



# 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  $\geq 1$  (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  $\geq 3.5$  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

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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

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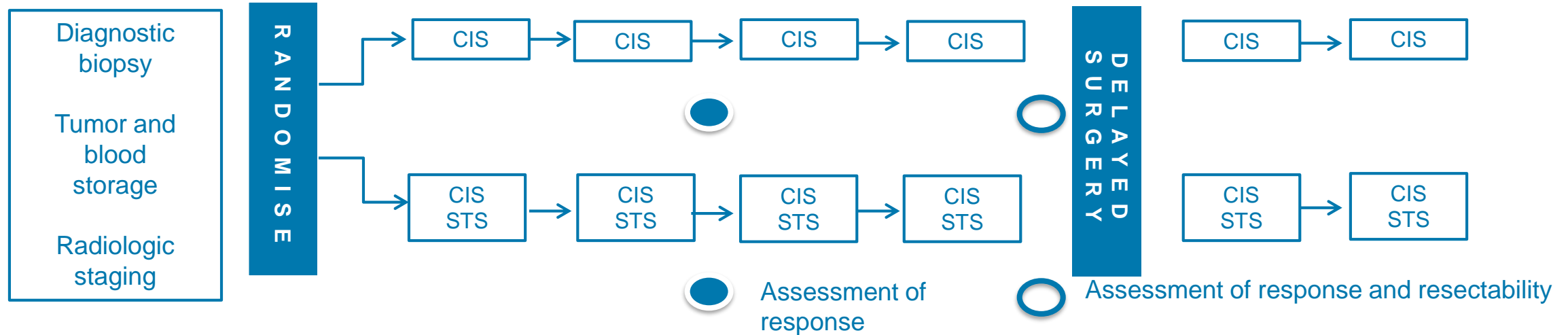
The results used are obtained by pure-tone audiometry from the "better" ear

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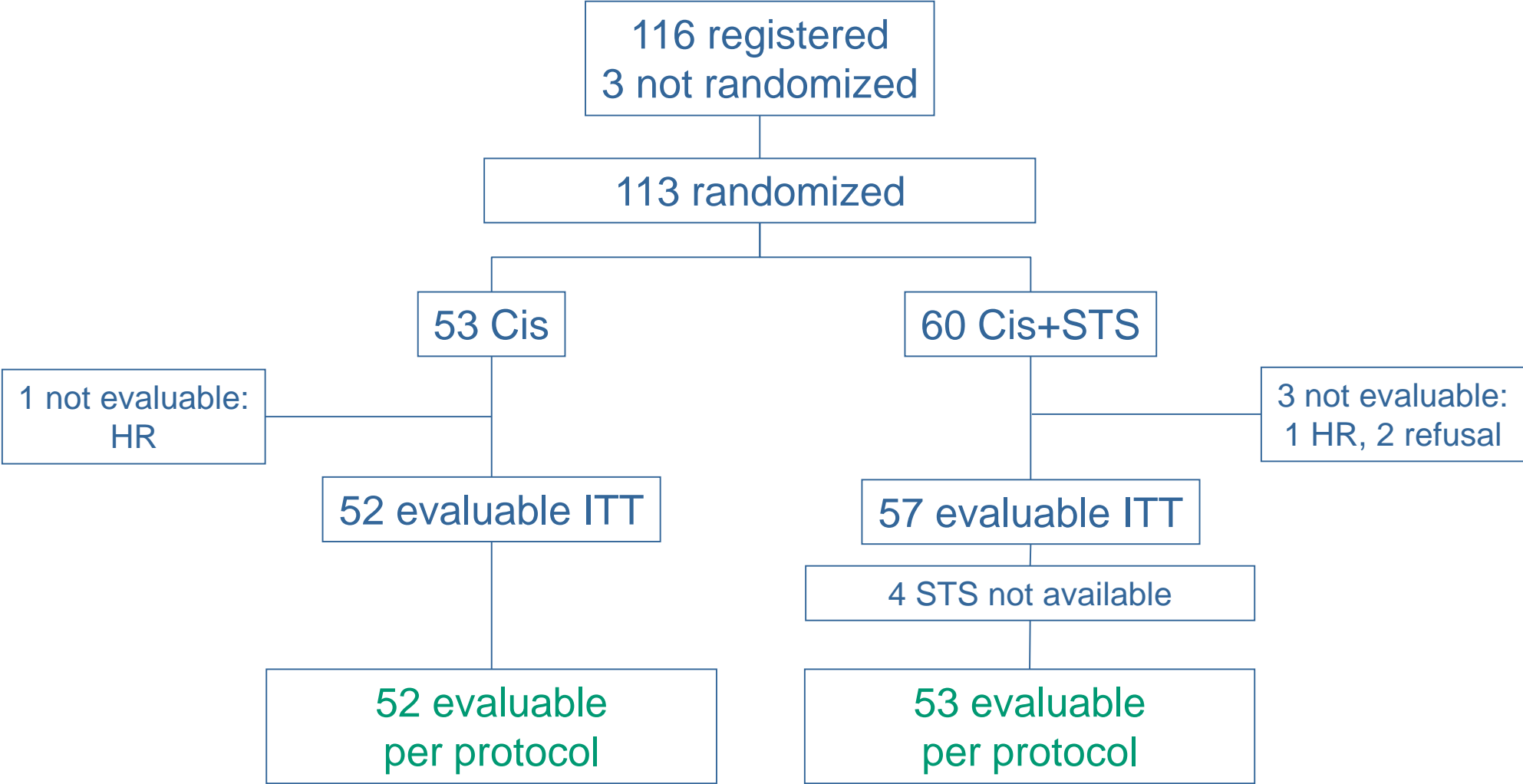
**Brock grade 0 is not equivalent to normal hearing**

