49.0	14.0 - 28.0

Safety results:

The median relative dose intensity for oxaliplatin was >80% in all treatment cohorts but patients with impaired renal function had a greater proportion of cycles at reduced doses and the dose reduction of oxaliplatin and/or 5-FU. Dose reduction of 5-FU occurred earlier in patients with renal impairment (see Table 3). None of the patients with severe renal impairment had oxaliplatin increased to 85 mg/m^2

Table 3 – Number of administered cycles – treated population

	Normal (N=12)	Mild (N=13)	Moderate (N=11)	Severe (N=5)
Total	96	71	73	21
Median	9.0	4.0	6.0	3.0
Min	2	1	1	1
Max	12	12	12	11

Safety results were similar across all cohorts for the pre-specified adverse events (GI disorders and nervous system disorders) and laboratory abnormalities. Within the nervous system disorder category no increase in occurrence of dysesthesia and of paresthesia has been reported (see Table 4).

Table 4 – Number of patients with selected laboratory abnormalities and adverse events

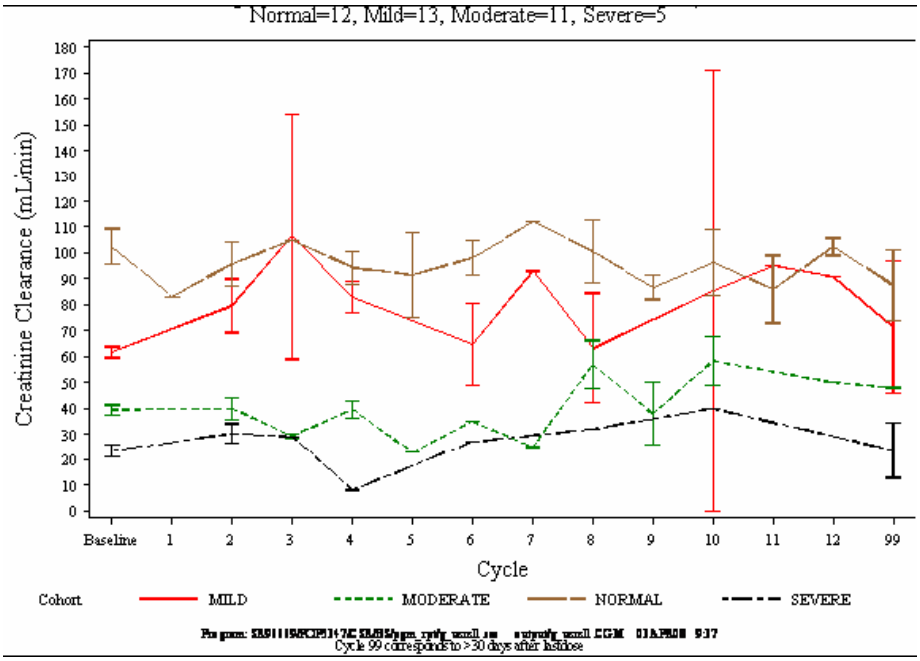
	Normal (n=12)		Mild (n=13)		Moderate (n=11)		Severe (n=5)	
	All grades	Grade 3,4	All grades	Grade 3,4	All grades	Grade 3,4	All grades	Grade 3,4
Laboratory								
Granulocytopenia	11	8	9	9	7	7	2	2
Thrombocytopenia	7	1	6	0	2	0	1	0
Adverse events								
Febrile neutropenia	1	1	1	1	2	2	0	0
Gastrointestinal disorders	10	2	12	5	10	1	4	0
Vomiting	5	0	8	1	5	0	1	0
Diarhea	6	0	9	3	6	1	3	0
Nervous system disorders	11	1	11	1	7	1	3	1
Paresthesia	7	0	7	0	4	1	2	1
Renal and urinary disorders	4	0	3	0	2	1	0	0

Three patients, 1 each on the normal, mild, and moderate cohort, died within 30 days of last treatment. These 3 deaths were due to bacterial sepsis, hypotension/respiratory distress/subdural hematoma, and cardiac arrest preceded by severe chest pain. Treatment emergent serious AEs were reported in 3/12 patients in the normal cohort, 7/13 patients in the mild cohort, 6/11 patients in the moderate cohort, and 1/5 patients in the severe cohort. Most serious AEs occurred in only 1 patient.

Fifteen patients discontinued treatment due to AEs. The proportion of patients who discontinued the study due to AEs was higher in the impaired renal function cohorts (1/12, 7/13, 5/11, and 3/5 patients in the normal mild, moderate, and severe cohorts, respectively). Across all cohorts, the most common hematologic abnormality was granulocytopenia, in most cases Grade 3,4. There were few clinical chemistry abnormalities during the study with no differences across cohorts.

