SIOPEL 6

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

International Childhood Liver Tumour Strategy Group - SIOPEL

Eudract Number: 2007-002402-21

Penelope Brock on behalf of the SIOPEL 6 Study Committee

Standard Risk Hepatoblastoma SR-HB

- Malignant embryonal tumour occurring at a young age (SIOPEL 6 median 13 months)
- Incidence SEER 1975-2012
  - 11.0 / 1,000,000 for children < 1 year old
  - 6.5 / 1,000,000 for children between 1 and 4 years old
- Overall survival > 90% in SR-HB with standard cisplatin chemotherapy started prior to surgery and continued 2 cycles after surgery. SIOPEL 3 trial NEJM Perilongo et. al. 2009
- Specific tumor marker : Serum alpha-foetoprotein (AFP)
- 60% of children develop irreversible ototoxicity with permanent high-frequency hearing loss of Brock grade ≥1 (data from SIOPEL 2 and 3)
- **In these young children hearing loss has a devastating and lifelong impact on their development and Quality of Life.**

SIOPEL 6

Objectives

- To assess the efficacy of STS to reduce the hearing impairment caused by Cisplatin
- To carefully monitor any potential impact of STS on response (protocol pre-specified tumor response review by IDMC at 20, 40, 60, 80 and 100 patients) to Cisplatin and overall survival

Study population

- Children 1 month –18 years old with histologically confirmed newly diagnosed SR-HB
- PRETEXT (PreTreatment EXTent of disease) I, II or III
- No vascular invasion, no extra-hepatic or metastatic disease
- serum AFP > 100 µg/L

Primary endpoint

- Centrally reviewed absolute hearing threshold, at the age of ≥3.5 yrs, by pure-tone audiometry, graded by Brock criteria (80% power to detect 60% vs. 35% hearing loss)
- Final results will be available once all patients have reached age 3.5 yrs, in 2017

Secondary endpoints: response, resection, EFS, OS and long term renal function

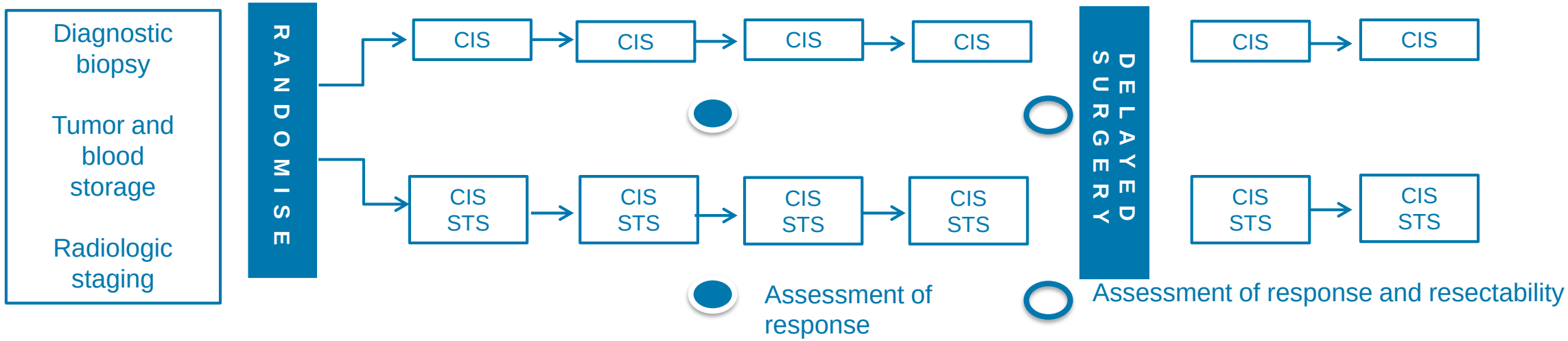
Brock classification of cisplatin-induced bilateral high-frequency hearing loss

Bilateral hearing loss	Grade	Designation
< 40 dB at all frequencies	0	Minimal
=/> 40 dB at 8,000 Hz only	1	Mild
=/> 40 dB at 4,000 Hz and above	2	Moderate
=/> 40 dB at 2,000 Hz and above	3	Marked
=/> 40 dB at 1,000 Hz and above	4	Severe

