CLINICAL TRIAL SUMMARY REPORT

Acronym: SIOPEL 6
Title: A multi-centre open label randomised phase III trial of the efficacy of Sodium Thiosulphate in reducing ototoxicity in patients receiving Cisplatin chemotherapy for Standard Risk Hepatoblastoma
Sponsor: University of Birmingham
Sponsor Ref Number: RG_09-205
EudraCT Number: 2007-002402-21
REC Reference Number: 07/MRE04/37
Details of Investigational Medicinal Product(s) Cisplatin and Sodium Thiosulphate (STS)
Details of Non-Investigational Medicinal Product(s) N/A
Arms: Cisplatin only **Cisplatin + STS**
Analysis Stage: Final
Start Date: Nov-2007
End of Trial: 08-May-2018

This report was prepared by the Chief Investigator and the Cancer Research UK Clinical Trials Unit (CRCTU) on behalf of the Sponsor.

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Date: **07-Nov-2018**

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1. SYNOPSIS

1.1 Trial overview

1.1.1 Primary objective

To assess the efficacy of Sodium Thiosulphate (STS) to reduce the hearing impairment caused by Cisplatin (CIS) chemotherapy

1.1.2 Primary end-point

Rate of Brock grade ≥1 hearing loss determined after end of trial treatment or at an age of at least 3.5 years, whichever is later (Brock 1991)

1.1.3 Secondary objectives

- To carefully monitor any potential impact of STS on response to Cisplatin and survival.
- To assess the short- and long-term tolerability of the combination of STS and Cisplatin.
- To prospectively evaluate and validate biological, radiological and pathological features of standard risk hepatoblastoma for future risk adapted management.
- To investigate the effect of STS on the formation of Cisplatin-DNA adducts.
- To prospectively collect patient DNA specifically for the analysis of possible genetic factors that may contribute to the development of treatment related ototoxicity and nephrotoxicity

1.1.4 Secondary endpoints

- Response to preoperative chemotherapy
- Complete resection
- Complete remission
- Event free survival (EFS)
- Overall survival (OS)
- Toxicity as graded by CTCAE v 3.0
- Long-term renal clearance
- Feasibility of central audiology review

1.1.5 Trial design

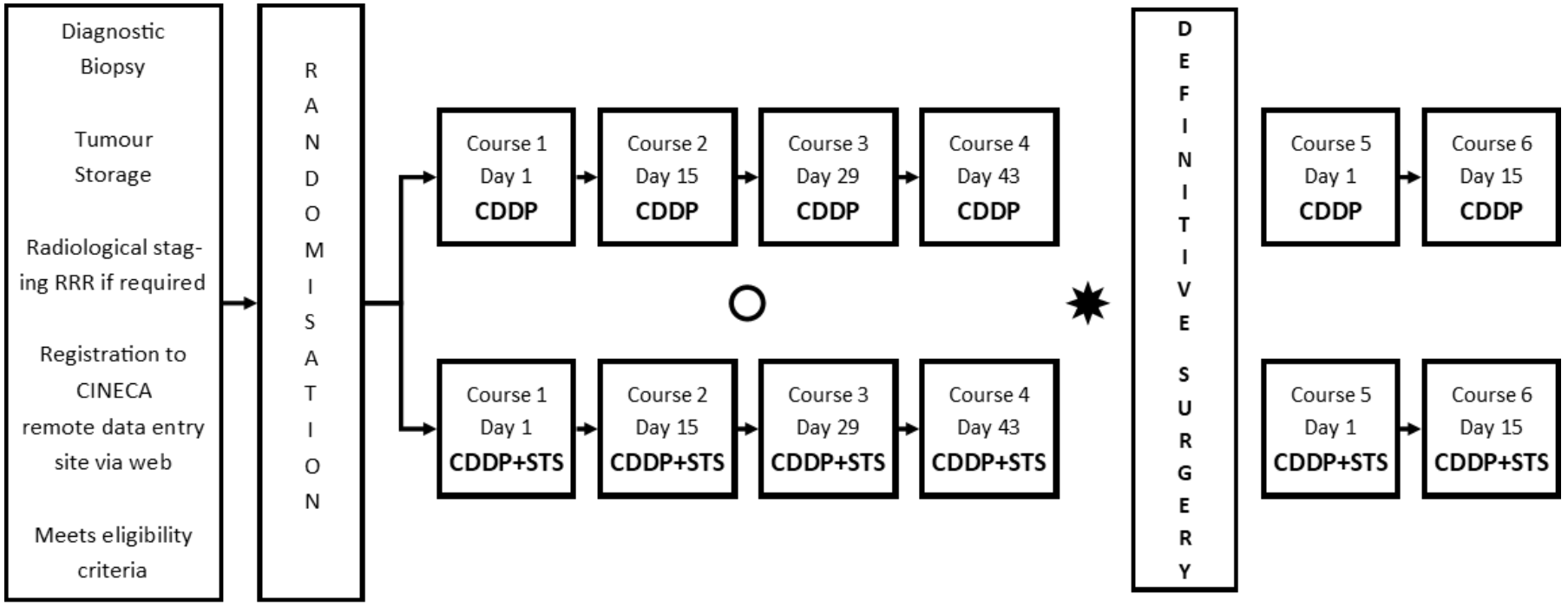
Randomised phase III clinical trial: 1:1 randomisation between Cisplatin alone and Cisplatin + Sodium Thiosulphate.

1.1.6 Eligibility

Standard-risk hepatoblastoma patients are patients who are considered operable at time of diagnosis. The main eligibility criteria are:

- Histologically confirmed newly diagnosed hepatoblastoma
- Standard risk hepatoblastoma
- PRETEXT I, II or III
- Serum alpha-fetoprotein (AFP) > 100 µg/L
- No additional PRETEXT criteria
- Age ≤ 18 years and > 1 month

1.2 Trial schema



○ Assessment of response in case of progressive disease (see section 9.4)

✸ Assessment of response and resectability. If surgery has to be delayed for any reason, 1 - 2 further courses of chemotherapy can be administered pre-operatively instead of post-operatively.

1.3 Trial conduct

The trial protocol was distributed to interested sites in October 2007 and activated in the first site (Great Ormond Street Hospital, London) in November 2007. It is the logical follow-up trial to the standard risk SIOPEL 3 randomised trial which showed that 4 cycles of pre-operative cisplatin monotherapy is not inferior to 4 cycles of the combination of cisplatin and doxorubicin (Perilongo 2009).

The primary objective was to assess the efficacy of Sodium Thiosulfate (STS) to reduce the hearing impairment caused by Cisplatin chemotherapy.

The present report reflects the status of the trial as of September 2018. It constitutes the final report of the trial.

The experimental substance STS was delivered free of charge by the company Adherex, now Fennec Pharma, 68 TW Alexander Drive, Research Triangle Park, NC 27709

The trial had no international sponsor, in each participating country, a national group or institution took over the responsibilities of the sponsor. This was the University of Birmingham in the UK post 1st April 2010 (Children's Cancer and Leukaemia Group, University of Leicester, pre-1st April 2010).

The overall SIOPEL 6 project was coordinated by SIOPEL (Société Internationale d'Oncologie Pédiatrique – Epithelial Liver Tumor Study Group) with an International Protocol Chairman, Dr. Penelope Brock. The central database was hosted by CINECA, Italy.

The analysis was conducted by Dr Rudolf Maibach, IBCSG Coordinating Center, Bern, Switzerland

1.4 Ethics

The trial protocol was submitted to and accepted by ethics committees and regulatory authorities according to national and local regulations. In the UK the study was approved by East Midlands - Derby Research Ethics Committee (formerly Trent Research Ethics Committee) under reference 07/MRE04/37 and the Medicines and Health Care products Regulatory Agency CTA 21275/0235/001-0001

Parents / children (as applicable) were asked to give and sign informed consent. Only patients for whom informed consent was signed were included in the protocol.

1.5 Treatment

Trial treatment consisted of the following phases (see trial schema):

Pre-surgery: 4 courses on day 1, 15, 29 and 43 (exceptionally, if surgery is delayed, courses may also be given on day 57 and 71).

Post-surgery: as soon as possible, but within 21 days: 2 courses (day 1 and 15). If surgery has to be delayed for any reason, 1-2 further courses of chemotherapy can be administered pre-operatively instead of post-operatively.

<u>Cisplatin</u>

For children > 10kg:	80 mg/m^2 IV infusion over 6 hours
For infants and children 5-10kg:	2.7 mg/kg IV infusion over 6 hours
For infants < 5kg:	1.8 mg/kg IV infusion over 6 hours

<u>Sodium Thiosulphate</u> for children randomised to receive STS:

For children > 10kg:	20 g/m^2 IV infusion over 15 minutes
For infants and children 5-10kg:	15 g/m^2 IV infusion over 15 minutes
For infants < 5kg:	10 g/m^2 IV infusion over 15 minutes

If there was progressive disease at evaluation after 2 or more cycles of trial treatment, i.e. Cisplatin with or without STS, the trial treatment was to be stopped. No further STS was to be given to the patient. As salvage treatment, it was advisable to give chemotherapy pre-operatively and the combination Cisplatin-Doxorubicin (PLADO) was recommended (standard arm of SIOPEL 3 treatment).

Surgical removal of all remaining tumour lesions or liver transplantation, if needed.

Post-operative chemotherapy (course 5 and 6), except if administered preoperatively.

1.6 Design and sample size

The trial was designed to detect a 25% reduction in the rate of Brock grade ≥1 hearing loss with a chi-squared test, from a 60% hearing loss in the Cisplatin alone arm to a 35% hearing loss in the Cisplatin + STS arm, using a one-sided chi-squared test with significance level of 5% and power of 80%. A total of 102 evaluable patients needed to be recruited to achieve this power.

