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Sponsor / Company: sanofi-aventis **Drug substance(s):** Larotaxel (XRP9881)	**Study Identifier:** NCT00625664 **Study code:** EFC6668
Title of the study: Randomized Study of Larotaxel + Cisplatin (LC) vs. Gemcitabine + Cisplatin (GC) in the First Line Treatment of Locally Advanced /Metastatic Urothelial Tract or Bladder Cancer (EFC6668)	
Study center(s): 98 centers in 18 countries	
Study period: Date first patient enrolled: 18/Feb/2008 Date last patientcompleted: 11/Feb/2010 (analysis cut-off date)	
Phase of development: Phase 3	
Objectives: Primary objective: To demonstrate a statistically significant increase in overall survival (OS) for larotaxel in combination with cisplatin relative to the control arm (gemcitabine in combination with cisplatin) in patients with locally advanced/metastatic urothelial tract or bladder cancer Main key secondary objectives: - To compare Progression Free Survival (PFS) and Objective Response Rate (ORR) between the 2 treatment arms, - To assess the overall safety of the 2 treatment arms	
Methodology: This was a prospective, multicenter, multinational, open label, randomized (1:1) study comparing LC versus GC in patients with locally advanced/metastatic urothelial tract or bladder cancer. During the study, the amendment #4 included the changes recommended by the Data Monitoring Committee: exclusion of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 at study entry and the reduction of doses of the combined chemotherapy in LC arm for all new and ongoing patients: larotaxel from 50 to 40 mg/m² and cisplatin from 75 to 60 mg/m². The CILAB study was prematurely discontinued following the sanofi-aventis decision to stop the larotaxel development, based on the following reasons: - Lack of efficacy for larotaxel over comparators in 3 previous randomized studies conducted in pancreatic and breast cancers. - Dose reduction for larotaxel and cisplatin in CILAB study (from 50 to 40 mg/m² for larotaxel and from 75 to 60 mg/m² for cisplatin) following DMC recommendations in March 2009. - Based on these 2 reasons, the ambitious hypothesis for primary efficacy objective on OS in CILAB study (hazard ratio reduction in OS by 25%) became very unlikely to be met and the study was prematurely stopped before interim analysis.	
Number of patients: Planned: 900 (450 per treatment arm) Randomized (efficacy): 337 (137 before amendment #4; 200 after amendment #4) Treated (safety): 328 (134 before amendment #4; 194 after amendment #4)	
Diagnosis and criteria for inclusion: Previously untreated patients with locally advanced/metastatic urothelial tract or bladder cancer. Patients must have had histology/cytology confirmed Transitional Cell Carcinoma (TCC) with advanced (T4b) or metastatic (M) urothelial tract or bladder cancer.	

Investigational product: Larotaxel (XRP9881) 40 mg/mL vial

Dose: 50 mg/m^2 (pre amendment #4); 40 mg/m^2 (post amendment #4) on Day 1 every 3 weeks

Administration: intravenous

The IP was combined with cisplatin:

Dose: 75 mg/m^2 (pre amendment #4), and 60 mg/m^2 (post amendment #4) on Day 1 every 3 weeks.

Administration: Intravenous

Duration of treatment: Patients were treated until disease progression, unacceptable toxicity, investigator's decision to discontinue, or withdrawal of consent.

Duration of observation: Patients were followed for safety up to 30 days after last infusion. In case of treatment discontinuation and no progression, patients were followed every 8 weeks until disease progression, death or study cut-off date, whichever came first. After progression, patients were to be followed every 3 months until death or cut-off date, whichever came first.

Reference therapy: Gemcitabine

Dose: 1000 mg/m^2 on Days 1, 8 and 15 every 4 weeks

Administration: Intravenous

The reference therapy was combined with Cisplatin:

Dose: 70 mg/m^2 on Day 1 every 4 weeks.

Administration: Intravenous

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was the OS defined as the number of months from the date of randomization to the date of death (from any cause). If death was not observed during the study, OS was censored at the last date the patient was known to be alive or the cut-off date, whichever was earlier.

Secondary efficacy endpoints were PFS and ORR. The PFS was defined as the number of months from the date of randomization to the date of progression (ie, radiological progression) or the date of death (from any cause), whichever earlier. If death or progression was not observed, PFS was censored at the date of last adequate tumor assessment without evidence of progression (ie, date of the latest tumor assessment within a cycle for which the derived overall response is stable disease [SD], partial response [PR] or complete response [CR]) or the cut-off date, whichever was earlier. Patient without post-baseline adequate tumor assessment was censored on the day of randomization. The ORR was defined as the proportion of patients with confirmed CR or PR, according to the RECIST criteria (version 1.0), relative to the number of patients in the intent-to-treat (ITT) population with measurable disease at study entry.