The results used are obtained by pure-tone audiometry from the "better" ear

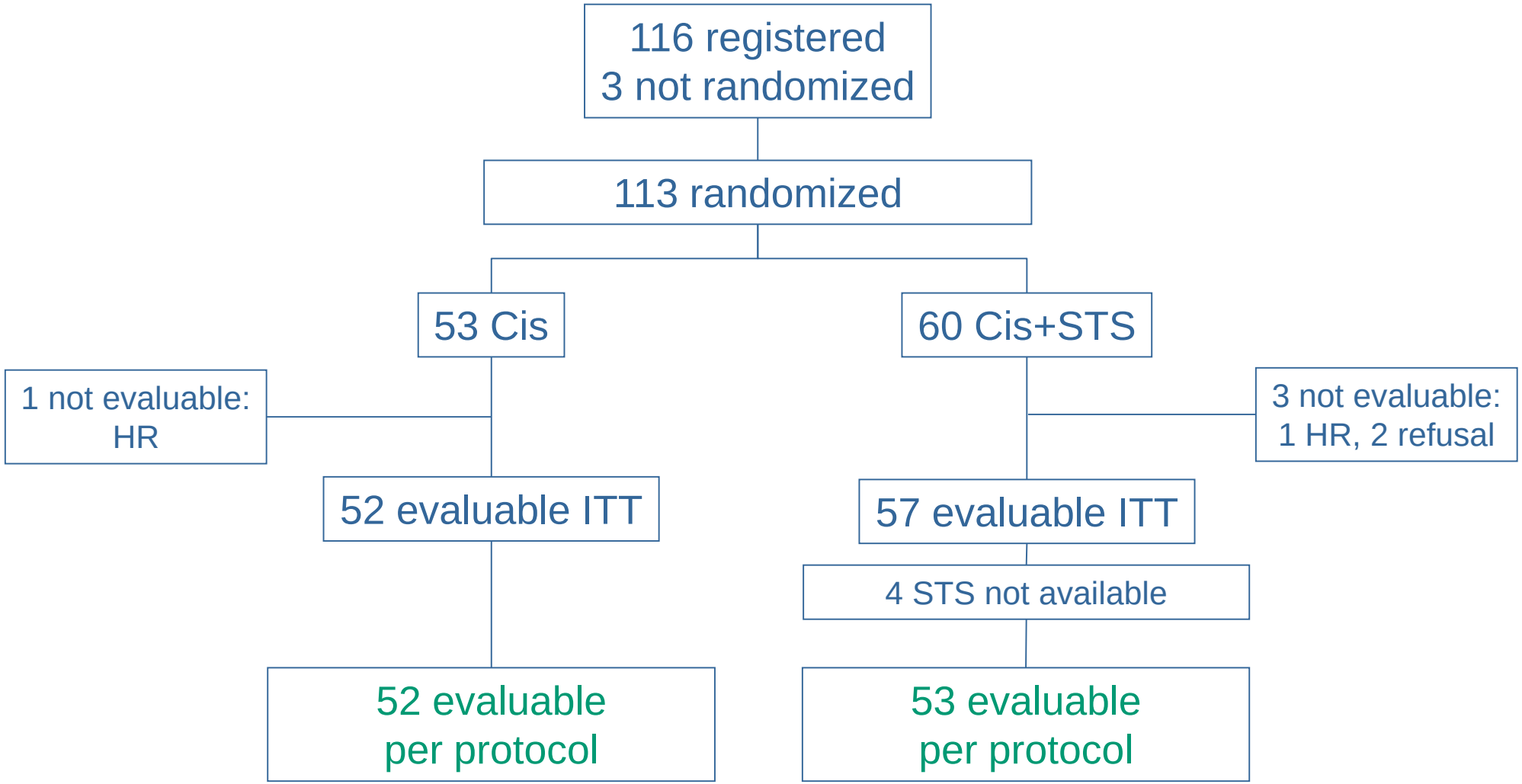
Brock grade 0 is not equivalent to normal hearing