1.7 Criteria for early stopping

Early stopping may be warranted in case of convincing evidence that a reduction in hearing impairment by at least 25% is corroborated. Interim analyses were conducted at 1/3 and 2/3 of process time, i.e. after 34 and 68 patients were evaluable for the primary endpoint. If the nominal alpha levels for the test of the primary endpoint were <0.00069 (34 pts), <0.016 (68 pts), early stopping of the trial was to be considered. The final test was to be carried out at nominal alpha level of 0.045.

In case of concerns of an adverse effect of STS on the short-term efficacy of the Cisplatin chemotherapy, the trial may be stopped early as well. Interim efficacy results on response to chemotherapy were evaluated after every 20 patients and submitted immediately to the International Data Monitoring Committee (IDMC) and the trial committee. The IDMC and the trial committee independently reviewed the results. The IDMC was to formulate a recommendation to the trial committee.

If interim efficacy results observed in this trial were worse than observed in SIOPEL 2 and 3, or if the rate of early progressive disease after 2 cycles had raised concerns, early closure of the trial was to be considered.

After each 20 patients (10 per arm), the rates of progression in the two arms and their difference (rate of PD in CIS+STS arm minus (rate of PD in CIS arm) were to be calculated. If the 95% lower confidence limit (LCL) for the difference were above zero this meant that there was a higher rate of early progression in the CIS+STS arm, and the trial would be recommended for closure due to a negative effect of STS on response to chemotherapy.

2. TRIAL PATIENTS

2.1 Participating sites

Patients were registered by 45 institutions from Australia, Belgium, Denmark, France, Ireland, Italy, Japan, New Zealand, Spain, Switzerland, UK, and USA.

The accrual only really started in 2010 due to major difficulties in starting up sites, mainly related to the lack of single global sponsorship. Recruitment of the 109 randomised and analysable patients (see section 2.2.) was:

Year	# patients
2007	2
2008	1
2009	8
2010	19
2011	16
2012	17
2013	17
2014	28

Recruitment by country:

Country	Frequency	Percent
Australia	5	4.59
Belgium	6	5.50
Denmark	1	0.92
France	32	29.36
Ireland	2	1.83
Italy	7	6.42
Japan	5	4.59
New Zealand	3	2.75
Switzerland	2	1.83
Spain	5	4.59
UK	39	35.78
USA	2	1.83

The first patient was recruited on 1512.2007; the last patient was recruited on 0912.2014. Last patient last visit was 28.02.2018. The first UK patient was recruited on 15.12.2007; the last UK patient was recruited on 22.02.2017

The following sites recruited the 109 analysed patients:

Country	Centre name	City	Count
Australia	John Hunter Children's Hospital	Newcastle	1
Australia	Sydney Children's Hospital	Randwick	1
Australia	Royal Children's Hospital	South Brisbane	3
Belgium	University Hospital Ghent	9000	3
Belgium	ZNA Child Hospital	Antwerp	1
Belgium	Clinique Universitaire Saint Luc	Brussels	1
Belgium	University Hospitals Leuven	Leuven	1
Denmark	Rigshospitalet	Copenhagen	1
France	Institute Gustave Roussy	Paris	5
France	Hopital des Enfants	Toulouse	1
France	CHU d'Amiens	Amiens	1
France	CHU de Besancon	Besancon	2
France	CHU Pellegrin - Enfant	Bordeaux	2
France	CHU Cote de Nacre	Caen	1
France	CHU Reims	Reims	1
France	CHU Dijon	Dijon	2
France	CHU Grenoble	Grenoble	1
France	Centre Oscar Lambret	Lille	2
France	CHU Timone Enfants	Marseille	3
France	CHU Arnaud de Villeneuve	Montpellier	1
France	HME Nantes	Nantes	1
France	G.H. Armand Trousseau	Paris	2
France	Institut Curie	Paris	4
France	CHU-Rouen	Rouen	1
France	CHU Hautepierre	Strasbourg	1
France	Hopitaux de Brabois-Hopital D'Enfants	Vandoeuvre	1
Ireland	Our Lady's Children's Hospital, Crumlin	Dublin	2
Italy	Policlinico of Catania	Catania	1
Italy	Department of Paediatrics	Padova	4
Italy	Ospedale Bambino Gesu IRCCS	Roma	2
Japan	Hiroshima University	Hiroshima	5
New Zealand	Starship Children's Hospital	Auckland	2
New Zealand	Christchurch Hospital	Christchurch	1
Switzerland	Universitätskinderspital beider Basel	Basel	1
Switzerland	University Children's Hospital	Zurich	1
Spain	University Hospital Reina Sofia	Cordoba	3
Spain	Hospital Materno-Infatil Carlos Haya	Malaga	2

Country	Centre name	City	Count
UK	Birmingham Children's Hospital	Birmingham	3
UK	Bristol Royal Hospital for Children	Bristol	4
UK	Addenbrooke’s Hospital	Cambridge	2
UK	Royal Hospital for Sick Children	Edinburgh	1
UK	Royal Hospital of Sick Children	Glasgow	3
UK	Leeds General Infirmary	Leeds	1
UK	Leicester Royal Infirmary	Leicester	1
UK	Great Ormond Street Hospital	London	13
UK	Sir James Spence Institute of Child Health	Newcastle upon Tyne	2
UK	Queen's Medical Centre	Nottingham	1
UK	Royal Manchester Children’s Hospital	Manchester	4
UK	Sheffield Children's Hospital	Sheffield	1
UK	Children's Hospital Cardiff	South Glamorgan	2
UK	Southampton General Hospital	Southampton	1
USA	Stanford University LPCH	Palo Alto	2

2.2 Patient populations

129 patients were registered in the database. Registration was done prior to the eligibility check, because SIOPEL's intent was to register all hepatoblastoma patients irrespective of their inclusion in a therapeutic trial.

116 patients were originally coded as eligible:

Randomised to	eligibility			
	Not documented	No	Yes	Total
Not randomised	10	2	3	15
CIS alone	0	0	53	53
CIS+STS	0	1	60	61
Total	10	3	116	129

Two were not randomised:

#166 Eligible, not rand. due to organisational problems

#188 Parent refusal, patient not randomised

114 patients were randomised. However, one patient was ineligible (#151). The eligibility was set to "no" by the central data manager 1 week after randomisation, upon request of site.

This leaves ***113 eligible and randomised***.

Of these, 2 had to be excluded due to parental refusal:

#185 Randomised to CIS+STS, but parents withdrew consent before treatment start

#205 Randomised to CIS+STS, not evaluable due to parental refusal of any further documentation, not treated with STS because arrived too late at the site.

two additional patients were identified as ***ineligible*** shortly ***after*** randomisation:

#212 randomised to CIS+STS but then scans were sent to review radiologist who reclassified the patient as high risk; patient was taken off protocol treatment and will not be documented or followed up

#207 randomised to CIS but then scans were sent to review radiologist who reclassified the patient as high risk; patient was taken off protocol treatment and will not be documented or followed up

These 4 patients are not documented any further and cannot be analysed.

Therefore, the ITT population consists of 109 pts, of which ***52 were randomised to the CIS arm and 57 to the CIS+STS arm***.

Per protocol population:

Four patients (#117, #141, #170, and #202) randomised to the CIS+STS arm never received any STS because the drug did not arrive at the treating site in time.

The per protocol population therefore comprises 105 patients, of which 52 were randomised to the CIS alone arm and 53 to the CIS+STS arm.

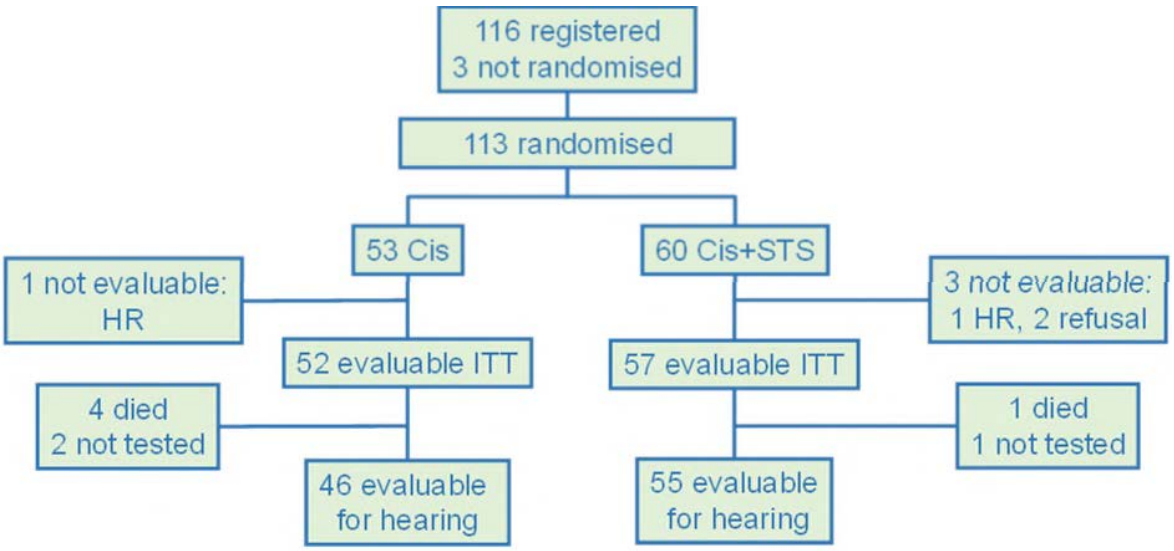
As treated population:

The four patients (#117, #141, #170, #202) randomised to the CIS+STS arm, but treated according to the CIS alone arm, are evaluated in the CIS alone arm. Any evaluation "as treated" of the primary endpoint provides only ancillary evidence, since it does not take the randomisation into account. It is however interesting with respect to the anti-cytotoxic effect of cisplatin chemotherapy.