# SIOPEL 6: Study Methods and Design



- Cisplatin over 6 hrs i.v. at a dose of 80mg/m<sup>2</sup> (dose reduction 5 -10Kg & <5Kg)
- STS over 15 mins i.v. 6 hrs after stopping Cisplatin at 20g/m<sup>2</sup> (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	0	10 19%
PRETEXT II	31 60%	27 51%
PRETEXT III	21 40%	16 30%

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

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PRETEXT		
I	0	10 19%
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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

	<b>CIS</b>	<b>CIS+STS</b>
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

	<b>CIS</b>	<b>CIS+STS</b>
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

	<b>CIS</b>	<b>CIS+STS</b>
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

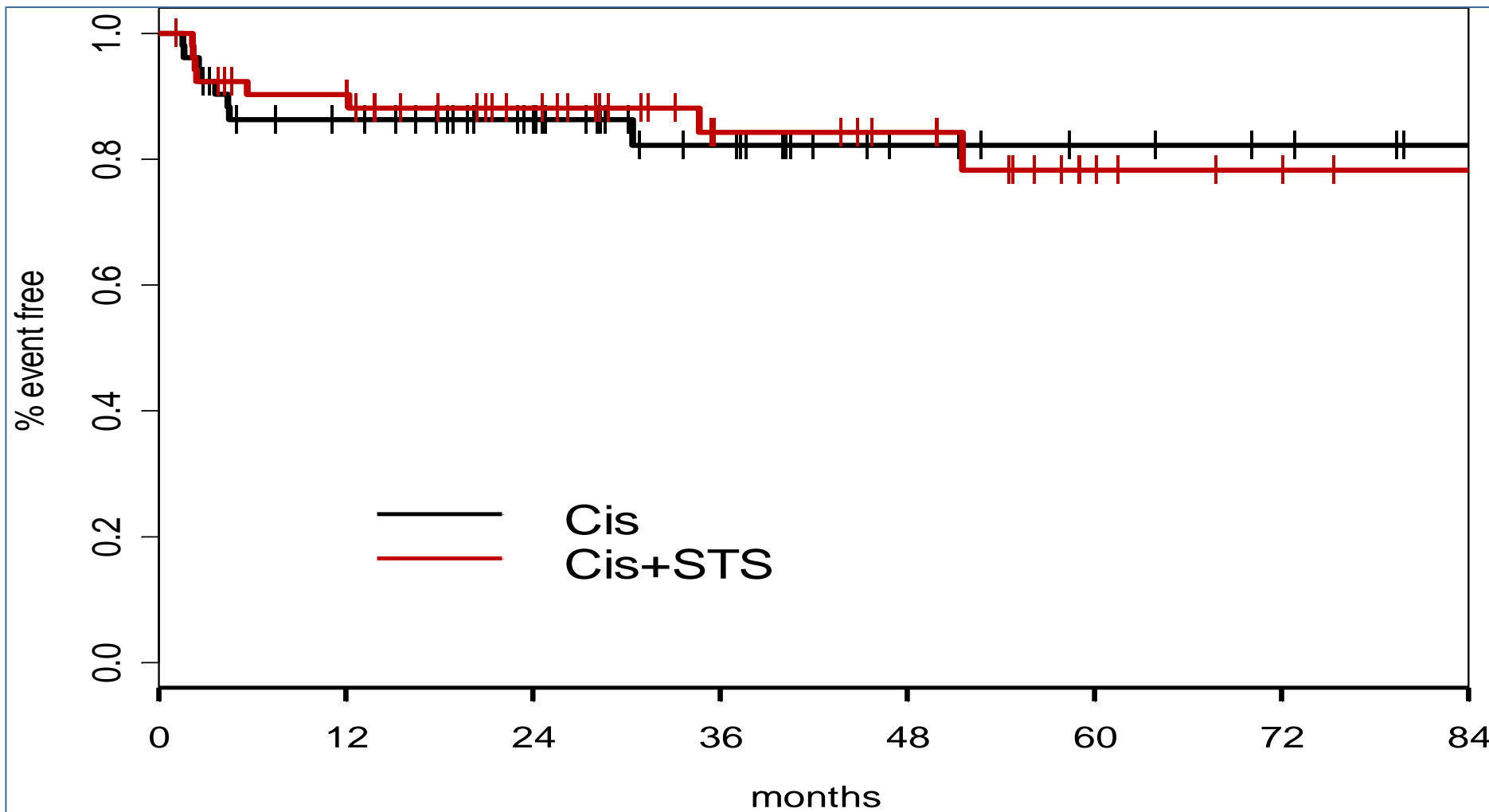
	<b>CIS</b>	<b>CIS+STS</b>
Complete remission	48 (92%)	50 (94%)
Partial remission	0	1 ( 2%)
Recurrent disease	0	1 ( 2%)
Death	4 ( 8%)	1 ( 2%)