Logistic regression analyses did not indicate a statistically significant relationship between baseline creatinine clearance and increased toxicity of the FOLFOX4 regimen ($p > 0.05$ for all toxicities). Creatinine clearance across cohorts over time is shown in Figure 1.

Figure 1 - Creatinine clearance by cycle – all cohorts



Pharmacokinetic results:

A gradual increase in AUC_{last} and AUC for platinum in plasma ultrafiltrate was found from normal to mild, moderate and to severe renal impairment, both in cycle 1 and cycle 2. Volume of distribution at steady state and clearance of platinum gradually decreased from normal to mild, moderate and severe renal impairment, both in cycle 1 and cycle 2. Maximum platinum concentration (C_{max}) was similar in the 4 cohorts, both in cycle 1 and cycle 2 (see Table 4).

Table 4 – Pharmacokinetic parameters of platinum in plasma ultrafiltrate

		Renal status			
Parameters	Cycle	Normal	Mild	Moderate	Severe
C_{max} (ng/mL)	1	923 ± 289	788 ± 289	848 ± 319	883 ± 273
		(31.4 %, 10)	(36.7 %, 13)	(37.6 %, 10)	(31 %, 4)
	2	893 ± 391	856 ± 217	947 ± 279	947 ± 169
		(43.8 %, 11)	(25.4 %, 12)	(29.4 %, 9)	(17.8 %, 4)
AUC_{last} (µg*h/mL)	1	10.7 ± 3.43	15.0 ± 7.63	20.9 ± 6.13	36.2 ± 16.2
		(32.2 %, 10)	(50.8 %, 13)	(29.3 %, 10)	(44.7 %, 4)
	2	10.4 ± 4.27	16.4 ± 7.95	20.2 ± 4.66	27.1 ± 10.6
		(40.8 %, 11)	(48.5 %, 12)	(23.1 %, 9)	(39.2 %, 4)
AUC (µg*h/mL)	1	11.3 ± 3.71	16.1 ± 8.12	23.8 ± 4.88	38.6 ± 16.8
		(32.8 %, 10)	(50.6 %, 13)	(20.5 %, 9)	(43.4 %, 4)
	2	11.3 ± 4.40	18.1 ± 8.20	22.9 ± 4.78	35.9 ± 12.2
		(39.0 %, 11)	(45.3 %, 12)	(20.9 %, 9)	(34.0 %, 3)
V_{ss} (L)	1	609 ± 156	445 ± 127	323 ± 117	166 ± 63.2
		(25.6 %, 10)	(28.4 %, 13)	(36.3 %, 9)	(38.0 %, 4)
	2	499 ± 245	529 ± 198	433 ± 265	181 ± 112
		(49.0 %, 11)	(37.5 %, 12)	(61.1 %, 9)	(61.9 %, 3)
CL (L/h)	1	7.80 ± 2.36	5.79 ± 1.86	3.32 ± 0.93	1.66 ± 0.67
		(30.3 %, 10)	(32.0 %, 13)	(28.0 %, 9)	(40.3 %, 4)
	2	7.78 ± 3.14	5.11 ± 1.65	3.32 ± 0.812	1.70 ± 0.63
		(40.3 %, 11)	(32.3 %, 12)	(24.7 %, 9)	(36.8 %, 3)

The half life of platinum in plasma ultrafiltrate continuously decreased for the alpha half life but steadily increased for beta and gamma half life from normal to mild, moderate to severe renal impairment.

Mean ± SD dose fraction of platinum excreted in urine continuously decreased within 24 and 48 hours in relation to renal impairment from normal to mild, moderate to severe. Likewise, renal clearance decreased depending on the renal impairment from normal, mild, moderate to severe (see Table 5).

Table 5 – Summary of platinum half life in plasma ultrafiltrate

Renal Status	**Alpha Half Life (hr)**	**Beta Half Life (hr)**	**Gamma Half Life (hr)**
Normal	0.425 ± 0.329	17.6 ± 5.47	279 ± 232
	(77.5 %, 11)	(31.1 %, 11)	(83.2 %, 11)
Mild	0.260 ± 0.246	22.1 ± 8.07	1620 ± 4760
	(95 %, 12)	(36.4 %, 12)	(294 %, 12)
Moderate	0.219 ± 0.0952	24.4 ± 5.51	561 ± 1040
	(43.5 %, 9)	(22.6 %, 9)	(186 %, 9)
Severe	0.221 ± 0.128	49.4 ± 30.5	6290 ± 11100
	(57.9 %, 4)	(61.8 %, 4)	(176 %, 4)

Efficacy:

There were 3 partial responses in the normal cohort and 1 partial response in the mild and moderate cohorts each. Stable disease was reported in 5 patients in the normal cohort, 8 patients in the mild cohort, 6 patients in the moderate, and 2 patients in the severe cohort.

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