



FENNEC PHARMA

February 2019 | Corporate Deck

# SAFE HARBOR STATEMENT

During the course of this presentation we will make statements that constitute forward-looking statements. These statements may include operating expense projections, the initiation, timing and results of pending or future clinical trials, the actions or potential action of the FDA, the status and timing of ongoing research, corporate partnering activities and other factors affecting Fennec Pharma's financial condition or operations. Such forward looking statements are not guarantees of future performance and involve risk, uncertainties and other factors that may cause actual results, performance or achievements to vary materially from those expressed or implied in such statements.

These and other risk factors are listed from time to time in reports filed with the SEDAR and the Securities and Exchange Commission, including but not limited to, reports on Forms 10-Q and 10-K. Fennec does not intend to update any forward looking information to reflect actual results or changes in the factors affecting forward-looking information.



# PLATINUM-BASED CHEMOTHERAPY: CISPLATIN

## Introduction: 1980s, "Penicillin of Cancer"

Demonstrated high efficacy in the treatment of a variety of solid pediatric tumors

## Effects

Can cause irreversible high frequency hearing loss, or ototoxicity in children

## Wide Use

Stand-alone and combination mainstay use despite the approval of new chemotherapy treatments, targeted agents and immunotherapy drugs

## Ototoxicity

Is permanent, severe and irreversible



## Health Care Surveillance

As high survival rates for childhood cancers have been achieved, there is a growing need for monitoring the long-term effects of platinum based chemotherapy in primary care settings

# COMPANY OVERVIEW

US-based biopharmaceutical company focused on the development of **PEDMARK™** (a unique formulation of sodium thiosulfate (STS)) for the prevention of platinum-induced ototoxicity in children with solid tumors

- **7.5 YEARS** US MARKET EXCLUSIVITY  
Pediatric Orphan Drug Designation
- **10 YEARS** EU MARKET EXCLUSIVITY  
Pediatric-use Marketing Authorization (PUMA)



# COMPANY OVERVIEW

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## **Proof of Concept Study: COG ACCL0431**

131 patients with heterogeneous solid tumors

Achieved primary efficacy endpoint - ASCO 2014

Final results: Lancet Oncology - December 2016

## **Pivotal Study: SIOPEL 6**

109 patients with standard risk hepatoblastoma (SR-HB)

Achieved primary efficacy endpoint - SIOP 2017

Showed no evidence of tumor protection

Final results: New England Journal of Medicine - June 2018

## **Granted Fast Track and Breakthrough Therapy Designation by FDA**

## **Positive opinion on Pediatric Investigation Plan (PIP) received by Pediatric Committee (PDCO) at EMA**

## **Initiated Rolling NDA to FDA**

PEDMARK is proposed to be indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 yrs of age with localized, non-metastatic, solid tumors

PEDMARK™ has the potential to fill a significant unmet medical need with no approved treatments on market

# PLATINUM HEARING LOSS EFFECTS

## Ototoxicity

Is often a dose-limiting side effect

## Effects

Can be seen after as little as the second or third dose

## Hearing Loss

Loss of high frequency hearing sensitivity (consonants f/th/p/k/h/t)

## Disability

Background noise compounds disability in critical settings

## Speech Language

Infants and young children at critical stage of development, lack speech language development and literacy

## Lack in Development

Older children and adolescents lack social-emotional development and educational achievement

At least **60%** of children develop irreversible **ototoxicity\***

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Devastating and **life-long** impact on quality of life