2.3 Patients included in report

The evaluation comprises the ITT population of 109 patients, and the per protocol population of 105 patients. 101 patients are evaluable for hearing.

CONSORT diagram:



2.4 Patient and disease characteristics at randomisation

For ITT population

Characteristic	**CIS Alone N=52**	**CIS+STS N=57**
Age (range), months	13.4 (3.0-70.2)	12.8 (1.2-98.6)
Sex, n (%) male	29 (56%)	30 (53%)
AFP, median (range), ng/mL	73,760 (187-2,175,690)	154,638 (273-4,536,500)
PRETEXT, n (%) I/II III	 31 (60%) 21 (40%)	 41 (72%) 16 (28%)
Weight class less than 5kg 5 - 10kg more than 10kg	 1 (2%) 27 (52%) 24 (46%)	 1 (2%) 31 (54%) 25 (44%)

3. TREATMENT

3.1 Pre- and postoperative chemotherapy

The 109 patients received a total of 664 cycles, 471 pre-surgery and 193 post-surgery, including 55 cycles documented on PLADO (=cisplatin + doxorubicin) forms.

Treatment	CIS	CIS+STS	Total
Pre-operative Course 1+2	104	114	218
Pre-operative Course 3+4	97	112	209
Pre-operative Course 5+6	86	96	182
Additional chemotherapy PLADO	27	28	55
Total	314	350	684

Four cycles were planned to be administered pre surgery. Patients received the following number of cycles preoperatively:

# cycles	Frequency	Percent
2	3	2.7
3	2	1.8
4	80	73.4
5	12	11.0
6	8	7.3
7	1	0.9
8	3	2.8

One patient received 7 and three received 8 cycles pre-operatively, for disease-related reasons.

Two cycles were planned to be administered after surgery. Patients received the following number of cycles postoperatively:

# cycles	Frequency	Percent
0	13	11.9
1	11	10.1
2	78	71.6
3	3	2.8
4	3	2.8
5	1	0.9

3.2 STS treatment

Several patients did not receive STS per protocol:

Four patients (#117, #141, #170, #202) randomised to the CIS+STS arm never received any STS because the drug did not arrive at the treating site in time.

Six patients did not receive all planned STS administrations due to non-medical reasons:

#109, cycle 1 (STS not yet available)

#132, cycle 1 (STS not yet available)

#160, postoperative cycles 5 and 6 (parental refusal)

#163, cycle 4 (STS not available)

#169, cycles 5-6 (parental refusal)

#220, cycles 4-6 (parental refusal)

#229, cycles 5-6 (parental refusal)

In addition, ten patients (#105, #109, #112, #135, #137, #138, #157, #179, #186, #204, #216, #225) stopped STS
due to early progression, toxicity, based on physician decision or parental refusal.

No patient randomised to CIS alone received any STS.

4. SAFETY

The adverse event CRF asked specifically about incidence of allergy, febrile neutropenia, infection, hypomagnesemia, hypernatremia, vomiting, nausea, left ventricular systolic dysfunction (=targeted events), and any “other” toxicities that were observed.

4.1 Adverse events under treatment

The following table shows number and percentage of patients (by randomised arm) who experienced grade 3 and 4 adverse events under chemotherapy in the CIS and in the CIS+STS arms and/or in further chemotherapy cycles. The maximum grade of events over all cycles is reported by randomised arm.

Adverse event	Grade	Arm: CIS Alone (n=52)		Arm: CIS+STS (n=57)	
		N	%	N	%
Allergy	3	1	1.9	-	-
	4	-	-	-	-
Febrile neutropenia	3	10	19.2	8	14.0
	4	-	-	-	-
Infection	3	16	30.8	13	22.8
	4	-	-	-	-
Hypomagnesemia	3	1	1.9	1	1.8
	4	-	-	-	-
Hypernatremia	3	-	-	1	1.8
	4	-	-	-	-
Vomiting	3	2	3.9	4	7.0
	4	-	-	-	-
Nausea	3	3	5.8	2	3.5
	4	-	-	-	-
Left ventricular systolic dysfunction	3/4	-	-	-	-
Renal	3/4	-	-	-	-
Other toxicities:					
Anemia	3	8	15.4	10	17.5
	4	-		1	1.8
Leukopenia	3	2	3.9	2	3.5
Neutropenia	3	3	5.8	7	12.3
	4	3	5.8	3	5.3
Thrombocytopenia	3	1	1.9	1	1.8
	4	1	1.9	1	1.8
PTT > 2xULN	3	1	1.9	-	-
Weight loss >=20%	3	1	1.9	-	-
Gastrointestinal	3	2	3.9	3	5.3
Elevated liver enzymes	3	6	11.5	3	5.3
	4	-	-	1	1.8
High cholesterol	4	-	-	1	1.8
Elevated serum glucose	3	2	3.9	1	1.8
Hypermagnesemia*	3	2	3.9	5	8.8
Hypophosphatemia	3	-	-	5	8.8
Hyperkalemia	3	2	3.9	-	-
Hypokalemia	3	-	-	4	7.0
	4	-	-	1	1.8
Dyspnea	3	1	1.9	-	-

*The protocol specified the addition of magnesium to the cisplatin hydration fluid.

4.2 Serious adverse events

There was a total of 68 reported SAEs (including 16 serious adverse reactions [SARs]). Appendix section 9 shows the list of all reported SAEs. The protocol specified that tumour progressions should be notified as SAEs. In total, 11 progressions were reported on the SAE form.

One unexpected SAR was reported in a child who developed metabolic acidosis during the third STS infusion. The STS infusion was stopped, and the child recovered rapidly with fluid resuscitation and no further STS was administered in subsequent cycles. The child is a long-term survivor but has developed grade 4 hearing loss. No reason could be found for the sudden deterioration in general condition and so the event was considered related to STS.

Of the 16 SARs, 8 were coded by the investigator as being possibly, probably, or definitely related to STS, including grade 3 infection in two children, grade 3 neutropenia in two children, grade 3 anaemia leading to transfusion in one child, and tumour progression in two children. In one child, grade 2 nausea and vomiting were reported, and the parents declined further STS after cycle 2. No deaths related to STS toxicity were reported.

5. PRIMARY ENDPOINT HEARING LOSS

Brock grade of hearing loss is the primary endpoint of the trial. It must be assessed at an age of approximately 3.5 years or more in order to have a reliable assessment. Most patients were not yet assessable at end of treatment, since their median age at diagnosis was about 1.5 years.

All audiology evaluations needed to be based on pure tone audiometry at 8, 6, 4, 2, 1 and 0.5 kHz. The investigator had to submit the results by uploading the audiogram into the database. The central reviewer, Dr. Kaukab Rajput (KR) at Great Ormond Street Hospital in London, UK, then evaluated the uploaded material, decided whether the investigation had been done according to protocol and fulfilled the criteria to be accepted as the result, and if yes, adjudicated the Brock Grade. Several sites submitted partial audiograms or simple descriptions only which meant that the evaluation was not acceptable and had to be repeated at the next scheduled visit. Other audiograms were judged by the central reviewer as not having been done in a reliable fashion; these had to be repeated as well.

Definitive audiology was available for 101 patients, 46 in the CIS alone arm and 55 in the CIS+STS arm. Five patients died before a reliable hearing assessment could be done; two could not be assessed due to their condition (one syndromic, one autistic); one was lost to follow-up.

Age in years at definitive hearing evaluation was:

arm	n	min	median	max
CIS	46	3.2	4.4	9.7
CIS+STS	55	2.7	4.1	9.0

5.1 ITT analysis

The distribution of the Brock grades adjudicated by the reviewer KR for the 101 evaluable patients is:

Brock Grade	arm		
	CIS	CIS+STS	Total
0	17 37.0%	37 67.3%	54
1	12 26.1%	10 18.2%	22
2	11 23.9%	6 10.9%	17
3	5 10.9%	1 1.8%	6
4	1 2.2%	1 1.8%	2
Total	46	55	101

The primary endpoint was “hearing loss yes/no”:

arm	Hearing loss		
	no	yes	Total
CIS	17 37.0%	29 63.0%	46
CIS+STS	37 67.3%	18 32.7%	55
Total	54	47	101

Summary statistics:

	CIS		CIS+STS		
	Rate	95% conf.int.	Rate	95% conf.int.	Chi-squared p
Hearing loss	29/46 = 63.0%	47.6% - 76.8%	18/55= 32.7%	20.7% - 46.7%	0.0024
Relative risk under CIS+STS: 0.52, 95% conf.int 0.33 – 0.81					

The pre-specified significance level for the final analysis (p = 0.045, see section 1.7) is not crossed.

To account for the stratification used at randomisation, a stratified Cochran-Mantel-Haenzel test was also carried out. The stratification was by

- Age at diagnosis <15 months vs age ≥15 months
- PRETEXT I/II vs III
- Group of countries: UK vs France vs other countries combined. The original stratification used country (not country group), but since the number of patients recruited per country ranges from
  1 to 39, and 5 countries contributed only between 1 and 3 patients, we decided to use the three groups mentioned for this analysis.

With a p = 0.0021, and a Mantel-Haenzel relative risk of 0.52 the results are virtually the same.

The potential influence of other factors on hearing loss was analysed by multiple logistic regression, with hearing loss as the outcome, and gender, age group <15 vs ≥15, group of countries, UK vs France vs other countries, and PRETEXT I/II vs III. None of the explanatory variables showed a significant correlation with hearing loss at a significance level of 5%, and the influence of the randomised arms was still significant with an adjusted p-value of 0.0054.

