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Sponsor / Company: sanofi-aventis **Drug substance(s):** oxaliplatin	**Study Identifier:** na **Study number:** ARD5531
Title of the study: Phase 1-2 study of weekly oxaliplatin in childhood refractory or relapsed malignant solid tumors.	
Study center(s): 8 centers in France	
Study period: Date first patient enrolled: 09/Oct/2001 Date last patient completed: 13/Nov/2004	
Phase of development: Phase 1/2	
Objectives: Primary: • to establish the maximum tolerated dose (MTD) of single agent weekly oxaliplatin, and thus, a recommended dose (RD) for Phase 2 study. Secondary: • to define dose limiting toxicities (DLTs); • to define the safety profile; • to examine pharmacokinetic parameters; • to evaluate efficacy.	
Methodology: Multi-center, Phase 1/2 study, open-label, non-comparative, non-randomized study with direct individual benefit.	
Number of patients: Phase 1: Planned: 6 to 46 Enrolled: 29 Treated: 28 Recommended dose (RD) cohort: Planned: 10 Enrolled: 16 Treated: 15 Pharmacokinetics (Phase 1 and RD cohort): 41	
Diagnosis and criteria for inclusion: • patients must have had histologically or cytologically confirmed malignant solid tumors. Histologically documented diagnosis of solid tumor was not required for brain stem tumors; • tumors refractory to first line or relapsing after conventional chemotherapy, ie, patients who had been treated previously by at least 2 lines of chemotherapy and/or for whom no effective treatment was available; • age: 6 months to 21 years; • life expectancy: more than 6 weeks; • no concomitant anti-cancer or investigational drug; • Eastern Cooperative Oncology Group (ECOG) Performance status ≤2 (or Lansky scale if patient less than 12 years of age); • at least 4 weeks must have elapsed since the last anti-cancer therapy (6 weeks since nitrosourea therapy); • patients must have had no clinical evidence of peripheral neuropathy sensory or motor (< Grade 2 National Cancer Institute – Common Toxicity Criteria [NCI-CTC]);	

Diagnosis and criteria for inclusion (cont'd):

- adequate bone marrow reserve:
  - platelets ≥75 x 10^9/L or ≥50 x 10^9/L in case of bone marrow involvement;
  - hemoglobin ≥8g/dL;
  - absolute neutrophil count >1.0 x 10^9/L.
- liver function:
  - aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN);
  - bilirubin ≤1.5 x ULN.
- renal function:
  - creatinine <3 x ULN for age (0-1 year old: <40 µmol/L; 1-15 years old <65 µmol/L; 15-21 years old <110 µmol/L).
- no other serious concomitant illness;
- no organ toxicity including ototoxicity ≥ Grade 2 NCI-CTC version 2;
- written informed consent (if patient was <18 years old, of parent/guardian and if possible child).

Investigational product: oxaliplatin

Phase 1 dose:

oxaliplatin was administered over 2 hours on Days (D) 1, 8, and 15 of each cycle, with a dose escalation of 20% per level (6 levels). Each cycle was repeated every 4 weeks. Patients could only be registered at a new dose level if toxicity during the first cycle had been evaluated in all patients treated at the dose level below:
Level 1: 40 mg/m²; Level 2: 50 mg/m²; Level 3: 60 mg/m²; Level 4: 75 mg/m²; Level 5: 90 mg/m²; Level 6: 110 mg/m².
Children younger than 1 year old were treated at the dose level currently investigated when they were registered. The dose was calculated in mg/kg:
Level 1: 1.3 mg/kg; Level 2: 1.7 mg/kg; Level 3: 2 mg/kg; Level 4: 2.5 mg/kg; Level 5: 3 mg/kg; Level 6: 3.7 mg/kg.

Recommended dose (RD): 90 mg/m^2

Administration: Intravenous (IV)

Duration of treatment: Patient continued study treatment until disease progression, unacceptable toxicity, patient refusal, or treatment delay >3 weeks.
In the absence of documented disease progression and in the absence of unacceptable toxicity after the first cycle, the treatment was continued as 1 cycle every 28 days for a maximum of 6 cycles. Treatment continuation beyond 6 cycles was discussed with the trial coordinator and the Sponsor.

Duration of observation: All included patients were followed until death or study cut-off.