Safety: Safety variables included adverse events (AEs) and clinical laboratory evaluation (including hematology and biochemistry).

Pharmacokinetics:

Sampling: For larotaxel and cisplatin, blood samples were to be collected at designated time-points.

Genotyping: For patients enrolled in LC arm, one blood sample per patient was to be collected before starting study treatment (pre-dosing) or later (before a cycle administration) on for those who have been already enrolled to enable investigation of allelic variants of drug metabolism enzymes and transporters.

Statistical methods:

Efficacy: The primary analysis was performed using the ITT population, which consists of all randomized patients. Overall survival was compared between the 2 treatment arms by the log-rank test procedure at the 5% significant level, stratified by extent of disease (locally advanced or metastatic) as specified at the time of randomization. The estimates of the hazard ratio and corresponding 95% confidence interval were provided using a Cox proportional hazard model stratified by extent of disease (locally advanced or metastatic) as specified at the time of randomization. Overall survival was analyzed using the Kaplan-Meier method and summarized with median and 95% CI of the median. In addition, probabilities of surviving at 3, 6, 9, 12, 15, 18, 21 and 24 months were provided for each treatment group. Kaplan-Meier curves for each of the 2 treatment arms are shown on a single set of axes.

Progression free survival was analyzed in the ITT population with the Kaplan-Meier method and compared between the 2 treatments using a log-rank test stratified by extent of disease (locally advanced or metastatic) as entered in the IVRS. The estimates of the hazard ratio and corresponding 95% confidence interval were provided using a Cox proportional hazard model stratified by extent of disease (locally advanced or metastatic) as specified at the time of randomization. Overall response rate was analyzed in the ITT population with measurable disease at study entry and was summarized using descriptive statistics and 95% confidence intervals. Comparison between treatment groups was performed using Cochran-Mantel-Haenszel test, stratified according to extent of disease (locally advanced or metastatic).

Safety: AEs and laboratory data were analyzed in the all-treated (AT) population. Adverse events were coded according to Medical Dictionary for regulatory activities (MedDRA) Version 13.0 and summarized by treatment group, using descriptive statistics. The National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) version 3.0 was used to grade AEs and laboratory abnormalities.

Pharmacokinetics: The PK calculations were not performed due to premature termination of the study but concentrations have been determined for some patients (results are included in bioanalytical reports).

The genotyping analysis was to be performed to investigate:

- relationships between the allelic variants of drug metabolism enzymes (CYP 2C8, CYP 3A5, CYP3A4, CYP1B1, CY4B1, GSTT1, GSTP1, GSTA4, NAT2, CHST3, SULT1C2, EPHX1) and of transporters (P-gp (ABCB1), BCRP (ABCG2), MPR2 (ABCC2), ABCC6, SLCO1B3) and plasma clearance of larotaxel.
- relationships between the allelic variants of drug metabolism enzymes and of transporters and safety endpoints.

Summary: The current report is a synopsis-style report, and as such, presents main efficacy and safety results. Detailed efficacy and safety data are available in the appendices.

The study was prematurely terminated on 11 February 2010 due to a sanofi-aventis decision to stop larotaxel development. Due to this premature discontinuation, only 337 patients were randomized and some analyses planned in the protocol were not performed.

Demography:

A total of 337 patients aged 35 to 85 years old were randomized and 278 patients were off treatment (82.5%) at the study cut-off date. The 2 main reasons for treatment discontinuation were disease progression (30.3%) and adverse event (28.2%). Among these 337 randomized patients, 277 (82.2%) were male and 60 (17.8%) were female. The ECOG PS was 0 in 141 patients (44.3%), 1 in 164 patients (51.6%) and 2 in 13 patients (4.1%) randomized before amendment # 4 (exclusion of patients with ECOG PS 2 at study entry).

Study treatment exposure:

The median number of cycles administered was 5 in LC arm (1 cycle = 3 weeks) and 4 in GC arm (1 cycle = 4 weeks), corresponding to a treatment exposure of 15 and 16 weeks, respectively.