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

CIS:9; CIS+STS:9

# Event free survival

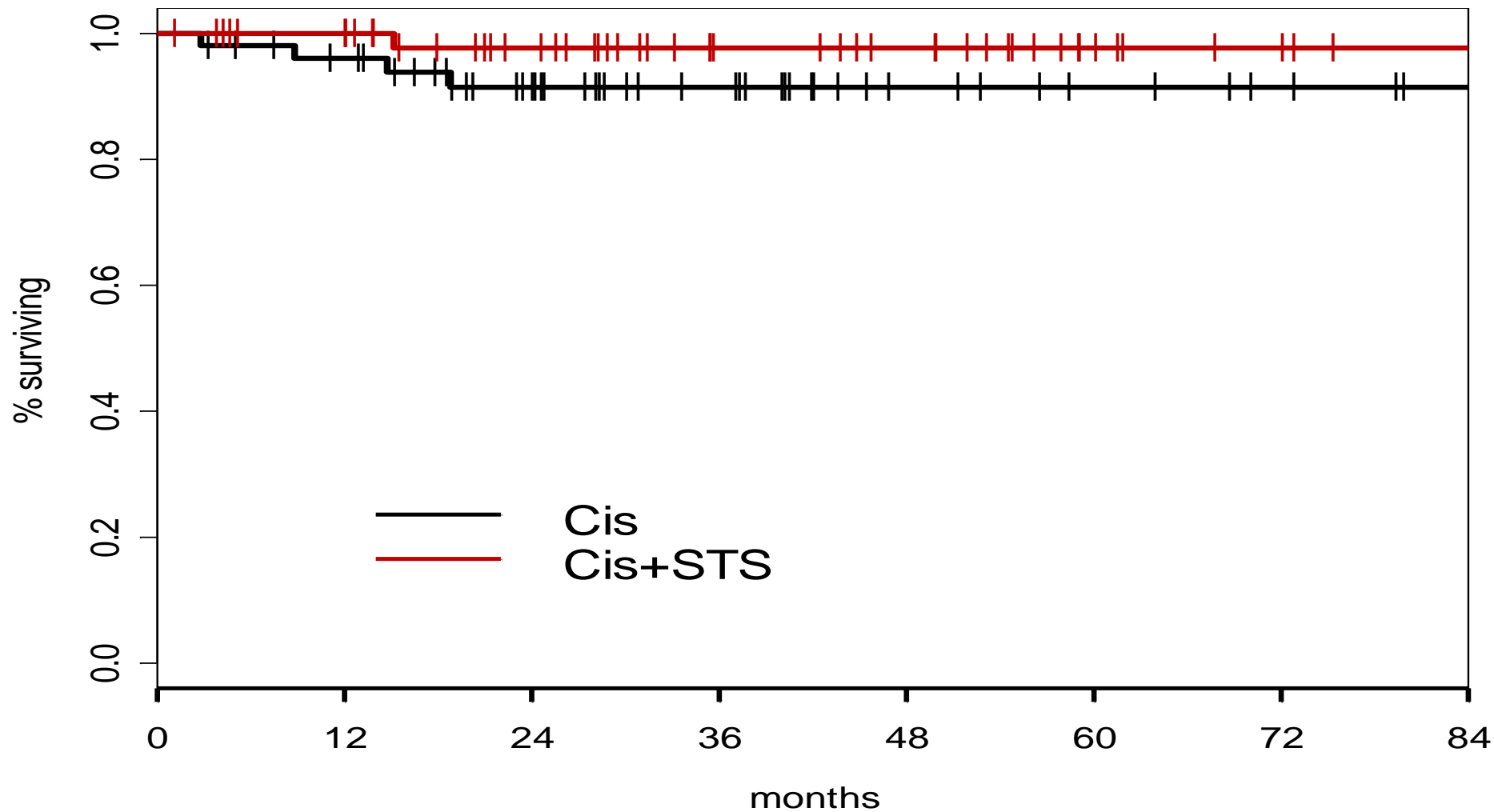
per protocol analysis  
median follow-up 34 months