\*Neuwelt and Brock. J Clin Oncol 2010;28:1630-1632

# DEVASTATING IMPACT ON QUALITY OF LIFE

Long term follow up of neuroblastoma survivors with hearing loss

## Grade Setbacks

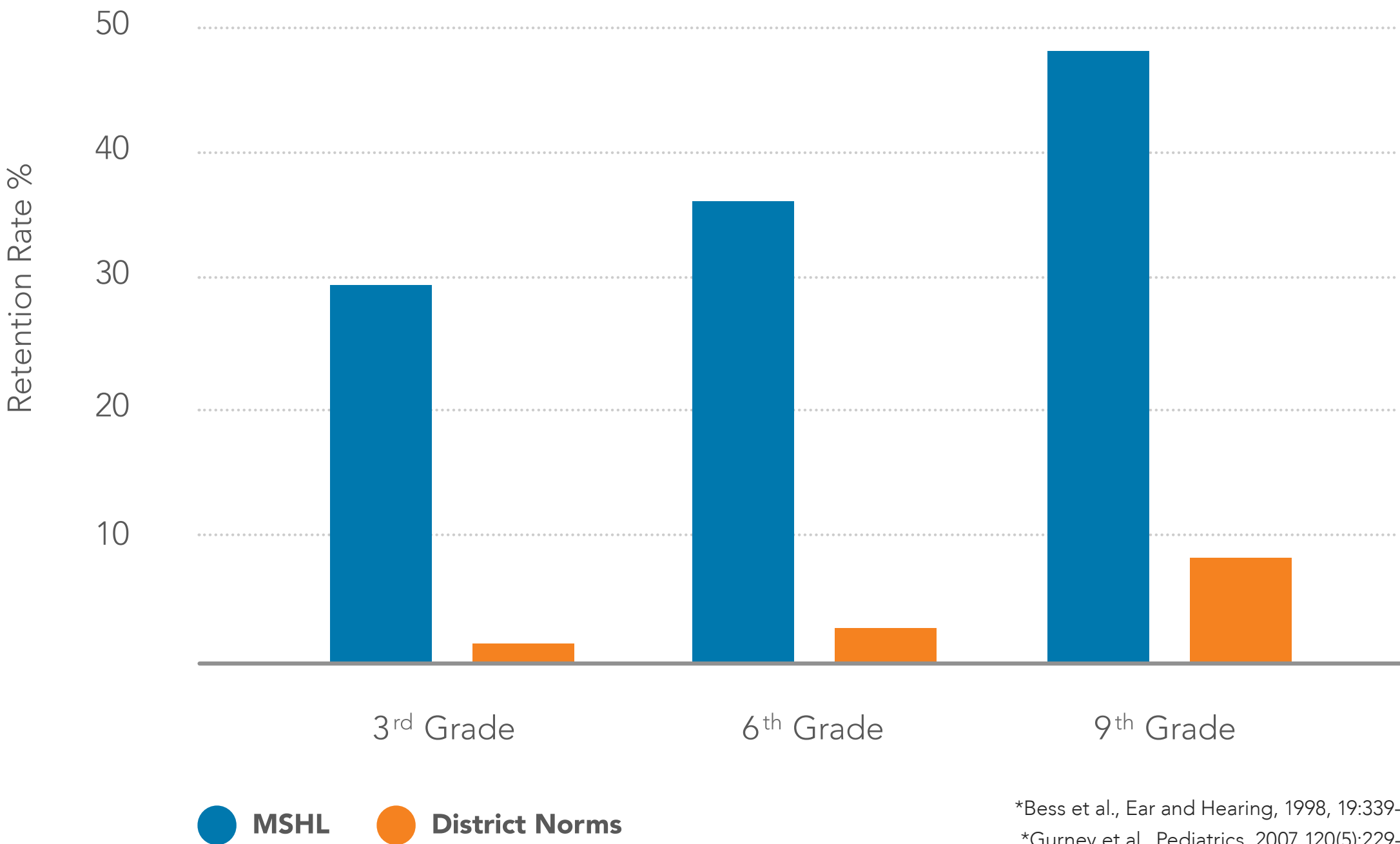
High risk for being held back a grade (37% versus 3%)

## Learning Problems

Twice the rate of parents reported problems with reading, math, attention and need for special education