SIOPEL 6: Study Methods and Design



- Cisplatin over 6 hrs i.v. at a dose of 80mg/m² (dose reduction 5 -10Kg & <5Kg)
- STS over 15 mins i.v. 6 hrs after stopping Cisplatin at 20g/m² (dose reduction 5 -10Kg & <5Kg)
- Serum sodium monitored 1 hr, 6 hrs and 18 hrs post STS
- Tumor response assessed preoperatively after 2 and 4 cycles with serum AFP and liver imaging
- **In case of progressive disease: stop STS and add doxorubicin**

CONSORT diagram



Patient characteristics

per protocol population

	Cis (N=52)	Cis+STS (N=53)
Age (months)	Median 13 Range 3.0 – 70	Median 13 Range 1.2 – 99
AFP (ng/mL)	Median 81,931 Range 187 – 24,760,000	Median 159,250 Range 273 – 4,536,500
Sex	M: 23 56% F: 29 44%	M: 25 53% F: 28 47%
PRETEXT I II III	0 31 60% 21 40%	10 19% 27 51% 16 30%

Patients were recruited between 2007 and 2014 from 53 centres in 11 countries

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SIOPEL 6 Response evaluation

Partial response: any tumor volume shrinkage associated with a decreasing serum AFP > 1 log fall below the original measurement

Stable disease: no tumor volume change and decreasing serum AFP < 1 log fall of the serum AFP from the original measurement

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 tumor re-growth

Response evaluation in early SIOPEL trials

Partial response: any tumor volume shrinkage and any drop in AFP level.

These criteria will also be shown in the result tables to enable a comparison to early SIOPEL trials. The rate of fall of serum AFP in hepatoblastoma has been shown to be of no prognostic significance.

SIOPEL 6 Response criteria after 2 cycles

per protocol population

	CIS	CIS+STS
Partial response	28 (54%)	21 (40%)
Stable disease	24 (46%)	32 (60%)

SIOPEL 6 Response criteria after 2 cycles

per protocol population

	CIS	CIS+STS
Partial response	28 (54%)	21 (40%)
Stable disease	24 (46%)	32 (60%)

Early SIOPEL Response criteria after 2 cycles

per protocol population

	CIS	CIS+STS
Partial response	49 (94%)	50 (94%)
Stable disease	3 (6%)	3 (6%)

SIOPEL 6 Response criteria after 4 cycles

per protocol population

	CIS	CIS+STS
Not evaluable	1 (2%)	2 (4%)
Partial response	40 (77%)	36 (68%)
Stable disease	6 (12%)	10 (19%)
Progressive disease	5 (10%)	5 (9%)

SIOPEL 6 Response criteria after 4 cycles

per protocol population

	CIS	CIS+STS
Not evaluable	1 (2%)	2 (4%)
Partial response	40 (77%)	36 (68%)
Stable disease	6 (12%)	10 (19%)
Progressive disease	5 (10%)	5 (9%)

Early SIOPEL Response criteria after 4 cycles

per protocol population

	CIS	CIS+STS
Not evaluable	1 (2%)	2 (4%)
Partial response	46 (88%)	46 (87%)
Stable disease	0 (0%)	0 (0%)
Progressive disease	5 (10%)	5 (9%)

Resection after preoperative chemotherapy

per protocol population

	CIS	CIS+STS
Partial hepatectomy	48 (92%)	49 (92%)
Liver transplantation	4 (8%)	4 (8%)

Status at end of treatment

per protocol population

	CIS	CIS+STS
Complete remission	44 (85%)	48 (91%)
Partial remission	4 (8%)	5 (9%)
Progressive disease	2 (4%)	0
Death	1 (2%)	0
Not evaluable	1	0