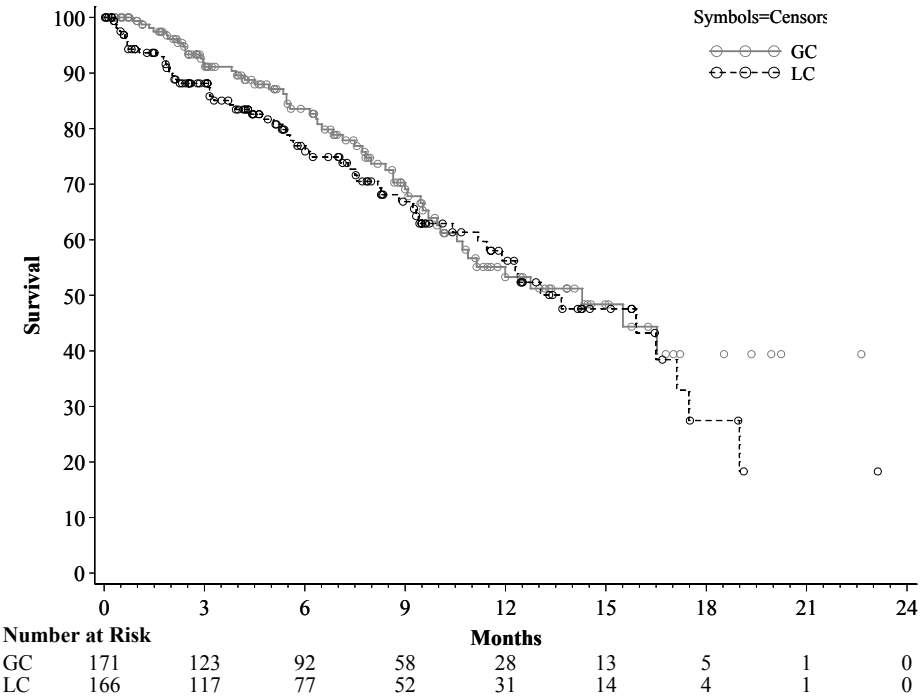
Efficacy results: The OS analysis was based on a total of 107 deaths (56 deaths in LC arm and 51 in GC arm). Median survival times were 13.67 months (95%CI: 11.17 to 17.12) in LC arm and 14.29 months (95%CI: 10.55 to not calculable) in GC arm. The stratified p-value of the statistical test on OS was 0.33. The hazard ratio of LC arm versus GC arm was 1.21 (95% CI: 0.825 to 1.763) (see Table 1). Kaplan-Meier plot of OS (months) by arm is presented in Figure 1.

Table 1 - Overall survival – ITT population

	Larotaxel + Cisplatin (N=166)	Gemcitabine + Cisplatin (N=171)
Overall Survival		
Number of events, n/N (%)	56/166 (33.7%)	51/171 (29.8%)
Median survival (95% CI) (months)	13.67 (11.170 to 17.117)	14.29 (10.546 to NC)
Probability of surviving (95% CI)		
3 months	0.881 (0.830 to 0.933)	0.911 (0.865 to 0.957)
6 months	0.769 (0.696 to 0.842)	0.836 (0.772 to 0.899)
9 months	0.668 (0.580 to 0.757)	0.703 (0.617 to 0.788)
12 months	0.562 (0.458 to 0.666)	0.533 (0.426 to 0.640)
15 months	0.476 (0.357 to 0.594)	0.484 (0.366 to 0.601)
18 months	0.274 (0.108 to 0.441)	0.394 (0.246 to 0.542)
21 months	0.183 (0.000 to 0.367)	0.394 (0.246 to 0.542)
24 months	0.183 (0.000 to 0.367)	0.394 (0.246 to 0.542)
Stratified Log-Rank test p-value[a] vs G+C	0.3343	-
Stratified Hazard ratio (95% CI)[a] vs G+C	1.206 (0.825 to 1.763)	-
Unstratified Log-Rank test p-value vs G+C	0.3365	-
Unstratified Hazard ratio (95% CI) vs G+C	1.204 (0.824 to 1.761)	-

[a]: Stratified on extent of disease as per randomization.
Median follow-up = 8.28 months for larotaxel + cisplatin arm and 8.77 months for gemcitabine + cisplatin arm
NC: not calculable

Figure 1 - Kaplan-Meier curves of overall survival – ITT population



The PFS analysis was based on a total of 184 events (101 events in LC arm and 83 events in GC arm). Median PFS were 5.62 months in LC arm and 7.62 months in GC arm. The hazard ratio of LC arm versus GC arm was 1.67 (95% CI: 1.243 to 2.246).