## Quality of Life

Poorer child-reported quality of life and school functioning

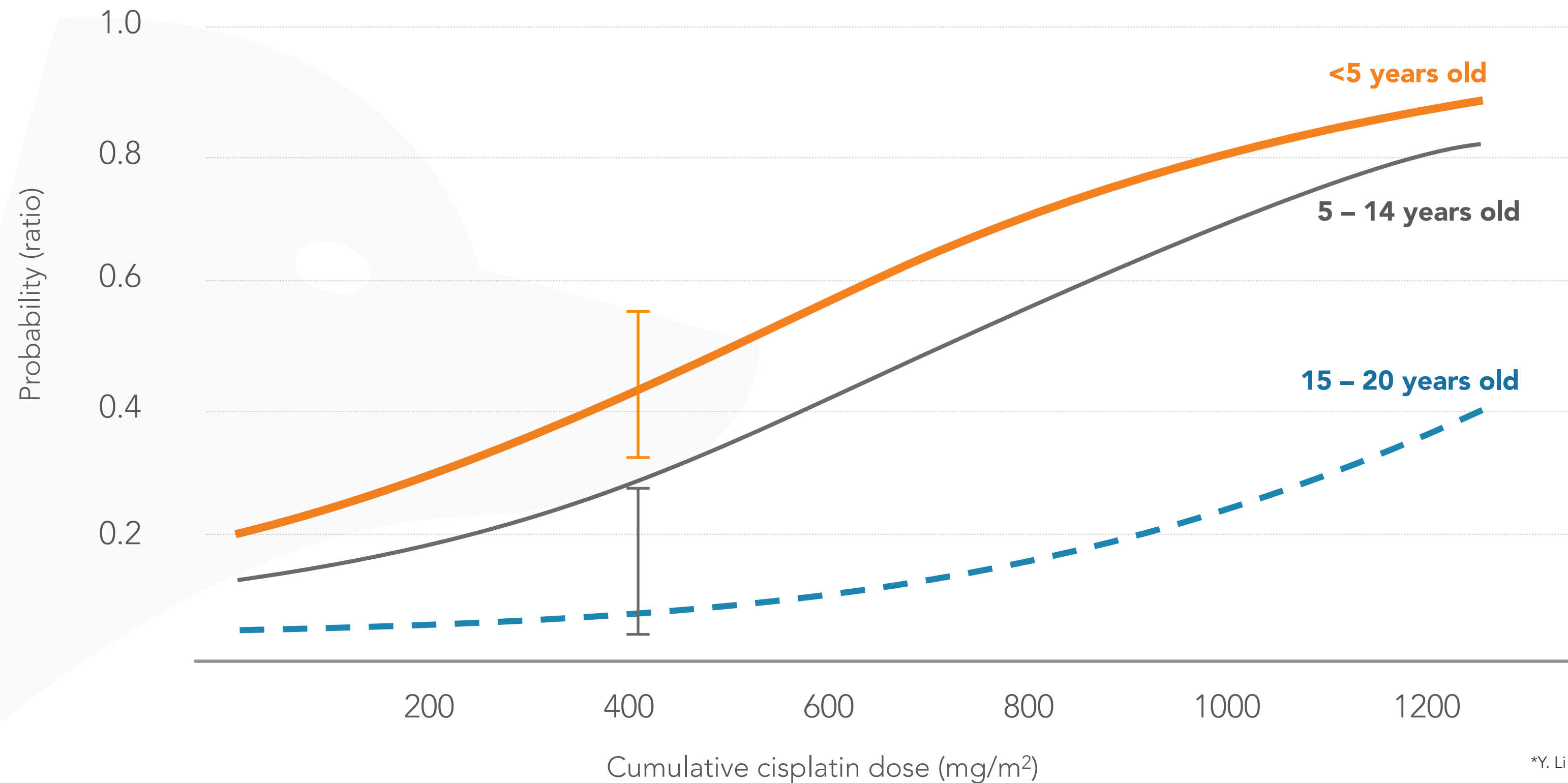


\*Bess et al., Ear and Hearing, 1998, 19:339-54  
\*Gurney et al., Pediatrics, 2007 120(5):229-36  
Minimum sensorineural hearing loss (MSHL)

Even minimal hearing loss is damaging

# RISK FACTORS

Probability of Brock's Level 2 or worse hearing loss



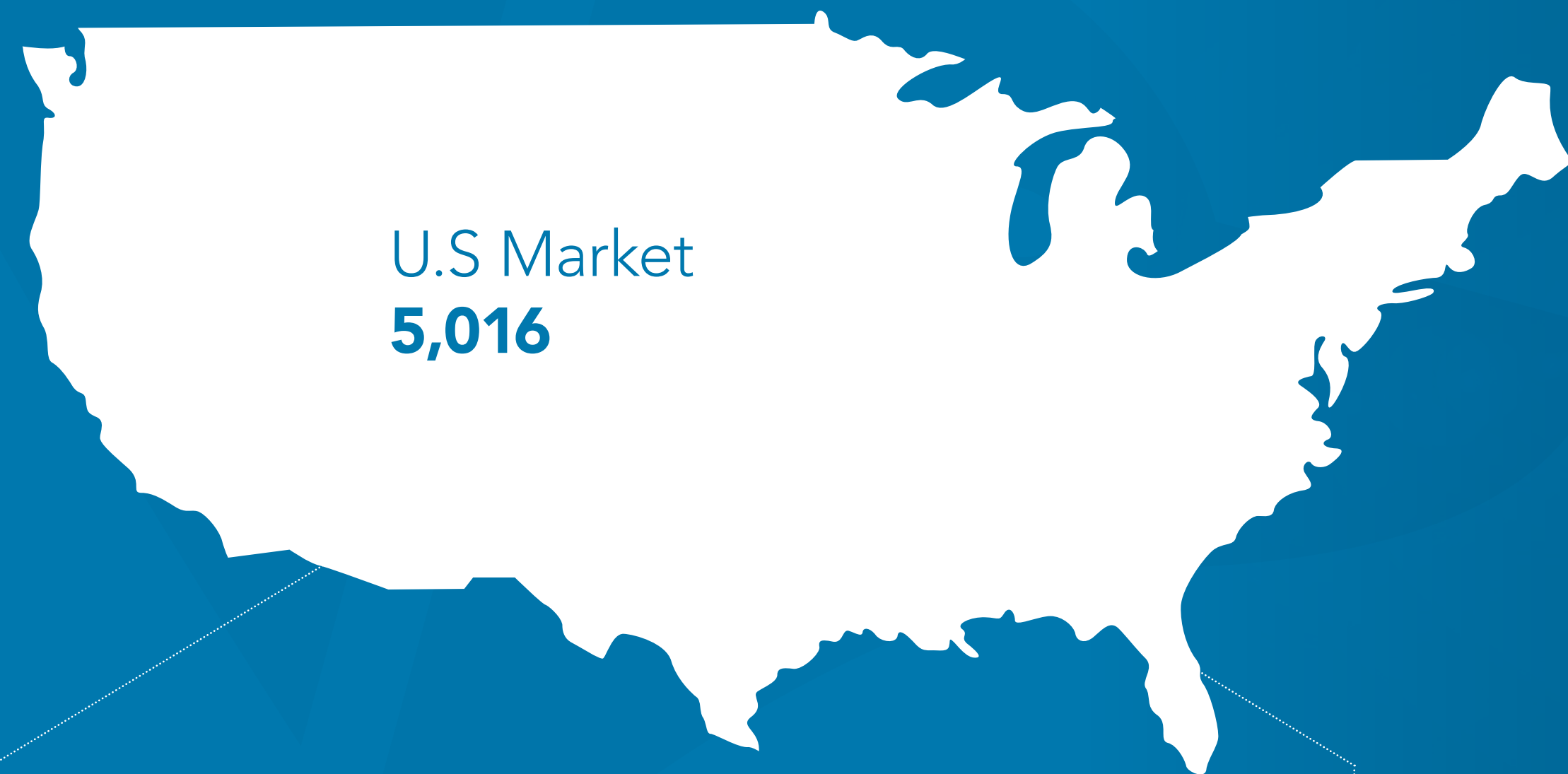
\*Y. Li et al. | European Journal of Cancer 40 (2004) 2445-2451

Children <5 years old: **21 times** the risk for hearing loss compared to adolescents



# MARKET OPPORTUNITY

Annual incidence of pediatric solid tumor cases eligible for Platinum-Based Therapy in both US and EU markets



**~30%** 1,462 Metastatic  
**~70%** 3,554 Localized, non-metastatic



**~30%** 1,711 Metastatic  
**~70%** 4,215 Localized, non-metastatic

\*Sources: Company estimates, ACCIS, and Ward, E. (2014). Childhood and Adolescent Cancer Statistics, 2014.