**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			
			Ireland	Our Lady's Children's Hospital, Crumlin, Dublin	2
Australia	John Hunter Children's Hospital	1	Italy	Policlinico of Catania	1
Australia	Sydney Children's Hospital	1	Italy	Department of Paediatrics, Padova	4
Australia	Royal Children's Hospital	3	Italy	Ospedale Bambino Gesu IRCCS, Roma	2
Belgium	University Hospital Ghent	3	Japan	Hiroshima University	5
Belgium	ZNA Child Hospital	1	New Zealand	Starship Children's Hospital, Auckland	2
Belgium	Clinique Universitaire Saint Luc	1	New Zealand	Christchurch Hospital	1
Belgium	University Hospitals Leuven	1	Switzerland	Univ. Children's Hospital Basel	1
Denmark	Rigshospitalet	1	Switzerland	Univ. Children's Hospital Zurich	1
France	Institute Gustave Roussy	5	Spain	Univ. Hospital Reina Sofia, Cordoba	3
France	Hopital des Enfants, Toulouse	1	Spain	Hospital Materno-Infantil Carlos Haya, Malaga	2
France	CHU d'Amiens	1	UK	Birmingham Children's Hospital	3
France	CHU de Besancon	2	UK	Bristol Royal Hospital for Children	4
France	CHU Pellegrin – Enfant, Bordeaux	2	UK	Addenbrooke's Hospital Cambridge	2
France	CHU Cote de Nacre, Caen	1	UK	Royal H. for Sick Children Edinburgh	1
France	CHU Reims	1	UK	Royal Hosp. of Sick Children Glasgow	3
France	CHU Dijon	2	UK	St James's University Hospital, Leeds	1
France	CHU Grenoble	1	UK	Leicester Royal Infirmary	1
France	Centre Oscar Lambret, Lille	2	UK	GOS Hospital London	13
France	CHU Timone Enfants, Marseille	3	UK	Sir James Spence Institute of Child Health, Newcastle upon Tyne	2
France	CHU A. de Villeneuve, Montpellier	1			
France	HME Nantes	1	UK	Queen's Medical Centre Nottingham	1
France	G.H. Armand Trousseau, Paris	2	UK	Royal Manchester Childrens Hospital Pendlebury	4
France	Institut Curie, Paris	4			
France	CHU-Rouen	1	UK	Sheffield Children's Hospital	1
France	CHU Hautepierre, Strasbourg	1	UK	Children's Hospital Cardiff	2
France	Hopital D'Enfants de Brabois	1	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
<b>Total</b>	<b>459</b>	<b>179</b>	<b>638</b>