Reference therapy: None

Criteria for evaluation:

Safety:

- DLT at the first cycle;

  The following toxicities were considered as a DLT if it was likely they were related to oxaliplatin:
  - prolonged Grade 4 neutropenia (<0.5 x 10^9/L) lasting more than 7 days;
  - prolonged Grade 4 thrombocytopenia(<10.0 x 10^9/L) lasting more than 7 days;
  - any other non-hematological and Grade 4 toxicity including Grade 4 infection whatever the duration of neutropenia (except alopecia);
  - any non-hematological toxicity ≥Grade 3 except:
    - Grade 3 AST/ALT that returned to baseline by the time of retreatment;
    - Grade 3 fever without documented infection;
    - Grade 3 nausea and vomiting in the absence of effective maximal antiemetic treatment;
    - Grade 3 mucositis.
    - > Grade 2 peripheral neuropathy that does not resolve prior to initiation of the next cycle of therapy;
    - life-threatening toxicity.
- tolerance profiles;
- adverse events (AEs) by NCI-Common Toxicity Criteria (Version 2.0);
- hematology and clinical chemistry.

Criteria for evaluation (cont'd):

Efficacy: Objective response rate, progression-free survival (PFS), response duration.

Pharmacokinetics:

Platinum: *Plasma and plasma ultrafiltrate (PUF)*: The following pharmacokinetic parameters were calculated for the first cycle only with non-compartmental analysis: maximum plasma concentration observed (C_{max}), area under the plasma concentration versus time curve from time 0 to the real time 48h (AUC_{0-48}), area under the plasma concentration versus time curve extrapolated to infinity (AUC), distribution volume at the steady-state (V_{ss}) and plasma clearance (Cl). In addition, the following parameters were calculated using compartmental analysis: alpha half life ($t1/2\alpha$), beta half-life ($t1/2\beta$), and gamma half-life ($t1/2\gamma$).

Pharmacokinetic sampling times and bioanalytical methods:

Sampling:
Week 1 (first cycle D1 to 3): pre-infusion, end-infusion, 30 min, 1, 2, 4, 6, 24, 48 h post-infusion
Week 2 (first cycle D8): pre-infusion and end-infusion.
Week 3 (first cycle D15): pre-infusion and end-infusion.
Week 4 (first cycle no drug, D22): 1 week post last infusion.
Week 5 (start second cycle, D29/D1): pre-infusion.
Assays: Platinum concentrations in plasma and in PUF were determined using a validated Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method with a limit of quantification (LOQ) of 3 and 1 ng/mL, respectively.

Statistical methods:

Safety:

Exposure to oxaliplatin was summarized by number of cycles administered. Total number of cycles, median, minimum, and maximum were shown for each dose group and for the total population.
Adverse events were summarized by all grades and Grade 3,4. Specific neurological events were summarized separately. Dose limiting toxicities were also summarized. All deaths were listed and deaths within 28 days of the last dose of oxaliplatin were summarized. Serious adverse events (SAEs) and AEs leading to study medication discontinuation were summarized.
Clinical laboratory results were summarized.

Efficacy:

Efficacy was not a primary objective of this study. Best overall response to treatment was summarized for all patients enrolled. Ninety-five% confidence limits were calculated.

Pharmacokinetics:

Plasma PK parameters were listed by patient and summarized using descriptive statistics by level.

Summary:

Patient characteristics:

Patient Disposition

	Phase 1	**RD cohort 90 mg/m²**
No. included	29	16
No. treated	28	15
No. in safety population	28	15

Summary (cont'd):

Patient characteristics (cont'd):

Demographic and Baseline Characteristics [n, (%)]

ITT Population	Phase 1	RD cohort 90 mg/m²
Sex: Male	17 (58.6)	7 (43.8)
Female	12 (41.4)	9 (56.3)
Median age (years)	9	7
ECOG		
0	23 (79.3)	10 (62.5)
1	2 (6.9)	4 (25.0)
2	3 (10.3)	1 (6.3)
3	1 (3.4)	0 (0.0)
Type of cancer		
Neuroblastoma	11 (37.9)	7 (43.8)
Osteosarcoma	6 (20.7)	2 (12.5)
Ewing Sarcoma	2 (6.9)	2 (12.5)
Nephroblastoma	2 (6.9)	1 (6.3)
Rhabdomyosarcoma	2 (6.9)	0 (0.0)
Medulloblastoma	1 (3.4)	1 (6.3)
Hepatoblastoma	0 (0.0)	2 (12.5)
Germ cells cancer	2 (6.9)	1 (6.3)
Other Brain tumor	2 (6.9)	0 (0.0)
Other malignant tumor	1 (3.4)	0 (0.0)
Current disease status		
Refractory	3 (10.3)	3 (18.8)
Relapse	26 (89.7)	13 (81.3)