# PEDMARK: SODIUM THIOSULFATE (STS)

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## Indication

Approved in US and some EU countries for the treatment of cyanide poisoning

## Drug Delivery

STS is administered 6 hours post cisplatin infusion in a bolus dose iv over 15 min

## Toxicology

STS is generally recognized as safe (GRAS in US)

## Mechanism of Action\*

Anticancer activity of cisplatin occurs during the first two hours after administration when the free (unbound) cisplatin distributes into the cancer cells

Inactivation of protein-bound platinum complexes causing ototoxicity in the inner ear

STS reacts irreversibly with cisplatin to form Pt (S<sub>2</sub>O<sub>3</sub>) which is not cytotoxic and is readily excretable

\*Howell and Taetle 1980; Neuwelt, Brummett et al. 1996

# PROOF OF CONCEPT STUDY

## COG ACCL0431 | Lancet Oncology 2016

1

### Primary Endpoint

Evaluate efficacy of STS for prevention of hearing loss in children receiving cisplatin chemotherapy (hypothesis: 50% relative reduction in hearing loss). Measured by hearing status at 4 weeks post-therapy defined by American Speech-Language-Hearing Association (ASHA) criteria:

> 20 dB loss at 1 frequency or > 10 dB at 2 consecutive frequencies

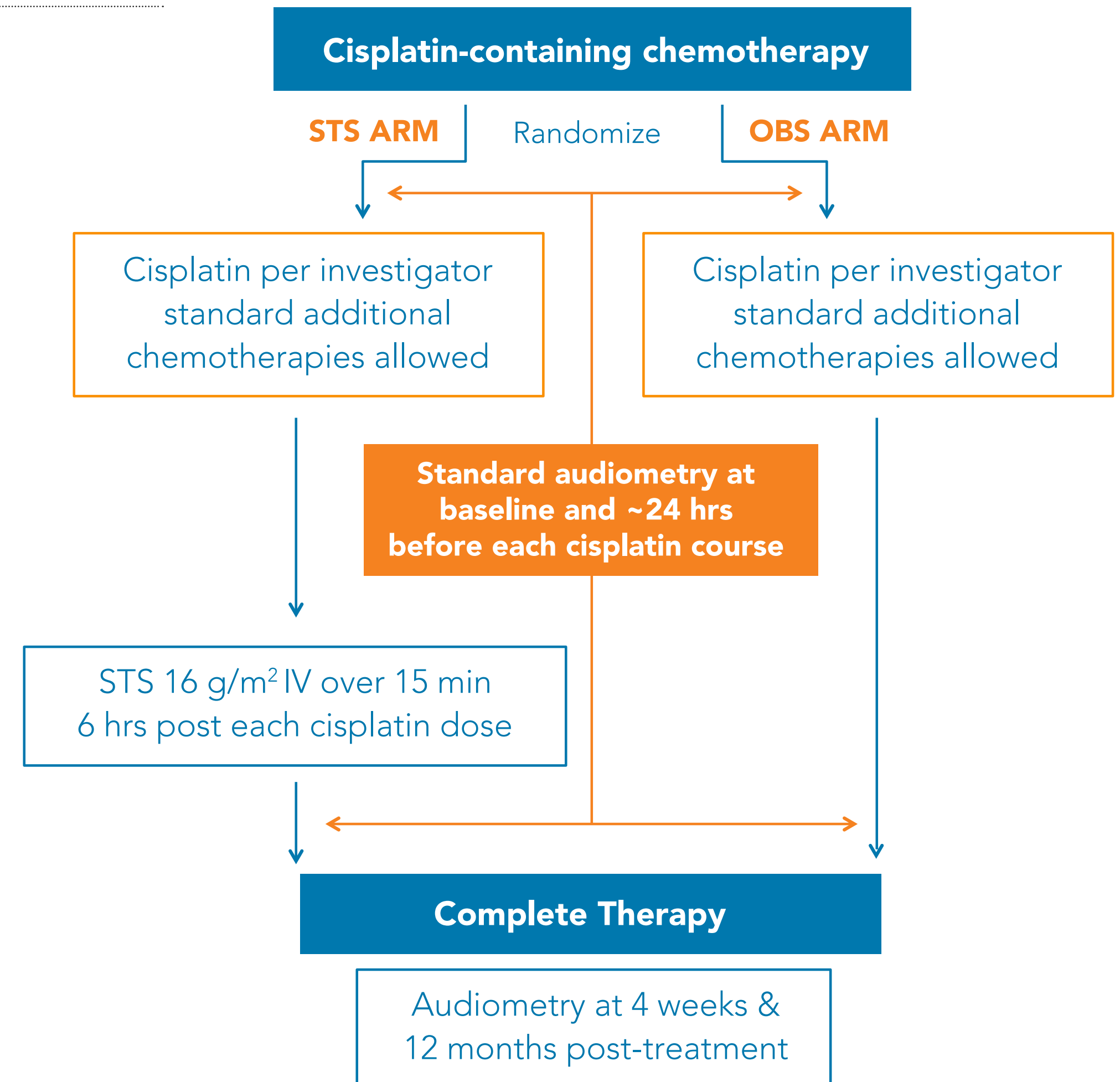
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### Secondary Endpoints

Compare change in mean hearing thresholds

Compare incidence of other Grade 3/4 toxicities (renal and hematological)