5.2 Per protocol analysis

As additional information, a per protocol analysis was also done, excluding 4 patients randomised to the CIS+STS arm who never received any STS.

arm	Hearing loss		
	no	yes	Total
CIS	17 37.0%	29 63.0%	46
CIS+STS	35 68.6%	16 31.4%	51
Total	52	45	97

The Chi-squared p value is 0.0018 and the relative risk is 0.54. The corresponding CMH test yields p = 0.0020 and relative risk of 0.51.

5.3 As treated analysis

In this analysis, the 4 patients in the CIS+STS arm who never received any STS are counted as CIS alone.

arm	Hearing loss		
	no	yes	Total
CIS	19 38.0%	31 62.0%	50
CIS+STS	35 68.6%	16 31.4%	51
Total	54	47	101

Chi-squared test p value = 0.0020; relative risk = 0.51.

8 patients randomised to CIS+STS did not receive STS in one or more cycles. 4 / 8 had hearing loss. If these are excluded from the CIS+STS evaluation of hearing loss, then 13/44 = 29.6% of the patients having received all STS had hearing loss. Discounting these 8 pts therefore does not alter the picture.

6. SECONDARY ENDPOINTS

Note: we report centrally reviewed response. Central review was done by the international protocol chairman P. Brock to make sure that the strict response criteria formulated in the protocol were adhered to. The response is based on both reported tumour diameters and the development of the AFP values.

P. Brock also graded the responses according to traditional SIOPEL criteria, see below. The difference between SIOPEL 6 criteria and traditional SIOPEL response criteria is as follows:

	SIOPEL 6 criteria	Traditional SIOPEL criteria
Complete response	no evidence of disease and normal serum AFP value (for age)	same
Partial response	any tumour volume shrinkage associated with a decreasing serum AFP value, ***>1 log below the original measurement***	any tumour volume shrinkage associated with a decreasing serum AFP value
Stable disease	no tumour volume change and no change, ***or < 1 log fall*** of the serum AFP concentration	no tumour volume change and no change of the serum AFP concentration
Progressive disease	unequivocal increase in 1 or more dimensions and/or any unequivocal increase of the serum AFP concentration (three successive 1-2 weekly determinations) even without clinical (physical and/or radiological) evidence of tumour re-growth	same

6.1 Response to preoperative chemotherapy

Abbreviations used: PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

6.1.1 Response after 2 cycles

6.1.1.1 Intention-to-treat

All 109 evaluable patients

Centrally reviewed

	CIS	CIS+STS	Total
PR	28	23	51
	53.9%	40.4%	
SD	24	34	58
	46.2%	59.7%	
Total	52	57	109

Centrally reviewed, traditional SIOPEL assessment

	CIS	CIS+STS	Total
PR	49	52	101
	94.2%	91.2%	
SD	3	5	8
	5.8%	8.8%	
Total	52	57	109

6.1.1.2 *Per protocol*

105 evaluable patients; 4 randomised to CIS+STS are excluded because they received no STS due to logistical problems.

Centrally reviewed

	CIS	CIS+STS	Total
PR	28	21	49
	53.9%	39.6%	
SD	24	32	56
	46.2%	60.4%	
Total	52	53	105

Centrally reviewed, traditional SIOPEL assessment

	CIS	CIS+STS	Total
PR	49	48	97
	94.2%	90.6%	
SD	3	5	8
	5.8%	9.4%	
Total	52	53	105

6.1.1.3 *As treated*

109 evaluable patients; 4 randomised to CIS+STS are evaluated in the CIS alone arm because they received no STS due to logistical problems.

Centrally reviewed

	As treated		
	CIS	CIS+STS	Total
PR	30	21	51
	53.4%	39.6%	
SD	26	32	58
	46.4%	60.4%	
Total	56	53	109

Centrally reviewed, traditional SIOPEL assessment

	As treated		
	CIS	CIS+STS	Total
PR	30	21	51
	53.4%	39.6%	
SD	26	32	58
	46.4%	60.4%	
Total	56	53	109

6.1.2 Response after 4 cycles

6.1.2.1 Intention-to-treat

All 109 evaluable patients, centrally reviewed

	CIS	CIS+STS	Total
PR	39	38	77
	75.0%	66.7%	
PD	5	5	10
	9.6%	8.8%	
SD	5	11	16
	9.7%	19.3%	
NE	3	3	6
	5.8%	5.3%	
Total	52	57	109

Centrally reviewed, traditional SIOPEL assessment

	CIS	CIS+STS	Total
NE	1	2	3
	1.9%	3.5%	
PD	5	5	10
	9.6%	8.8%	
PR	46	50	96
	88.5%	87.7%	
Total	52	57	109

6.1.2.2 Per protocol

105 evaluable patients; 4 randomised to CIS+STS are excluded because they received no STS due to logistical problems.

Centrally reviewed

	CIS	CIS+STS	Total
PR	39	35	74
	75.0%	66.0%	
PD	5	5	10
	9.6%	9.4%	
SD	5	10	15
	9.6%	18.9%	
NE	3	3	6
	5.8%	5.7%	
Total	52	53	105

Centrally reviewed, traditional SIOPEL assessment

	CIS	CIS+STS	Total
NE	1	2	3
	1.9%	3.8%	
PD	5	5	10
	9.6%	9.4%	
PR	46	46	92
	88.5%	86.8%	
Total	52	53	105

6.1.2.3 As treated

109 evaluable patients; 4 randomised to CIS+STS are evaluated in the CIS alone arm because they received no STS due to logistical problems.

Centrally reviewed

	As treated		
	CIS	CIS+STS	Total
PR	42	35	77
	75.0%	66.0%	
PD	5	5	10
	8.9%	9.4%	
SD	6	10	16
	10.7%	18.9%	
NE	3	3	6
	5.4%	5.7%	
Total	56	53	109

Centrally reviewed, traditional SIOPEL assessment

	As treated		
	CIS	CIS+STS	Total
NE	1	2	3
	1.8%	3.8%	
PD	5	5	10
	8.9%	9.4%	
PR	50	46	96
	89.3%	86.8%	
Total	56	53	109

6.1.3 Further exploration of response to treatment

This section compares patient status at various stages of assessment. It is based exclusively on centrally reviewed response. These purely exploratory investigations address concerns about a potential tumour-protecting effect of STS.

The percentage of patients with stable disease was 60% in the CIS+STS arm, whereas this percentage was 46% in the CIS alone arm. Are patients who had stable disease after 2 cycles at higher risk of impaired long-term outcome? This is further explored below. Abbreviations used:

Respcyc2 = response after cycle 2

Respcyc4 = response after cycle 4

StatusEoT = status at end of treatment

statusLFU = status at last follow-up

CR = complete remission (determined at end of treatment)

Cross-classification of response after 2 and after 4 cycles:

respcyc4	respcyc2		
	PR	SD	Total
PR	45	32	77
	88.2%	55.2%	
PD	2	8	10
	3.9%	13.8%	
SD	0	16	16
	00.0%	27.6%	
NE	4	2	6
	7.8%	3.5%	
Total	51	58	109

This table shows that 88% of patients with a PR after 2 cycles are in PR after 4 cycles, as opposed to 55% of those with SD after 2 cycles.

Cross-classification of response after 2 cycles with status and end of treatment:

StatusEoT	respcyc2		
	PR	SD	Total
CR	46	50	96
	90.2%	86.2%	
PR	3	6	9
	5.9%	10.3%	
PD	1	1	2
	2.0%	1.7%	
NE	1	0	1
	2.0%	0.00%	
died	0	1	1
	0.0%	1.7%	
Total	51	58	109

This table shows that 90% of patients in PR after 2 cycles are in CR at EoT, as opposed to 86% of those with SD after 2 cycles.

StatusLFU	respcyc2		
	PR	SD	Total
CR	50	53	103
	98.0%	91.4%	
died of	1	4	5
disease	2.0%	6.9%	
died of other	0	1	1
causes	0.0%	1.7%	
Total	51	58	109

This table shows that 98% of patients in PR after 2 cycles are in CR at last follow-up (which can be anything from EoT to several years after EoT), as opposed to 91% of those with SD after 2 cycles. It also shows that 5 patients with SD after 2 cycles have died, as opposed to only 1 patient with PR.

Cross-classification of status at end of treatment with response after 4 cycles:

StatusEoT	respcyc4				
	PR	PD	SD	NE	Total
CR	68	9	15	4	96
	88.3%	90.0%	93.8%	66.7%	
PR	7	1	1	0	9
	9.1%	10.0%	6.3%	0.00%	
PD	2	0	0	0	2
	2.6%	0.00%	0.00%	0.00%	
NE	0	0	0	1	1
	0.00%	0.00%	0.00%	16.7%	
died	0	0	0	1	1
	0.0%	0.00%	0.00%	16.7%	
Total	77	10	16	6	109

This table shows that of the 16 patients in SD after 4 cycles, 15 were in CR at EoT, as well as 9 out of 10 patients with progressive disease.

statusLFU	respcyc4				
	PR	PD	SD	NE	Total
Complete remission	75 97.4%	8 80.0%	15 93.8%	5 83.3%	103
Died of disease	2 2.6%	2 20.0%	1 6.3%	0	5
Died of other causes	0	0	0	1 16.7%	1
Total	77	10	16	6	109

This table shows that 15 out of the 16 patients in SD after 4 cycles are still in complete remission at last follow-up, and that 3 out of the 5 patients who died from the tumour (not due to surgical complications) were either in SD or PD after 4 cycles.

Cross-classification of status at last follow-up with status at end of treatment:

StatusLFU	StatusEoT					
	CR	SD	PD	NE	died	Total
CR	93	8	1	1	0	103
	96.9%	88.9%	50.0%	100.0%	0.0%	
died of disease	3	1	1	0	0	5
	3.1%	11.1%	50.0%	0.0%	0.0%	
died of other causes	0	0	0	0	1	1
	0.0%	0.0%	0.0%	0.0%	100.0%	
Total	96	9	2	1	1	109

This table shows that 3 of the 96 patients in CR at EoT died, as well as 1/9 in PR and 1/2 in PD.