Treatment Administration

Treated Population	Phase 1	RD cohort 90 mg/m²
Number of cycles administered		
40 mg/m²	7	NA
50 mg/m²	13	NA
60 mg/m²	16	NA
75 mg/m²	6	NA
90 mg/m²	10	28
110 mg/m²	7	NA
Total	**59**	**28**
Median (range)	2 (1 – 6)	2 (1 – 4)

NA=not applicable

Safety results:

Dose limiting toxicities

Dose Level	Treated	Evaluable for Toxicity	Protocol Defined DLT	Number of events
40 mg/m²	3	3	None	0
50 mg/m²	6	6	Sepsis	1
60 mg/m²	6	6	None	0
75 mg/m²	4	4	None	0
90 mg/m²	6	6	Dysaesthesia	1
110 mg/m²	3	3	Dysaesthesia Paresthesia	1 1

Summary (cont'd):
Safety results (cont'd):

NCI toxicities (All Grades and Grade 3 + 4) by patient (%)

	Phase 1	RD cohort 90 mg/m^2
	All/Gr 3+4	All/Gr 3+4
Adverse event	**N = 28**	**N = 15**
Any adverse event	100/82	100/73
Paresthesia[a]	50/4	60/7
Abdominal pain	39/11	13/0
Pyrexia	36/4	40/7
Asthenia	29/0	20/0
Headache	25/7	7/0
Vomiting	25/4	27/13
Diarrhea	21/0	27/0
Dysaesthesia	18/7	0/0
Nausea	18/0	7/0

[a] oxaliplatin specific scale

On-study hematology results by patient (%)

	Phase 1	RD cohort 90 mg/m^2
	All/Gr 3+4	All/Gr 3+4
Laboratory test	**N = 28**	**N = 15**
Hemoglobin	86/14	87/27
Neutrophils	39/7	40/7
Platelets	79/29	87/47

Summary of SAEs, withdrawals, and deaths [n, (%)]

	Phase 1 N=28	RD cohort 90 mg/m^2 N=15
Patients with any serious AE	17 (60.7)	8 (52.3)
Patients who discontinued study due to AE	5 (17.9)	6 (40.0)
Number of deaths within 28 days of last dose	2 (7.1)	3 (20.0)
Total number of deaths	23 (82.1)	11 (73.3)

To summarize:
- The DLTs were sepsis at 50 mg/m^2, dysesthesia at 90 mg/m^2 and dysesthesia and paresthesia at 110 mg/m^2. The MTD in the Phase 1 portion of this study was 90 mg/m^2, which was the RD;
- A total of 25 patients (17 Phase 1 and 8 RD cohort) experienced SAEs; 11 patients (5 Phase 1 and 6 RD cohort) withdrew from the study due to AEs;
- There were 23 deaths during Phase 1 and 11 deaths in the RD cohort. Five deaths (2 Phase 1 and 3 RD cohort) were within 28 days of last dose. All deaths were due to disease progression;
- All doses were tolerable; there was mild hematologic toxicity and neurological toxicity;

Summary (cont'd):

Efficacy results:

Best Overall Response Rate

	Number of patients (N=43)
Response rate (n, %)	2 (4.7)
95% confidence interval	0.0-16.0
Tumor control (n, %)	
(CR + PR + SD)	9 (20.9)
95% confidence interval	10.0-37.0

CR = complete response; PR = partial response; SD = stable disease

The 2 partial responses were in neuroblastoma and osteosarcoma

Progression free survival (PFS)

Parameter	**Phase 1 (N= 29)**	**RD Cohort 90 mg/m^2 (N= 16)**
Number of progressors (%)	27 (93.1)	15 (100.0)
Median PFS (months)	1.8	1.8
(95% confidence limits)	(1.3, 1.9)	(1.2, 2.1)