Thirty-one patients (20.9%) in LC arm and 54 patients (33.5%) in GC arm had a complete or partial response.

Safety results: Overall incidence of treatment emergent adverse events all grades (NCI-CTCAE v.3.0) was comparable between the 2 arms (97.5% in LC arm and 98.8% in GC arm) but more grade 3-4 events were reported with GC than with LC (77.1% versus 56.8%).

The most frequent (>20%) treatment emergent adverse events (TEAEs) by preferred term any grade and grade 3-4 in LC arm (excluding laboratory abnormalities) were fatigue (64.2%; grade 3-4: 13.6%), nausea (55.6%; grade 3-4: 3.1%), diarrhea (45.7%; grade 3-4: 12.3%), vomiting (37.7%; grade 3-4: 4.9%), decreased appetite (31.5%; grade 3-4: 3.7%), constipation (24.7%; grade 3-4: 1.2%), neuropathy sensory (22.8%; grade 3-4: 3.1%), abdominal pain (20.4%; grade 3-4: 1.2%) and alopecia (20.4%; no grade 3-4).

The most frequent (>20%) TEAEs by preferred term any grade and grade 3-4 in GC arm (excluding laboratory abnormalities) were fatigue (65.1%; grade 3-4: 13.9%), nausea (50.6%; grade 3-4: 2.4%), vomiting (28.9%; grade 3-4: 3.0%), constipation (27.7%; grade 3-4: 0.6%) and decreased appetite (21.1%; no grade 3-4).

The following TEAEs by preferred term any grade were more frequent (>10%) in LC arm than in GC arm: diarrhea (45.7% vs. 16.9%) and decreased appetite (31.5% vs. 21.1%).

Grade 3-4 hematological abnormalities were more frequent in GC arm than in LC arm: neutropenia (60.2% vs. 35.3%), anemia (21.7% vs 7.5%), and thrombocytopenia (45.2% vs. 1.9%). The incidence of febrile neutropenia was similar between both arms (3 patients in each arm). The incidence of neutropenic infection was 1.9% and 4.2% in LC and GC arms, respectively.

A total of 14 (8.6%) and 12 (7.2%) patients died during the on-treatment period (ie, within 30 days after last dose) in LC and GC arms, respectively. More patients died due to adverse event in LC arm than in GC arm (4.9% vs. 1.2%). The 8 fatal AEs in LC arm were acute respiratory failure, cardiac arrest, convulsion, diarrhea, neutropenic infection, pneumonia aspiration, septic shock and shock haemorrhagic. The 2 fatal AEs in GC arm were neutropenic infection and pulmonary embolism.

A total of 64 (39.5%) and 65 (39.2%) patients experienced at least one serious adverse event (SAE) in LC and GC arms, respectively. The following SAEs were more frequent in LC arm than in GC arm: diarrhea (6.2% vs. 0%) and vomiting (5.6% vs. 0.6%).

A total of 45 (27.8%) and 50 (30.1%) patients discontinued study treatment due to adverse event in LC and GC arms, respectively. The following AEs leading to treatment discontinuation were more frequent in LC arm than in GC arm: neuropathy sensory (4.9% vs. 0.6%), fatigue (3.7% vs. 2.4%), nausea (3.1% vs. 0.6%) and diarrhea (2.5% vs. 0%).

Three patients experienced Grade 3-4 AST and/or ALT in LC arm.

In LC arm, the number of patients with TEAE grade 3-4, the number of patients who died during the study treatment period and the number of patients who discontinued the study treatments due to TEAEs decreased after amendment # 4: 61.8% vs. 53.2%, 14.7% vs. 4.3% and 35.3% vs. 22.3%, respectively.

Table 2 - Overview of TEAEs, number (%) of patients – Safety population

n(%)	Larotaxel + Cisplatin (N=162)	Gemcitabine + Cisplatin (N=166)
Patients with any TEAE	158 (97.5%)	164 (98.8%)
Patients with any TEAE of grade ≥ 3	92 (56.8%)	128 (77.1%)
Patients with any TEAE of grade ≥ 3 excluding laboratory abnormalities	82 (50.6%)	81 (48.8%)
Patients with any TEAE of grade ≥ 3 excluding clinical progression	92 (56.8%)	128 (77.1%)
Patients with any TEAE of grade ≥ 3 excluding laboratory abnormalities and clinical progression	82 (50.6%)	80 (48.2%)
Patients with any related TEAE	151 (93.2%)	150 (90.4%)
Patients with any related grade 3-4 TEAE	70 (43.2%)	109 (65.7%)
Patients with any treatment emergent SAE	64 (39.5%)	65 (39.2%)
Patients with any related treatment emergent SAE	37 (22.8%)	29 (17.5%)
Patients with any TEAE leading to death	14 (8.6%)	12 (7.2%)
Patients with any TEAE leading to permanent treatment discontinuation	45 (27.8%)	50 (30.1%)