In summary, it appears that having a stable disease instead of a response after 2 cycles of chemotherapy does not adversely affect later outcome.

6.2 Resection

The liver tumours of all 109 evaluable patients were resected. Three of the partial hepatectomies had suspected microscopic residual disease; all three patients were randomised to CIS+STS (125, 128 and 141). Patients 125 and 128 were in complete remission at EoT; patient 141 (randomised to CIS+STS but treated with CIS alone) was in partial remission at EoT due to elevated AFP (10ng/mL). All three patients were in CR at last documented follow-up.

	CIS	CIS+STS	Total
Liver Transplantation	4	4	8
	7.7%	7.0%	
Partial hepatectomy	48	53	101
	92.3%	93.0%	
Total	52	57	109

Among the 8 liver transplants, 7 tumours were PRETEXT III; one was PRETEXT II at diagnosis. The imaging of two of them was centrally reviewed and the patients were classified as standard risk (=eligible for the trial). In all 8 cases the reason given for the transplant was “unexpectedly inoperable tumour”. Seven out of 8 tumours were solitary. One was diagnosed as “main and left portal vein: tumour close to but not abutting (touching) vessel; right portal vein: Complete obstruction or encasement of vessel”.

In no patients were there any metastases which would have had to be excised.

6.3 Status at end of treatment

6.3.1 Intention-to-treat

Centrally reviewed status:

	CIS	CIS+STS	Total
Died at surgery	1	0	1
	71.9%	0.0%	
CR	44	52	96
	84.6%	91.2%	
PR	4	5	9
	7.7%	8.8%	
PD	2	0	2
	3.9%	0.0%	
NE	1	0	1
	1.9%	0.0%	
Total	52	57	109

Centrally reviewed status, using traditional SIOPEL criteria:

	CIS	CIS+STS	Total
CR	48	56	104
	92.3%	98.3%	
PD	2	0	2
	3.9%	0.0%	
PR	0	1	1
	30.0%	1.8%	
death	1	0	1
	1.9%	0.0%	
NE	1	0	1
	1.9%	0.0%	
Total	52	57	109

6.3.2 Per protocol

Centrally reviewed status:

	CIS	CIS+STS	Total
CR	44	49	93
	92.3%	98.1%	
PR	4	4	8
	7.7%	7.6%	
PD	2	0	2
	3.9%	0.0%	
NE	2	0	2
	3.9%	0.0%	
Total	52	57	109

Traditional SIOPEL criteria:

	CIS	CIS+STS	Total
CR	48	52	100
	92.3%	98.1%	
NE	1	0	1
	1.9%	0.0%	
PD	2	0	2
	3.9%	0.0%	
PR	1	0	1
	1.9%	0.0%	
death	0	1	1
	0.0%	1.9%	
Total	52	53	105

6.3.3 As treated

Centrally reviewed:

	CIS	CIS+STS	Total
died at surgery	1	0	1
	92.3%	0.0%	
CR	47	49	96
	83.9%	92.5%	
PR	5	4	9
	8.9%	7.6%	
PD	2	0	2
	3.6%	0.0%	
NE	1	0	1
	1.8%	0.0%	
Total	56	53	109

	As treated		
	CIS	CIS+STS	Total
CR	52	52	104
	92.9%	98.1%	
NE	1	0	1
	1.8%	0.0%	
PD	2	0	2
	83.6%	0.0%	
PR	0	1	1
	0.0%	1.9%	
death	1	0	1
	1.8%	0.0%	
Total	56	53	109

6.4 Follow-up

Follow-up information is available for 108/109 patients. One patient died from surgical complications and therefore has no follow-up.

Status at ***first follow-up*** (mostly within 6 months from end of treatment), according to intention to treat:

	CIS	CIS+STS	Total
Complete remission	47	53	100
	90.4%	93.0%	
Died of disease	1	0	1
	1.9%	0.0%	
Died of surgical complications	1	0	1
	1.9%	0.0%	
Partial remission	0	1	1
	0.0%	1.8%	
Progressive disease	3	2	5
	5.8%	3.5%	
Recurrent disease	0	1	1
	0.0%	1.8%	
Total	52	57	109

first follow-up, per protocol

	CIS	CIS+STS	Total
Complete remission	47	49	96
	90.4%	92.5%	
Died of disease	1	0	1
	1.9%	0.0%	
Died of surgical complications	1	0	1
	1.9%	0.0%	
Partial remission	0	1	1
	0.0%	1.9%	
Progressive disease	3	2	5
	5.8%	3.8%	
Recurrent disease	0	1	1
	0.0%	1.9%	
Total	52	53	105

first follow-up, as treated

	CIS	CIS+STS	Total
Complete remission	51	49	100
	91.1%	92.5%	
Died of disease	1	0	1
	1.8%	0.0%	
Died of surgical complications	1	0	1
	1.8%	0.0%	
Partial remission	0	1	1
	0.0%	1.9%	
Progressive disease	3	2	5
	5.4%	3.8%	
Recurrent disease	0	1	1
	0.0%	1.9%	
Total	53	56	109

Status at ***last follow-up*** (some patients only have 1 follow-up, for them the information is the same as in the above tables), according to intention to treat:

	CIS	CIS+STS	Total
Complete remission	48	55	103
	92.3%	96.5%	
Died of disease	3	2	5
	5.8%	3.5%	
Died of surgical complications	1	0	1
	1.9%	0.0%	
Total	52	57	109

Per protocol:

	CIS	CIS+STS	Total
Complete remission	48	51	99
	92.3%	96.2%	
Died of disease	3	2	5
	5.8%	3.8%	
Died of surgical complications	1	0	1
	1.9%	0.0%	
Total	52	53	105

As treated:

	CIS	CIS+STS	Total
Complete remission	52	51	103
	92.9%	96.2%	
Died of disease	3	2	5
	5.4%	3.8%	
Died of surgical complications	1	0	1
	1.8%	0.0%	
Total	56	53	109

6.5 Progressions, relapses and deaths

This is a detailed enumeration of patients with PD, relapse, or both:

Event	Outcome	CIS alone	CIS+STS	Total
PD	salvaged (=extra chemo)	#122, 68/2 #127, 18/4 #155, 240/2 #162, 85/7 #224, 10/7 #167, 302/2	#105, 68/2 #157, 16/2 #204, 21/2 #216, 86/3 #225, 66/6 #149, 302/1	12
PD	died	#152, 15/6 #180, 65/1		2
PD, later relapse	salvaged	#119, 211/3	#135, 75/1	2
PD, later relapse	died	#222, 16/3	#186, 66/5	2
Relapse alone	salvaged		#137, 85/4 #165, 8/3	2
Relapse alone	died		#138, 6/2	1
Surgical death		#215, 113/1		1
Toxic death	(under salvage treatment)	(#180, 65/1 *, counted under PD above)		
Total		11	11	22

*) 65/1: Patient died in cardiac arrest, but taxol is given as possibly related.

During or after treatment, a total of 10/52 patients in the CIS group and 11/57 in the CIS+STS group had either progressive disease (8 and 6, respectively), relapse (0 and 3, respectively) or both (2 and 2, respectively). In addition, there was one surgical death; therefore, there are 11 EFS events in each of the randomised arms.

Number of EFS events:

Event	CIS alone	CIS+STS	Total
Progressive disease	8	6	14
Progressive disease, later relapse	2	2	4
Relapse alone	0	3	3
Surgical death	1	0	1
Total number of EFS events	11	11	22

Description of relapsed or died patients:

Patient #119 (211/3 CIS alone), was in complete remission at end of treatment, had a relapse with a single lung metastasis 17 months after end of treatment which was surgically removed, and patient treated with carbo/doxorubicin. One year later, the patient was in complete remission.

Patient #152 (15/6, CIS alone) never achieved complete remission, progressed and died.

Patient #180 (65/1, CIS alone) responded well to pre-op chemo, was operated after 4 cycles with complete resection of the tumour by partial hepatectomy, received post-op chemotherapy and progressed after 2 cycles. The patient died 9 months after randomisation.

Patient #215 (113/1 on CIS alone) had a very big tumour, PRETEXT III confirmed by central review; the patient had stable disease after 2 cycles, no response evaluation after 4 cycles (but AFP decline from 727'500 to 30'294). Died at surgery, no details available.

Patient #222 (16/3 (CIS alone): PD after 4 cycles, then surgery; in CR at EoT (normal AFP). Relapsed

with peritoneal metastasis and died 15 months after surgery.

#135 (75/1, CIS+STS) was classified as progressive disease at first follow-up, recurrent disease at second follow-up. The patient was re-operated (central tumour) and then received chemotherapy. One year after first surgery the patient reached an AFP of 7.2; the patient was in complete remission 3 years after randomisation.

Patient #137 (85/4 CIS+STS), SD after 2 and 4 cycles. Patient was transplanted; after transplant, the patient had second surgery to redo biliodigestive anastomosis. Then, because of rejection, he was treated with metilprednisolone and increased FK-506 therapy. He did not receive any other chemotherapy. Relapse after 28 months with metastatic single peri hilar lymph node. Resection then 2xIrinotecan/Vin. In complete remission 3 years later.

Patient #138 (6/2 CIS+STS) CIS+STS x3+CIS, PLADOx2, change to CIS alone and then PLADO due to initial small rises in AFP between cycles which subsequent fall. EoT=CR based on fast fall of AFP post end of treatment, Relapse with metastasis in lungs and mediastinum 4 years after surgery; died.