Monitor EFS and OS in two randomized groups



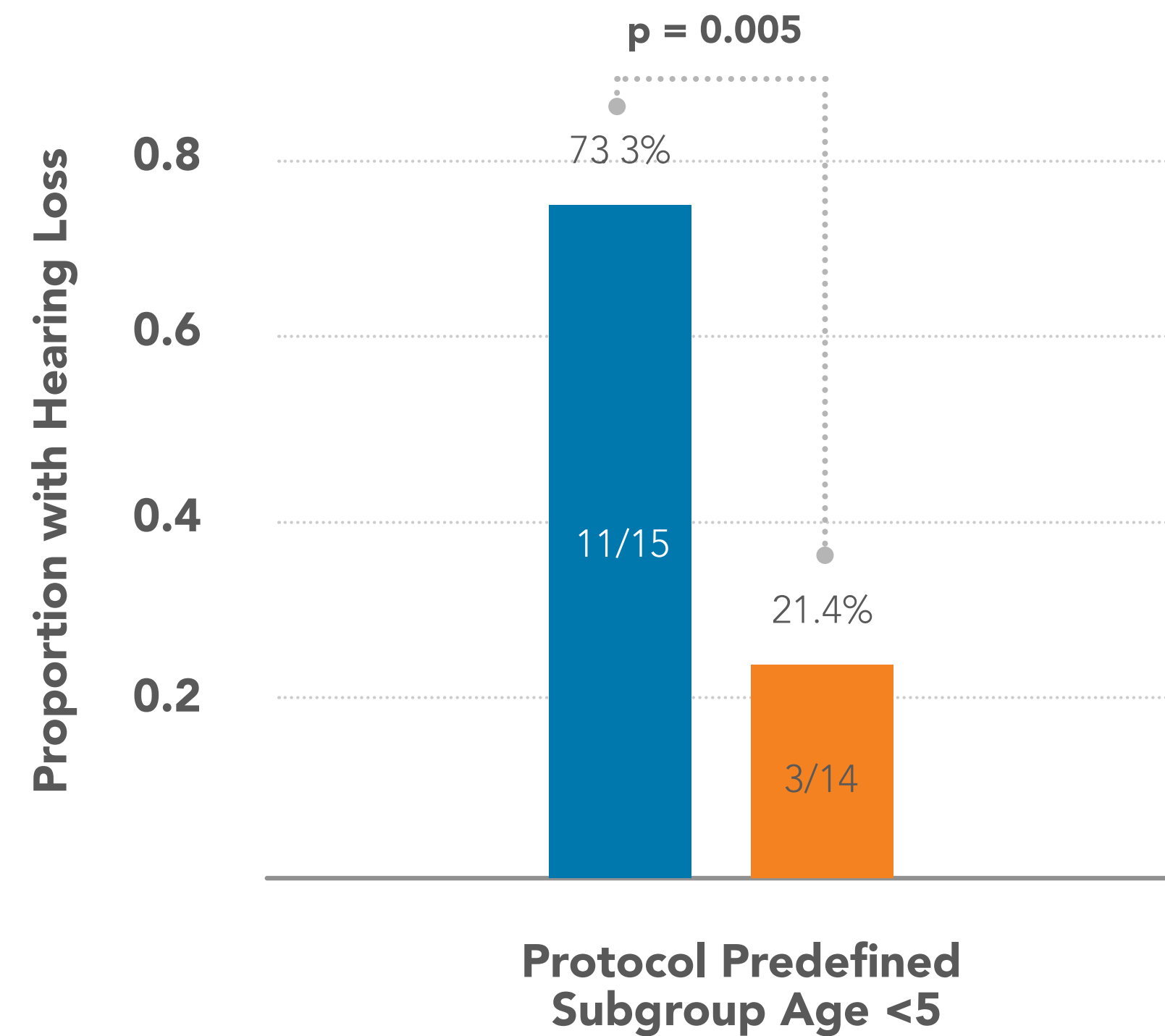
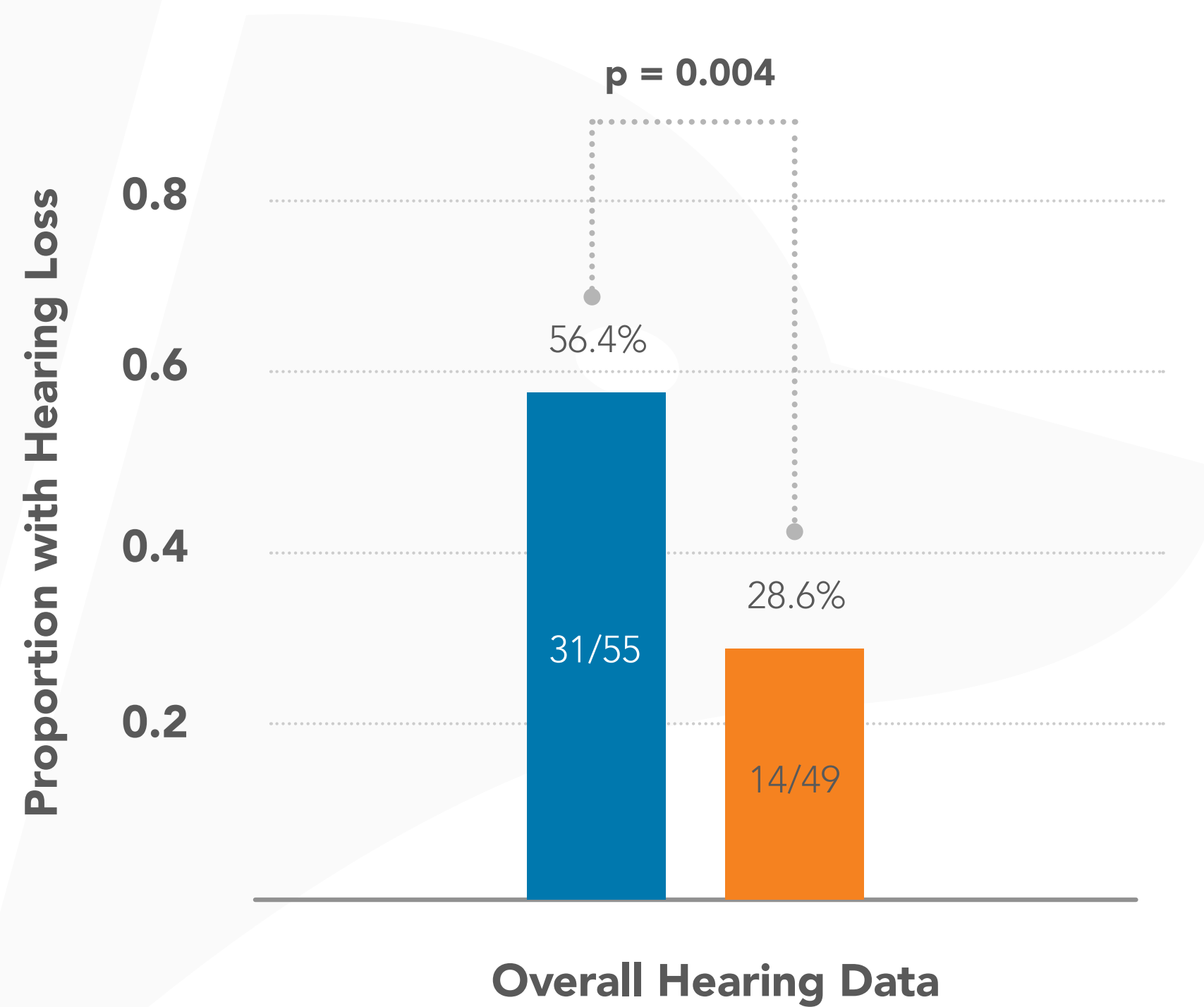
# PARTICIPANT CHARACTERISTICS