Status at last follow-up
per protocol

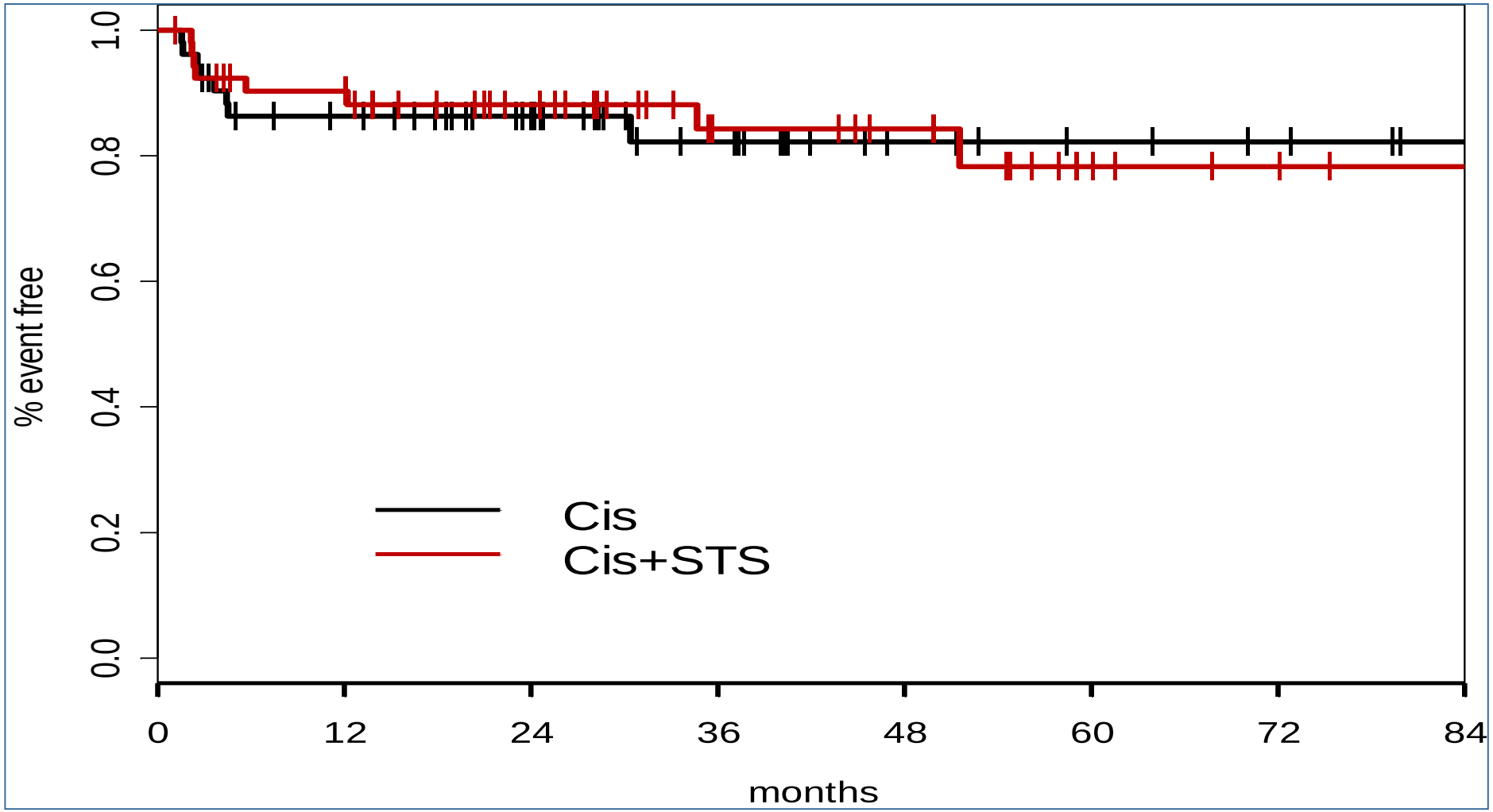
	CIS	CIS+STS
Complete remission	48 (92%)	50 (94%)
Partial remission	0	1 (2%)
Recurrent disease	0	1 (2%)
Death	4 (8%)	1 (2%)

18 patients received between 1 and 6 courses of doxorubicin during initial therapy