TEAE: Treatment emergent adverse event, SAE: Serious Adverse Event
n (%) = number and percentage of patients with at least one TEAE

Table 3 - Summary of TEAEs occurring in at least 5% of patients or at least 2 patients for grade 3-4 events presented by grouped preferred term (worst grade by patients) and sorted by decreasing order of frequency in larotaxel arm, number (%) of patients – Safety population

	Larotaxel + Cisplatin (N=162)		Gemcitabine + Cisplatin (N=166)	
Grouped preferred term	**All grades**	**Grades 3,4**	**All grades**	**Grades 3,4**
Any events	158 (97.5%)	92 (56.8%)	164 (98.8%)	128 (77.1%)
Fatigue[a]	104 (64.2%)	22 (13.6%)	108 (65.1%)	23 (13.9%)
Nausea	90 (55.6%)	5 (3.1%)	84 (50.6%)	4 (2.4%)
Diarrhea including Colitis and Enteritis[a]	74 (45.7%)	20 (12.3%)	28 (16.9%)	2 (1.2%)
Vomiting	61 (37.7%)	8 (4.9%)	48 (28.9%)	5 (3.0%)
Decreased appetite	51 (31.5%)	6 (3.7%)	35 (21.1%)	0
Constipation	40 (24.7%)	2 (1.2%)	46 (27.7%)	1 (0.6%)
Neuropathy sensory[a]	37 (22.8%)	5 (3.1%)	23 (13.9%)	1 (0.6%)
Abdominal pain[a]	33 (20.4%)	2 (1.2%)	19 (11.4%)	2 (1.2%)
Alopecia	33 (20.4%)	0	20 (12.0%)	0
Urinary tract infection	29 (17.9%)	5 (3.1%)	26 (15.7%)	6 (3.6%)
Neutropenia	22 (13.6%)	17 (10.5%)	71 (42.8%)	62 (37.3%)
Stomatitis/Mucositis[a]	22 (13.6%)	1 (0.6%)	13 (7.8%)	1 (0.6%)
Dysgeusia	21 (13.0%)	0	14 (8.4%)	0
Fever[a]	19 (11.7%)	0	32 (19.3%)	1 (0.6%)
Weight decreased	19 (11.7%)	1 (0.6%)	12 (7.2%)	0
Oedema peripheral	18 (11.1%)	1 (0.6%)	19 (11.4%)	1 (0.6%)
Creatinine renal clearance decreased	16 (9.9%)	3 (1.9%)	8 (4.8%)	0
Back pain	14 (8.6%)	2 (1.2%)	20 (12.0%)	3 (1.8%)
Insomnia	13 (8.0%)	0	14 (8.4%)	0
Blood creatinine increased	12 (7.4%)	0	15 (9.0%)	0
Hypersensitivity	12 (7.4%)	4 (2.5%)	0	0
Dyspepsia	11 (6.8%)	0	7 (4.2%)	0
Headache	10 (6.2%)	1 (0.6%)	14 (8.4%)	1 (0.6%)
Arthralgia	9 (5.6%)	2 (1.2%)	6 (3.6%)	2 (1.2%)
Dizziness	9 (5.6%)	1 (0.6%)	13 (7.8%)	0
Dyspnoea	9 (5.6%)	2 (1.2%)	16 (9.6%)	1 (0.6%)
Hiccups	9 (5.6%)	0	8 (4.8%)	0
Haematuria	8 (4.9%)	0	14 (8.4%)	0
Pain in extremity	8 (4.9%)	0	11 (6.6%)	1 (0.6%)
Renal impairment	7 (4.3%)	2 (1.2%)	8 (4.8%)	2 (1.2%)
Anxiety	6 (3.7%)	0	9 (5.4%)	0
Cough	6 (3.7%)	0	14 (8.4%)	0
Anaemia	5 (3.1%)	2 (1.2%)	21 (12.7%)	11 (6.6%)
Deep vein thrombosis	5 (3.1%)	4 (2.5%)	12 (7.2%)	5 (3.0%)
Dehydration	5 (3.1%)	2 (1.2%)	4 (2.4%)	0
Pain	5 (3.1%)	2 (1.2%)	6 (3.6%)	2 (1.2%)