		n CONTROL %		n STS %	
<b>Number Eligible</b>		64	–	61	–
Age (years)	<b>&lt;5</b>	22	34.4	22	36.1
	<b>5 – 9</b>	13	20.3	7	11.5
	<b>10 – 14</b>	14	21.9	16	26.2
	<b>15 – 18</b>	15	23.4	16	26.2
Diagnosis	<b>Germ Cell Tumor</b>	16	25.0	16	26.2
	<b>Hepatoblastoma</b>	5	7.8	2	3.2
	<b>Medulloblastoma/PNET</b>	14	21.9	12	19.7
	<b>Neuroblastoma</b>	12	18.8	14	23.0
	<b>Osteosarcoma</b>	15	23.4	14	23.0
	<b>Other</b>	2	3.1	3	4.9
Extent of disease	<b>Localized</b>	38	59.4	39	63.9
	<b>Disseminated</b>	26	40.6	21	34.4
	<b>Unknown</b>	0	0	1	1.6



COG ACCL0431 | Lancet Oncology 2016

# HEARING LOSS RANDOMIZED ARM

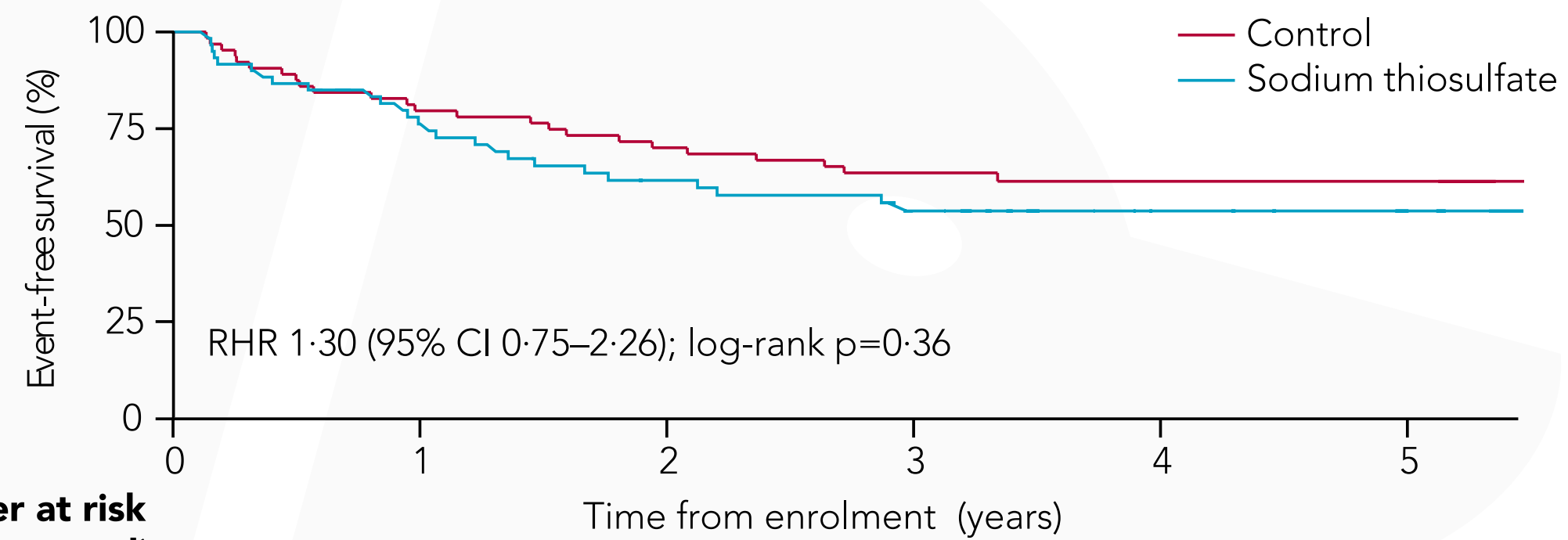


N = 104 evaluable patients

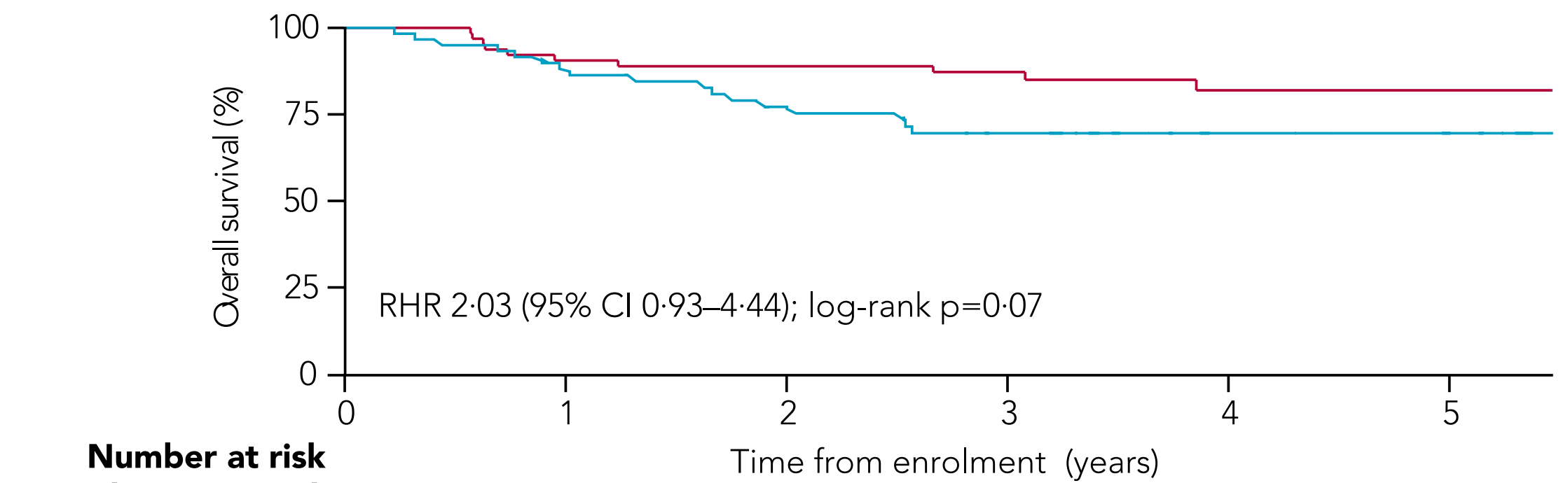
● OBS ● STS

COG ACCL0431 | Lancet Oncology 2016

# EFS/OS: ALL PARTICIPANTS



	0	1	2	3	4	5
<b>Number at risk (number censored)</b>						
Control	64 (0)	50 (1)	44 (0)	34 (6)	19 (14)	4 (15)
Sodium thiosulfate	61 (0)	43 (3)	32 (3)	25 (3)	10 (15)	6 (4)