Patient #165 (8/3 CIS+STS) had an AFP recurrence after having reached complete remission at EoT; imaging revealed left lower lobe of lung tumour indicating clinically isolated metastatic recurrence. The patient was treated with 3 cycles of carboplatin+doxorubicin, and then a lower lobe lobectomy was performed. The patient was in complete remission 29 months after randomisation.

Patient #186 (66/5 CIS+STS): CIS+STSx4, initial progression recovered by PLADOx2, in CR at EoT. Died 1 year after surgery from relapse.

6.6 Event free and overall survival

The median follow-up time of live patients is 52.3 months, 50.4 months in the CIS and 54.6 months in the CIS+STS arm.

6.6.1 Event free survival

Event free survival is calculated as difference from date of randomisation to first date of an EFS event (progression, relapse or death from any cause).

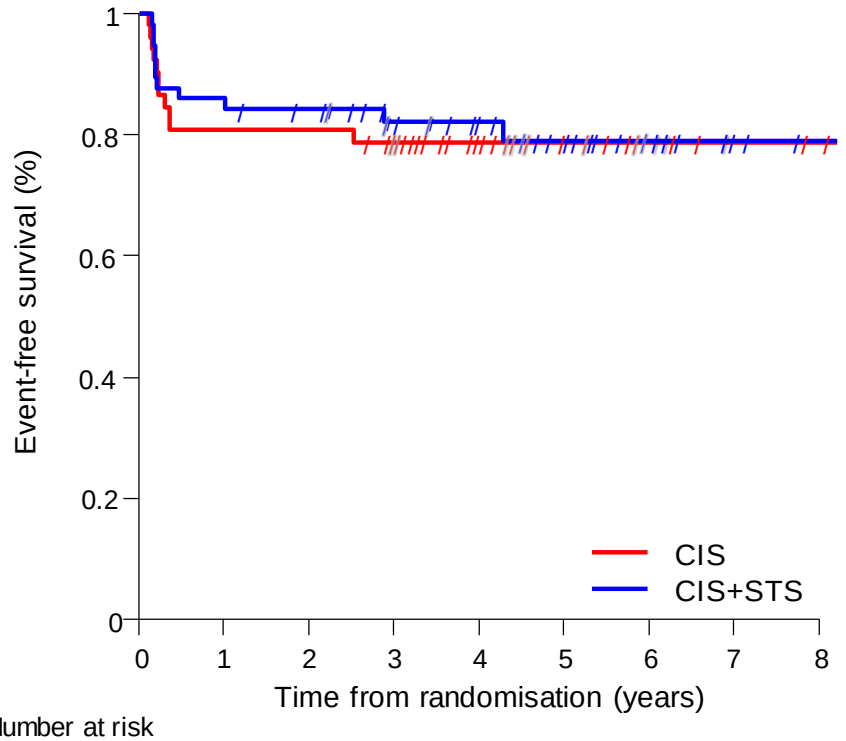
The difference between the two curves is not significant, with p = 0.78.

Summary of the number of Censored and Uncensored Values				
Stratum arm	Total	Failed	Censored	Percent Censored
1 CIS	52	11	41	78.85
2 CIC+STS	57	11	46	80.70
Total	109	22	87	79.82

The following table shows the 3-year event free survival rates with their 95% confidence intervals:

arm	EFS 3 year	lower95CI	upper95CI
CIS	0.788	0.651	0.877
CIS+STS	0.821	0.692	0.900

Kaplan-Meier plot of event-free survival, by intention-to-treat:



Number at risk
(number censored)

CIS	52 (0)	42 (0)	42 (0)	37 (4)	22 (15)	13 (9)	8 (5)	3 (5)	2 (1)
CIS+STS	57 (0)	49 (0)	46 (2)	37 (8)	29 (8)	19 (9)	9 (10)	3 (6)	1 (2)

6.6.2 Overall survival

Overall survival is calculated as difference from date of randomisation to date of death from any cause.

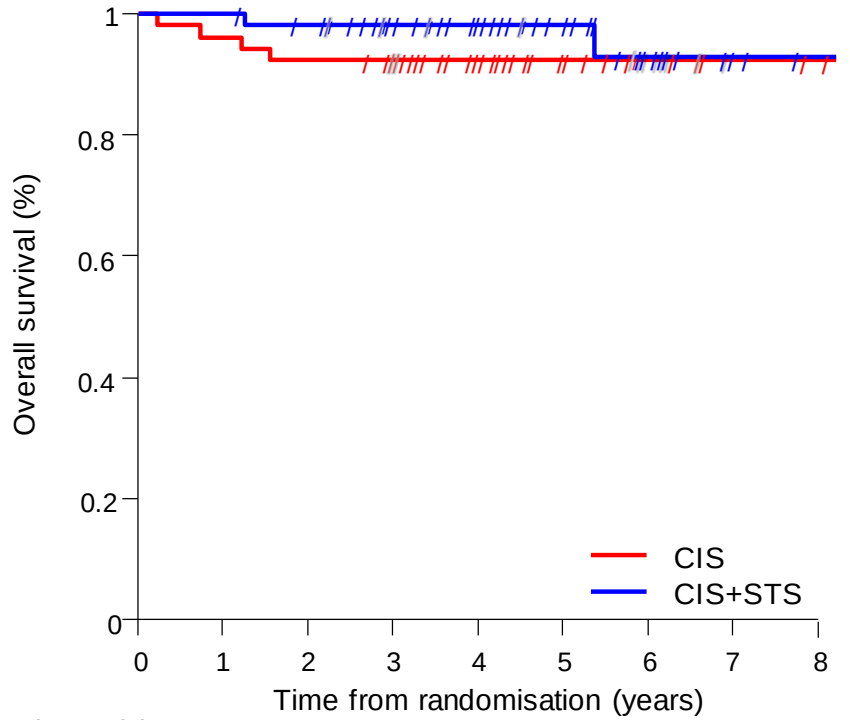
The difference between the two curves is not significant, with a logrank test p = 0.33.

Summary of the number of Censored and Uncensored Values				
Stratum arm	Total	Failed	Censored	Percent Censored
1 CIS	52	4	48	92.31
2 CIS+STS	57	2	55	96.49
Total	109	6	103	94.50

The following table shows the 3-year overall survival rates with their 95% confidence intervals:

arm	OS 3 year	lower95CI	upper95CI
CIS	0.923	0.808	0.970
CIS+STS	0.982	0.880	0.997

Kaplan-Meier plot of overall survival, by intention-to-treat:



Number at risk
(number censored)

CIS	52 (0)	50 (0)	48 (0)	43 (5)	28 (15)	17 (11)	11 (6)	3 (8)	2 (1)
CIS+STS	57 (0)	57 (0)	54 (2)	45 (9)	35 (10)	24 (11)	12 (11)	4 (8)	1 (3)

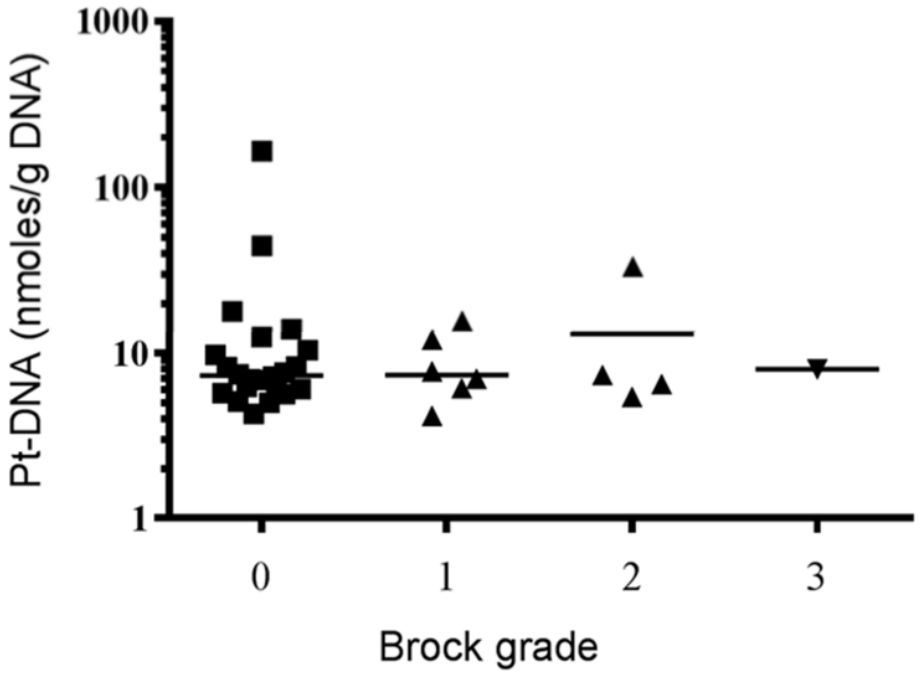
6.7 DNA adducts

Analysis carried out by Dr Gareth J Veal, Northern Institute for Cancer Research, Newcastle University

Platinum-DNA adduct levels were measured in whole blood samples (5-10mL), taken before cisplatin treatment and 24 hours following the start of a 6-hour cisplatin infusion, by inductively coupled plasma mass spectrometry analysis in peripheral blood lymphocytes

Blood samples were collected from a total of 36 children: 12/36 (33%) in the cisplatin alone group and 24/36 (67%) in the CIS+STS group. The difference after minus before cycle 1 cisplatin was calculated; for patient #203 the samples were taken in cycle two instead of one. 12 patients were treated with CIS alone, 24 with CIS+STS.

Platinum-DNA adduct levels ranged from 4.3 to 166nmol/g DNA. No correlations were observed between platinum-DNA adduct levels and outcome in terms of hearing loss, response, event-free or overall survival. The following figure shows the relationship between platinum-DNA adduct level and Brock grade hearing loss. Brock grades are available for 33/36 patients:



There is no correlation between hearing loss yes vs no and adducts dichotomised into <7.4 nmol/g DNA vs ≥7.4 nmol/g DNA; the Spearman (rank sum) correlation coefficient is 0.08 (p = 0.64). The 2x2 table of audio toxicity and the adduct groups:

Hearing Loss	adductgroup		
	<7.4	7.4+	Total
No	10	8	18
	58.8%	50.0%	
Yes	7	8	15
	41.1%	50.0%	
Total	17	16	33

Fisher's exact test yields a p value of 0.73.