Pharmacokinetic results:

Summary of platinum in plasma pharmacokinetic parameters after the first infusion (first cycle)

Level	**1**	**2**	**3**	**4**	**5**	**6**
Dose	**40 mg/m^2**	**50 mg/m^2**	**60 mg/m^2**	**75 mg/m^2**	**90 mg/m^2**	**110 mg/m^2**
Parameter	**(N=3)**	**(N=6)**	**(N=6)**	**(N=3)**	**(N=20)**	**(N=3)**
C_{max} (ng/mL)	1020 (204)	1210 (209)	1480 (433)	1650 (171)	2070 (495)	2770 (362)
AUC_{0-48} (ng.h/mL)	22000 (1580)	25800 (2910)	30800 (5530)	34800 (4830)	44500 (11100)	60100 (5380)
AUC (ng.h/mL)	69400 [a]	76500 [b] (6980)	92900 [c] (10400)	94000 [a]	121000 [d] (29900)	207000 [e]
$t_{1/2\alpha}$ (h)	0.279 (0.111)	0.259 [f] (0.118)	0.281 (0.164)	0.393 (0.223)	0.386 [g] (0.376)	0.259 [a]
$t_{1/2\beta}$ (h)	8.07 (2.03)	11.8 [f] (1.28)	12.0 (5.30)	15.1 (4.59)	12.1 [g] (7.55)	8.10 [a]
$t_{1/2\gamma}$ (h)	121 (12.2)	124 [f] (19.8)	223 (227)	166 (47.4)	152 [g] (66.4)	129 [a]

[a]: N=2, [b]: N=4, [c]: N=3, [d]: N=8, [e]: N=1, [f]: N=5, [g]: N=18.

C_{max}, AUC_{0-48}, AUC were determined by non-compartmental analysis. AUC values excluded if extrapolated portion of AUC > 30%. $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined by compartmental analysis.

Summary (cont'd):

Pharmacokinetic results (cont'd):

Summary of platinum in PUF pharmacokinetic parameters after the first infusion (first cycle)

Level	1	2	3	4	5	6
Dose	**40 mg/m²**	**50 mg/m²**	**60 mg/m²**	**75 mg/m²**	**90 mg/m²**	**110 mg/m²**
Parameter	**(N=3)**	**(N=6)**	**(N=4)**	**(N=3)**	**(N=17)**	**(N=3)**
C_{max} (ng/mL)	344 (82.2)	481 (143)	489 (171)	669 (400)	696 (287)	926 (45.8)
AUC_{0-48} (ng.h/mL)	1830 (262)	3020 (764)	2990 (624)	3120 (1340)	4880 (1240)	6370 (1090)
AUC (ng.h/mL)	2240 [a]	4350 [b] (947)	4100 (910)	4790 [a]	6670 [c] (1790)	7910 [a]
$t_{1/2\alpha}$ (h)	0.161 (0.038)	0.168 [d] (0.101)	0.193 [e] (0.080)	0.378 [a]	0.248 [f] (0.226)	0.133 [a]
$t_{1/2\beta}$ (h)	10.6 (2.10)	9.61 [d] (2.63)	13.4 [e] (2.66)	10.3 [a]	10.8 [f] (4.89)	13.4 [a]
$t_{1/2\gamma}$ (h)	337 (318)	281 [a] (319)	224 [e] (98.7)	390 [a]	282 [f] (281)	390 [a]
V_{ss} (L)	321 [a]	280 [b] (82.9)	303 (92.4)	349 [a]	362 [c] (206)	273 [a]
Cl (L/h)	8.14 [a]	7.02 [b] (1.58)	7.09 (1.38)	8.04 [a]	8.65 [c] (5.06)	6.66 [a]

[a]: N=2, [b]: N=5, [c]: N=16, [d]: N=5, [e]: N=3, [f]: N=13.

C_{max}, AUC_{0-48}, AUC, V_{ss} and CL values were determined by non-compartmental analysis. $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined by compartmental analysis.

For a 2.75-fold increase in oxaliplatin dose, mean C_{max}, AUC_{0-48} and AUC of platinum in plasma increased by approximately 2.71-, 2.73- and 2.98-fold, respectively, while the values for platinum in PUF increased by approximately 2.69-, 3.48- and 3.53-fold, respectively.

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