CIS:9; CIS+STS:9

Event free survival

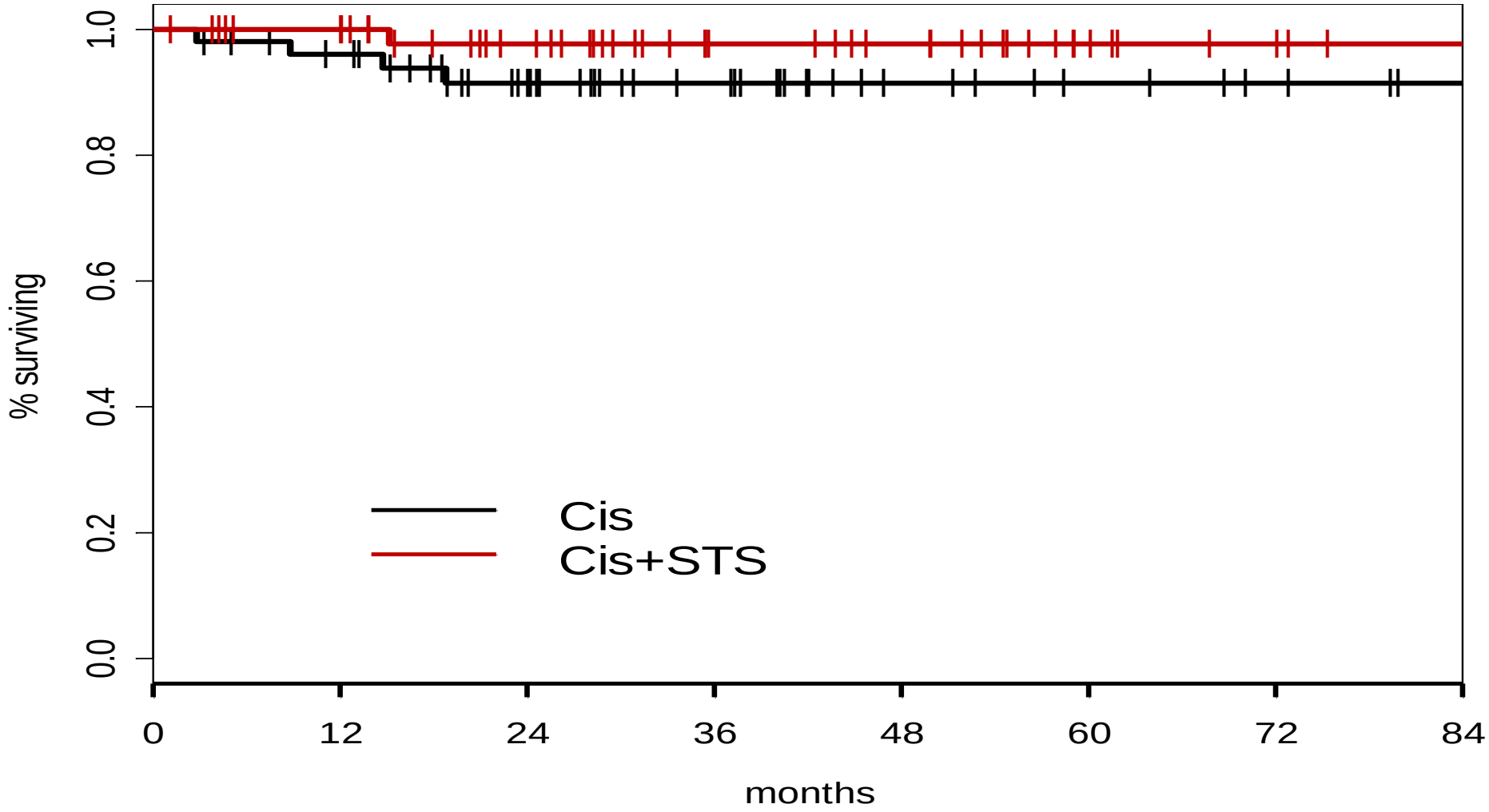
per protocol analysis
median follow-up 34 months