There is no significant correlation between Brock grades and adducts; the Spearman (rank sum) correlation coefficient is 0.11 (p = 0.53).

The distribution by Brock grade is:

Brock Grade	Adduct level		
	<7.4	7.4+	Total
0	10	9	18
	58.82	50.0	
1	4	5	9
	23.53	31.25	
2	3	2	5
	17.65	12.50	
3	0	1	1
	0.00	6.25	
Total	17	16	33

with a p value 0.68 (Chi-squared test)

6.8 Renal function

Long term development of renal function is of interest since cisplatin may affect renal function permanently. Renal monitoring should be carried out before every second cycle of chemotherapy, at the end of treatment and at follow-up. Glomerular filtration rate was to be recorded. It could be either determined through the Cr51 EDTA method, Iohexol, isotope GFR, or calculated from serum creatinine.

The central review of the recorded GFR values revealed a rather high variability, and values which were at times not usable, probably because the wrong units were specified. For many patients, no GFR was recorded in follow-up. For such cases, a serum creatinine value was therefore collected retrospectively.

To identify a plausible value at baseline (or as near to baseline as possible) and as far down in follow-up as possible, a list of all GFR values and creatinine values was generated and then reviewed centrally, and these two values identified and then compared.

For the calculation of GFR in ml/min/1.73m^2 from serum creatinine (Scr), the Schwartz equation (Schwartz 1976) was used:

CrCl (ml/min/1.73m^2) = [length (cm) × k] / Scr in mg/dL

where

k = 0.45 for infants 1 to 52 weeks old
k = 0.55 for children 1 to 13 years old
k = 0.55 for adolescent females 13-18 years old
k = 0.7 for adolescent males 13-18 years old

Renal function chosen as baseline or during chemo (1 pt. in the CIS arm has no baseline value):

arm	n	min	median	max	mean
CIS	51	41.0	121	278	126.0
CIS+STS	57	44.4	130	309	139.9

This is the renal function chosen at the last follow-up. (2 pts in the CIS arm have no follow-up value)

arm	n	min	median	max	mean
CIS	50	49	111.35	281	119.0
CIS+STS	57	57	118.00	260	124.1

The difference between renal function in follow-up and baseline yielded

arm	n	min	quart 1	median	quart 3	max	mean
CIS	49	-101.2	-35.2	-6	5	120	-8.0
CIS+STS	57	-140.0	-39	-12	21.7	106	-9.8

The renal functions therefore diminished by a median of 6 ml/min/1.73m^2 in the CIS arm and 12 ml/min/1.73m^2 in the CIS+STS arm.

A total of six patients had a GFR value <60ml/min. which was considered insufficient, 2 at baseline and 4 in follow-up:

Randomised to CIS:

#100 (11/7) started off with a value of 41 at age 3.1 months and achieved 49 at a follow-up time of 5 months (age 12 months).

#224 (10/7) had a baseline value of 110 (10.1 months) and was at 56 at month 8 of follow-up (age 23 months).

Randomised to CIS+STS:

#125 (5/3) had a baseline of 56 at age 4.5 months and achieved 92 at age 33.7 months.

#139 (85/5) had a baseline of 45 at age 1 month (within normal range for this young age according to the protocol) and achieved 58 at age 36.6 months.

#169 (11/9) started off with a normal value of 126 (age 9.3 months) and had a value of 57 at EoT, and no further GFR recorded in follow-up.

#214 (45/6) had a baseline value of 44.4 (age 14.9 months) and in follow-up a value of 87 at age 39 months.

7. DISCUSSION AND CONCLUSIONS

In this trial, the addition of delayed STS to cisplatin produced a 48% reduction in relative risk of hearing loss. Hearing loss of Brock grade ≥ 1 occurred in 63.0% of children who did not receive otoprotection compared to 32.7% of children who did. STS administration was associated with a trend towards reduced ototoxicity in all Brock grades. Children with Brock grade 0 do not have completely normal hearing but can manage life with little or no additional help. Children with Brock grade ≥1 hearing loss requires further intervention with each increasing grade, all of them requiring educational support. In the UK, young children with Brock grade 1 and all children with Brock grade 2 and 3 will be offered hearing aids. Children with Brock grade 4 will require cochlear implants. The impact of high-frequency hearing loss and hearing support varies across the world, the reasons for which are multi-factorial but include the variation in sound frequencies used in different languages. The analysis of these variables was beyond the scope of this trial.

Importantly in this trial the same number of children developed progressive tumour in each arm and there was no difference in event-free or overall survival between the two arms of the trial.

The incidence of acute adverse events was as expected; only 1 child developed an unexpected reaction. No child stopped STS treatment due to hypertension or high serum sodium. The otoprotective dose of STS was associated with a high sodium load; a factor to consider in planning treatment. STS is emetogenic; nausea and vomiting were the most common adverse events and required prophylactic antiemetic's. STS did not alter the necessity for 24-hour hydration post-cisplatin administration. Renal function was acceptable in these young children, only 4 children experienced a GFR <60mL/min/1.73m^2 at the end of treatment/follow up. Initiation of STS administration after a 6-hour delay from completion of cisplatin administration caused no tumour protection and did not adversely affect disease outcome.

Platinum-DNA adduct formation measured in peripheral blood lymphocytes showed no correlation between adduct levels and outcome in terms of hearing loss or clinical response. This confirms results from previous studies suggesting that quantification of platinum-DNA adduct levels in peripheral blood lymphocytes, does not provide a useful biomarker for patient response or platinum-induced toxicities due to a lack of correlation between adduct levels in lymphocytes and those in tumour and other host tissues. Indeed, recent evidence suggests that cisplatin-induced ototoxicity is associated with long-term retention of cisplatin, specific to the cochlea.

In conclusion, SIOPEL 6 was a randomised, Phase III trial in children with localised hepatoblastoma undergoing chemotherapy with cisplatin alone versus cisplatin+STS and showed that addition of delayed STS significantly reduced the incidence of cisplatin-induced hearing loss, with no evidence of tumour protection.

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9. APPENDIX: LIST OF SAE/SAR/SUSAR

Ordered by treatment arm delivered ("as treated") and patient ID

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
UK	86	CIS	Chemother apy PLADO	26/01/2009	Life threatening	GASTROINTE STINAL	Enteritis (inflammation of the small bowel)	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	SAE	doxorubici n	definite	Resolved	05/02/2009
France	119	CIS	SURGERY	27/05/2010	Required prolonged or unplanned hospitalisation	GASTROINTE STINAL	Ascites (non-malignant)	Symptomatic, invasive procedure indicated	SAE	none		Resolved with sequelae	27/07/2010
France	119	CIS	Follow Up	16/08/2010	Required prolonged or unplanned hospitalisation	PAIN	Pain	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	SAE	none		Resolved	17/08/2010
France	119	CIS	Follow Up	18/12/2010	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Localized, local intervention indicated	SAE	none		Resolved	22/12/2010
France	119	CIS	Follow Up	31/08/2012	Tumor progression				PD	none		Resolved	08/02/2013
France	121	CIS	Chemother apy course 1	14/03/2010	Required prolonged or unplanned hospitalisation	GASTROINTE STINAL	Dehydration	IV fluids indicated <24 hrs.	SAE	none		Resolved	18/03/2010
France	122	CIS	Chemother apy course 6	30/06/2010	Tumor progression				PD	none		Resolved	15/05/2014

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
UK	124	CIS	Chemotherapy course 6	04/08/2010	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	SAE	none		Resolved	06/08/2010
UK	144	CIS	Chemotherapy course 1	23/03/2011	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	SAR	cisplatin	definite	Resolved	26/03/2011
UK	147	CIS	SURGERY	28/07/2011	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	SAE	none		Resolved	01/08/2011
UK	147	CIS	Chemotherapy course 6	13/08/2011	Required prolonged or unplanned hospitalisation	DERMATOLOGY/SKIN	Rash/desquamation	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	SAE	none		Resolved	15/08/2011
France	148	CIS	SURGERY	19/08/2011	Required prolonged or unplanned hospitalisation	LYMPHATICS	Lymphatics - Other (Specify, __)	Severe	SAE	none		Resolved	07/09/2011

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
UK	152	CIS	Chemotherapy course 1	24/09/2011	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	SAE	none		Resolved	27/09/2011
UK	152	CIS	Chemotherapy course 6	15/12/2011	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	SAE	none		Resolved	19/12/2011
New Zealand	155	CIS	Chemotherapy course 3	02/12/2011	Tumor progression				PD	none		Resolved	24/02/2012
UK	159	CIS	Chemotherapy course 4	13/02/2012	Required prolonged or unplanned hospitalisation	INFECTION	Infection - Other (Specify, __)	Severe	SAE	none		Resolved	17/02/2012
France	168	CIS	Chemotherapy course 6	11/12/2012	Other reason	ALLERGY/IMMUNOLOGY	Allergy/Immunology - Other (Specify, __)	Moderate	SAE	cisplatin	possible	Resolved	11/12/2012
SWITZERLAND	170	CIS	Chemotherapy course 3	01/11/2012	Required prolonged or unplanned hospitalisation	VASCULAR	Thrombosis/embolism (vascular access-related)	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	SAE	none		Resolved	01/11/2012
France	174	CIS	Chemotherapy course 2	12/11/2012	Required prolonged or unplanned hospitalisation	BLOOD/BONE MARROW	Hemoglobin	<10.0 - 8.0 g/dL <6.2 - 4.9 mmol/L <100 - 80g/L		cisplatin	probable	Resolved	15/11/2012