Grouped preferred term	Larotaxel + Cisplatin (N=162)		Gemcitabine + Cisplatin (N=166)	
	All grades	Grades 3,4	All grades	Grades 3,4
Pelvic pain	5 (3.1%)	0	4 (2.4%)	3 (1.8%)
Gastrointestinal obstruction[a]	4 (2.5%)	4 (2.5%)	2 (1.2%)	2 (1.2%)
Febrile neutropenia	3 (1.9%)	3 (1.9%)	3 (1.8%)	3 (1.8%)
Hyponatraemia	3 (1.9%)	3 (1.9%)	1 (0.6%)	1 (0.6%)
Neutropenic infection	3 (1.9%)	2 (1.2%)	7 (4.2%)	5 (3.0%)
Renal failure	3 (1.9%)	3 (1.9%)	0	0
Renal failure acute	3 (1.9%)	3 (1.9%)	4 (2.4%)	4 (2.4%)
Syncope	3 (1.9%)	3 (1.9%)	2 (1.2%)	2 (1.2%)
Atrial fibrillation	2 (1.2%)	1 (0.6%)	3 (1.8%)	2 (1.2%)
Bacteraemia	2 (1.2%)	2 (1.2%)	1 (0.6%)	0
Disease progression	2 (1.2%)	2 (1.2%)	8 (4.8%)	8 (4.8%)
Hydronephrosis	2 (1.2%)	1 (0.6%)	4 (2.4%)	3 (1.8%)
Leukopenia	2 (1.2%)	2 (1.2%)	9 (5.4%)	7 (4.2%)
Respiratory failure	2 (1.2%)	2 (1.2%)	0	0
Urinary retention	2 (1.2%)	0	3 (1.8%)	2 (1.2%)
Urosepsis	2 (1.2%)	2 (1.2%)	3 (1.8%)	3 (1.8%)
Ischaemic stroke	1 (0.6%)	1 (0.6%)	2 (1.2%)	2 (1.2%)
Pulmonary embolism	1 (0.6%)	1 (0.6%)	8 (4.8%)	6 (3.6%)
Sudden death	1 (0.6%)	1 (0.6%)	2 (1.2%)	2 (1.2%)
Neutrophil count decreased	0	0	3 (1.8%)	3 (1.8%)
Platelet count decreased	0	0	11 (6.6%)	9 (5.4%)
Thrombocytopenia	0	0	77 (46.4%)	59 (35.5%)
White blood cell count decreased	0	0	3 (1.8%)	2 (1.2%)

[a]: Grouped preferred term
TEAE: Treatment emergent adverse event
MEDDRA 13.0
N= number of patients

One 59-year-old patient, from Netherlands, was inadvertently treated on 23 May 2008 with the CILAB study treatment whereas this patient was not randomized in the study. This patient had a lung cancer and was to receive docetaxel and cisplatin. Following the administration of the treatment (larotaxel 87 mg and cisplatin 130 mg), she experienced the following related adverse events: nausea grade 1, alopecia grade 1, mucositis grade 2 and hypotension grade 1. All these adverse events were on going as of 13 June 2008 (except hypotension which recovered on 12 June 2008). The treatment was corrected and she received her right treatment (docetaxel and cisplatin) with a total of 4 cycles of docetaxel and cisplatin. No safety concerns noticed during the further evaluations (last one performed in January 2010).

Genotyping:

None of the genotyped loci was associated to diarrhea and neutropenia (grade 3-4) at the pre-specified false discovery rate of 5%. In this study the largest effect size (allelic odds ratio) and the lowest p-value are detected with neutropenia (grade 3-4) and 2 uncorrelated (r^2=0.19) loci located within the SLCO1B3 gene. The haplotype SLCO1B3 334-699 has an allelic odds ratio of 5.56 (95% CI [1.45 to 21.34]) and a FDR-adjusted p-value of 0.2. The locus SLCO1B3_rs2117032 (mutation in 3'UTR of the SLC01B3 gene) has an allelic odds ratio of 0.28 (95% CI [0.10 to 0.77]) and a FDR-adjusted p-value of 0.2. Further investigation of association between taxoid-induced neutropenia (grade 3-4) and candidate genes polymorphisms, with particular emphasis on the SLCO1B3 gene is suggested.

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