2yr-EFS Cis 86.3%, Cis+STS 89.0%

Overall survival

per protocol analysis
median follow-up 34 months



2yr-OS Cis 91.4%, Cis+STS 97.7%

SIOPEL 6 Adverse Events

Adverse event	Grade	CIS		CIS+STS	
		N	%	N	%
Febrile neutropenia	3	3	6.4	5	10.4
	4	-	-	-	-
Infection	3	5	10.6	6	12.6
	4	-	-	-	-
Hypomagnesemia	3	1	2.1	1	2.1
	4	-	-	-	-
Hypernatremia	3	-	-	1	2.1
	4	-	-	-	-
Vomiting	3	1	1.2	2	4.2
	4	-	-	-	-
Nausea	3	3	6.4	2	4.2
	4	-	-	-	-

SIOPEL 6 Conclusions

- It is safe to deliver Sodium Thiosulphate for otoprotection in Standard Risk Hepatoblastoma treated according to the SIOPEL 6 regimen.
- There is no evidence of tumor protection.
- Results for the audiology primary end point will be available in 2017.
- The interim results of the first 68 patients achieving centrally reviewed pure tone audiometry at or above 3.5 years of age were encouraging.

Acknowledgements and Thanks

- To all participating families, professionals, centres and countries.
- To Professor Edward Neuwelt and the OHSU team for the pre clinical data and ongoing collaboration.
- To Fennec for providing STS
- To CINECA for the database
- To National charities for funding

Recruitment closed on 31.12.2014 with 109 analysable patients

Year	# patients
2007	2
2008	1
2009	9
2010	19
2011	17
2012	17
2013	17
2014	27

All participating centres

Country	Centre name	pts
Australia	John Hunter Children's Hospital	1
Australia	Sydney Children's Hospital	1
Australia	Royal Children's Hospital	3
Belgium	University Hospital Ghent	3
Belgium	ZNA Child Hospital	1
Belgium	Clinique Universitaire Saint Luc	1
Belgium	University Hospitals Leuven	1
Denmark	Rigshospitalet	1
France	Institute Gustave Roussy	5
France	Hopital des Enfants, Toulouse	1
France	CHU d'Amiens	1
France	CHU de Besancon	2
France	CHU Pellegrin – Enfant, Bordeaux	2
France	CHU Cote de Nacre, Caen	1
France	CHU Reims	1
France	CHU Dijon	2
France	CHU Grenoble	1
France	Centre Oscar Lambret, Lille	2
France	CHU Timone Enfants, Marseille	3
France	CHU A. de Villeneuve, Montpellier	1
France	HME Nantes	1
France	G.H. Armand Trousseau, Paris	2
France	Institut Curie, Paris	4
France	CHU-Rouen	1
France	CHU Hautepierre, Strasbourg	1
France	Hopital D'Enfants de Brabois	1
Ireland	Our Lady's Children's Hospital, Crumlin, Dublin	2
Italy	Policlinico of Catania	1
Italy	Department of Paediatrics, Padova	4
Italy	Ospedale Bambino Gesu IRCCS, Roma	2
Japan	Hiroshima University	5
New Zealand	Starship Children's Hospital, Auckland	2
New Zealand	Christchurch Hospital	1
Switzerland	Univ. Children's Hospital Basel	1
Switzerland	Univ. Children's Hospital Zurich	1
Spain	Univ. Hospital Reina Sofia, Cordoba	3
Spain	Hospital Materno-Infatil Carlos Haya, Malaga	2
UK	Birmingham Children's Hospital	3
UK	Bristol Royal Hospital for Children	4
UK	Addenbrooke's Hospital Cambridge	2
UK	Royal H. for Sick Children Edinburgh	1
UK	Royal Hosp. of Sick Children Glasgow	3
UK	St James's University Hospital, Leeds	1
UK	Leicester Royal Infirmary	1
UK	GOS 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 Childrens Hospital Pendlebury	4
UK	Sheffield Children's Hospital	1
UK	Children's Hospital Cardiff	2
UK	Southampton General Hospital	1
USA	Stanford University LPCH, Palo Alto	2

Patients received a documented total of 638 cycles of chemotherapy

	pre-surgery	post-surgery	total
Pre-operative Course 1+2	213	3	216
Pre-operative Course 3+4	201	8	209
Post-operative Course 5+6	22	148	170
Additional Chemotherapy: PLADO	23	20	43
Total	459	179	638