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
France	180	CIS	Chemotherapy course 3	27/03/2013	Other reason	COAGULATION	PTT (Partial Thromboplastin Time)	>2 x ULN	SAR	cisplatin	possible	Resolved	05/04/2013
France	180	CIS	Chemotherapy course 6	24/05/2013	Tumor progression				PD	none		Death	08/11/2013
France	180	CIS	Follow Up	08/11/2013	Death	CARDIAC GENERAL	Cardiac General - Other (Specify, __)	Death	SAE	taxol	possible	Death	08/11/2013
Belgium	182	CIS	Chemotherapy course 1	26/03/2013	Required prolonged or unplanned hospitalisation	PULMONARY/ UPPER RESPIRATORY	Dyspnea (shortness of breath)	Dyspnea with ADL	SAE	none		Resolved	02/04/2013
France	187	CIS	Follow Up	01/10/2013	Required prolonged or unplanned hospitalisation	INFECTION	Infection - Other (Specify, __)	Moderate	SAE	cisplatin	possible	Resolved	03/10/2013
UK	200	CIS	SURGERY	29/04/2014	Life threatening	METABOLIC/LABORATORY	Potassium, serum-high (hyperkalemia)	>6.0 - 7.0 mmol/L	SAR	cisplatin	possible	Resolved	09/05/2014
France	201	CIS	Chemotherapy course 1	05/02/2014	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	SAE	none		Resolved	09/02/2014

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
France	201	CIS	Chemotherapy course 2	28/02/2014	Required prolonged or unplanned hospitalisation	INFECTION	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)	Present	SAR	cisplatin	probable	Resolved	01/03/2014
France	201	CIS	Chemotherapy course 4	16/04/2014	Required prolonged or unplanned hospitalisation	INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	SAE	none		Resolved	19/04/2014
France	211	CIS	Chemotherapy course 3	09/05/2014	Required prolonged or unplanned hospitalisation	INFECTION	Infection - Other (Specify, __)	Severe	SAR	cisplatin	definite	Resolved	11/05/2014
UK	224	CIS	Follow Up	12/02/2015	Tumor progression				PD	none		Resolved	20/02/2015
UK	227	CIS	Chemotherapy course 5	04/03/2015	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	SAE	none		Resolved with sequelae	12/03/2015
France	105	CIS +STS	Chemotherapy course 4	21/07/2009	Tumor progression				PD	STS	possible	Resolved	13/08/2009

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
France	105	CIS +STS	Chemotherapy course 5	29/07/2009	Other reason	BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)	<1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L	SAR	cisplatin	probable	Resolved	24/08/2009
UK	112	CIS +STS	SURGERY	21/10/2009	Required prolonged or unplanned hospitalisation	SURGERY/INTRA-OPERATIVE INJURY	Intra-operative injury	Primary repair of injured organ/structure indicated	SAE	none		Resolved	22/10/2009
UK	120	CIS +STS	Chemotherapy course 3	05/04/2010	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Localized, local intervention indicated	SAE	none		Resolved	06/04/2010
UK	125	CIS +STS	Chemotherapy course 5	02/09/2010	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	SAR	cisplatin STS	probable probable	Resolved	21/10/2010
France	129	CIS +STS	Chemotherapy course 1	04/08/2010	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	SAE	cisplatin	probable	Resolved	07/08/2010
France	129	CIS +STS	Chemotherapy course 1	05/08/2010	Other reason	BLOOD/BONE MARROW	Hemoglobin	<8.0 - 6.5 g/dL <4.9 - 4.0 mmol/L <80 - 65 g/L	SAR	cisplatin	probable	Resolved	06/08/2010
France	129	CIS +STS	Chemotherapy course 3	27/08/2010	Other reason	BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)	<1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L	SAR	cisplatin	probable	Resolved	30/08/2010

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
France	132	CIS +STS	Chemotherapy course 1	04/09/2010	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	SAR	none		Resolved	09/09/2010
France	133	CIS +STS	Chemotherapy course 1	02/09/2010	Required prolonged or unplanned hospitalisation	SURGERY/INTRA-OPERATIVE INJURY	Intra-operative Injury - Other (Specify, __)	Primary repair of injured organ/structure indicated	SAE	none		Resolved	11/09/2010
France	135	CIS +STS	Chemotherapy course 1	20/10/2010	Other reason	METABOLIC/LABORATORY	Cholesterol, serum-high (hypercholesteremia)	>500 mg/dL >12.92 mmol/L	SAE	none		Resolved	18/10/2014
France	135	CIS +STS	Chemotherapy course 4	03/12/2010	Other reason	BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)	<1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L	SAR	cisplatin	probable	Resolved	07/12/2010
France	135	CIS +STS	Chemotherapy course 5	20/12/2010	Other reason	BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)	<1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L	SAR	cisplatin STS	probable probable	Resolved	27/12/2010
France	135	CIS +STS	Chemotherapy course 5	28/12/2010	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	SAR	cisplatin	probable	Resolved	29/12/2010
France	135	CIS +STS	Chemotherapy course 6	03/01/2011	Other reason	BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)	<1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L	SAR	cisplatin	probable	Resolved	05/01/2011
France	135	CIS +STS	Follow Up	10/06/2011	Tumor progression				PD	none		Resolved	16/09/2011

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
UK	138	CIS +STS	Chemotherapy course 3	25/01/2011	Life threatening	MUSCULOSKELETAL/SOFT TISSUE	Musculoskeletal/Soft Tissue - Other (Specify, __)	Life-threatening; disabling	SAE	none		Resolved	13/06/2011
France	146	CIS +STS	Chemotherapy course 6	25/07/2011	Other reason	BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)	<1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L	SAE	none		Resolved	01/08/2011
UK	157	CIS +STS	Chemotherapy course 5	20/02/2012	Tumor progression				PD	none		Resolved	08/08/2012
France	160	CIS +STS	Chemotherapy course 5	07/05/2012	Required prolonged or unplanned hospitalisation	INFECTION	Infection - Other (Specify, __)	Moderate	SAE	none		Resolved	11/05/2012
France	160	CIS +STS	Chemotherapy course 6	30/05/2012	Required prolonged or unplanned hospitalisation	INFECTION	Infection - Other (Specify, __)	Moderate	SAE	none		Resolved	05/06/2012
France	160	CIS +STS	Chemotherapy course 6	05/06/2012	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	SAE	none		Resolved	06/06/2012
UK	161	CIS +STS	Chemotherapy course 1	29/02/2012	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	SAR	cisplatin STS	definite unlikely	Resolved	29/02/2012
UK	169	CIS +STS	Chemotherapy course 4	01/11/2012	Required prolonged or unplanned hospitalisation	ALLERGY/IMMUNOLOGY	Allergic reaction/hypersensitivity (including drug fever)	Rash; flushing; urticaria; dyspnea; drug fever >=38 degrees C (>=100.4 degrees F)	SUSAR	STS cisplatin	definite unlikely	Resolved	02/11/2012

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
UK	173	CIS +STS	Chemotherapy course 1	26/10/2012	Required prolonged or unplanned hospitalisation	METABOLIC/ LABORATORY	Sodium, serum-low (hyponatremia)	<130 - 120 mmol/L	SAE	cisplatin STS	unlikely unlikely	Resolved	28/10/2012
UK	173	CIS +STS	Chemotherapy course 1	29/10/2012	Required prolonged or unplanned hospitalisation	GASTROINTESTINAL	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	SAE	cisplatin STS	unlikely unlikely	Resolved	31/10/2012
France	183	CIS +STS	Chemotherapy course 3	17/05/2013	Other reason	BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)	<1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L	SAR	cisplatin	probable	Resolved	27/05/2013
France	186	CIS +STS	Chemotherapy course 1	26/05/2013	Required prolonged or unplanned hospitalisation	INFECTION	Infection - Other (Specify, __)	Mild	SAE	none		Resolved	05/06/2013
France	186	CIS +STS	Follow Up	11/12/2013	Tumor progression				PD	none		Death	21/08/2014
France	191	CIS +STS	Chemotherapy course 4	15/11/2013	Other reason	BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)	<1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L	SAR	cisplatin STS bactrim	probable possible possible	Resolved	20/11/2013
UK	203	CIS +STS	Chemotherapy course 2	10/03/2014	Required prolonged or unplanned hospitalisation	GASTROINTESTINAL	Colitis	Abdominal pain; mucus or blood in stool	SAE	none		Resolved	09/04/2014
UK	204	CIS +STS	Chemotherapy course 4	26/04/2014	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	SAE	none		Resolved	27/04/2014
UK	204	CIS +STS	Chemotherapy course 5	13/05/2014	Tumor progression				PD	none		Resolved	21/05/2014

country	Pat. ID	Arm (as treated)	trial phase	Onset date	reason for seriousness	CTCAE SOC	CTCAE PT	severity	classi-fication	suspected drug	Causa-lity	Outcome	Outcome date
UK	204	CIS +STS	Chemotherapy course 5	17/05/2014	Required prolonged or unplanned hospitalisation	INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Localized, local intervention indicated	SAE	none		Resolved	20/05/2014
France	225	CIS +STS	Chemotherapy course 3	20/11/2014	Tumor progression				PD	STS	possible	Resolved	20/04/2015
France	226	CIS +STS	Chemotherapy course 3	09/12/2014	Required prolonged or unplanned hospitalisation	COAGULATION	Coagulation - Other (Specify, __)	Mild	SAE	none		Resolved	11/12/2014
UK	229	CIS +STS	Chemotherapy course 2	23/12/2014	Required prolonged or unplanned hospitalisation	CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	SAE	none		Resolved	26/12/2014