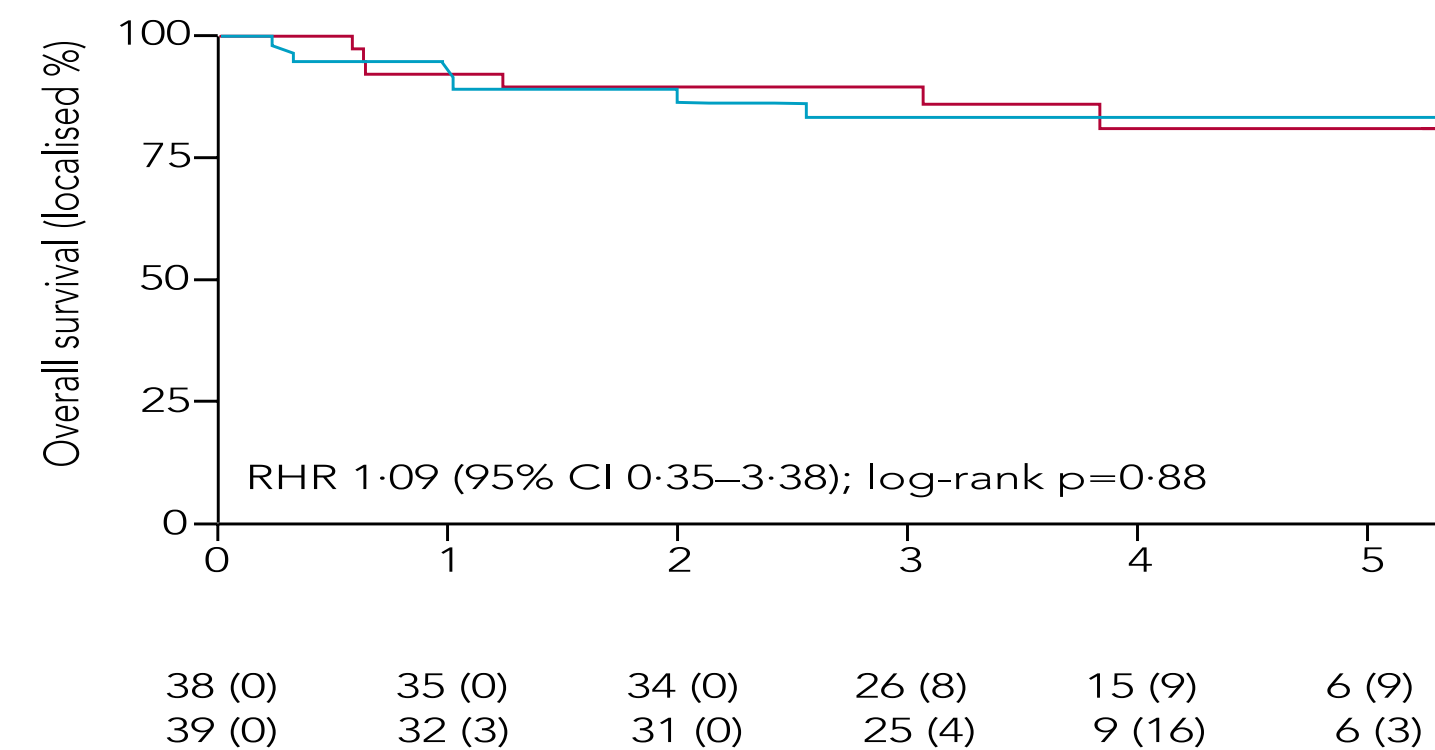
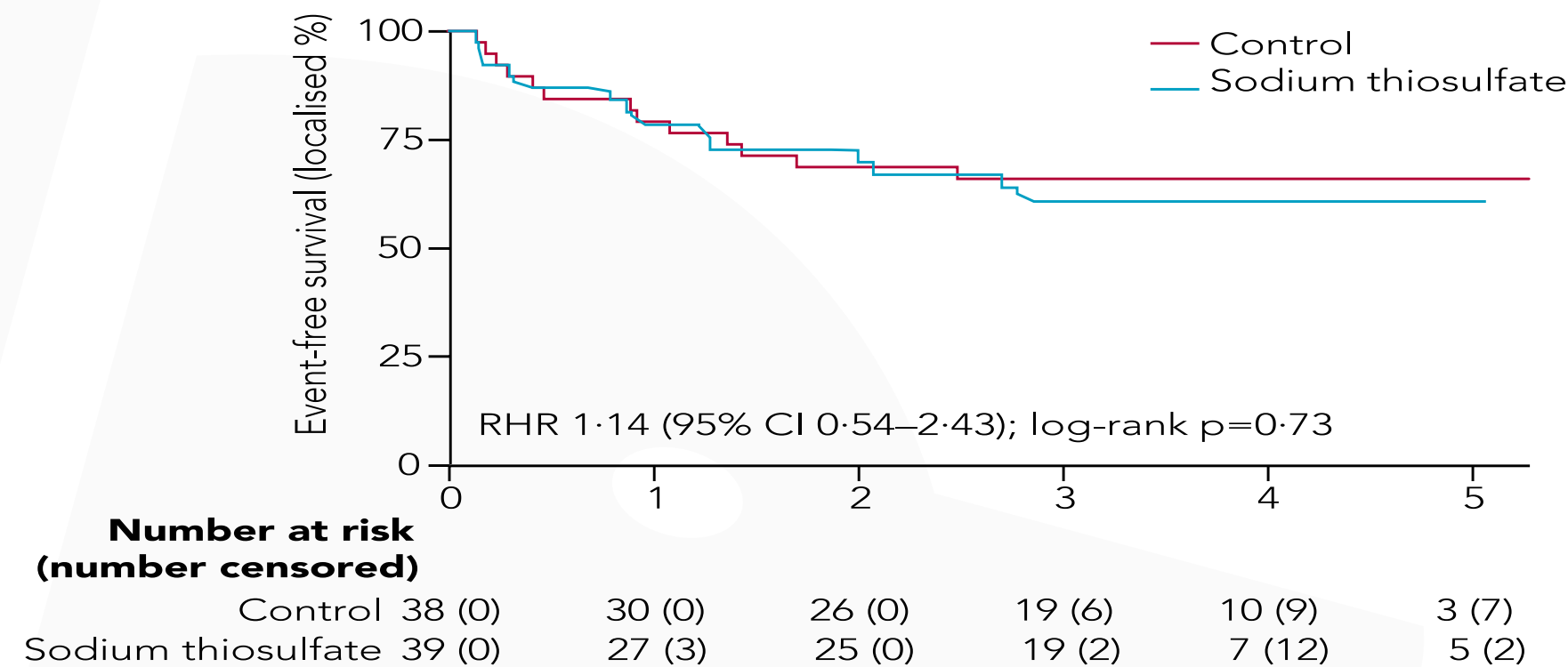


	0	1	2	3	4	5
<b>Number at risk (number censored)</b>						
Control	64 (0)	56 (2)	54 (1)	44 (9)	26 (16)	8 (18)
Sodium thiosulfate	61 (0)	50 (3)	41 (3)	32 (5)	13 (19)	8 (5)

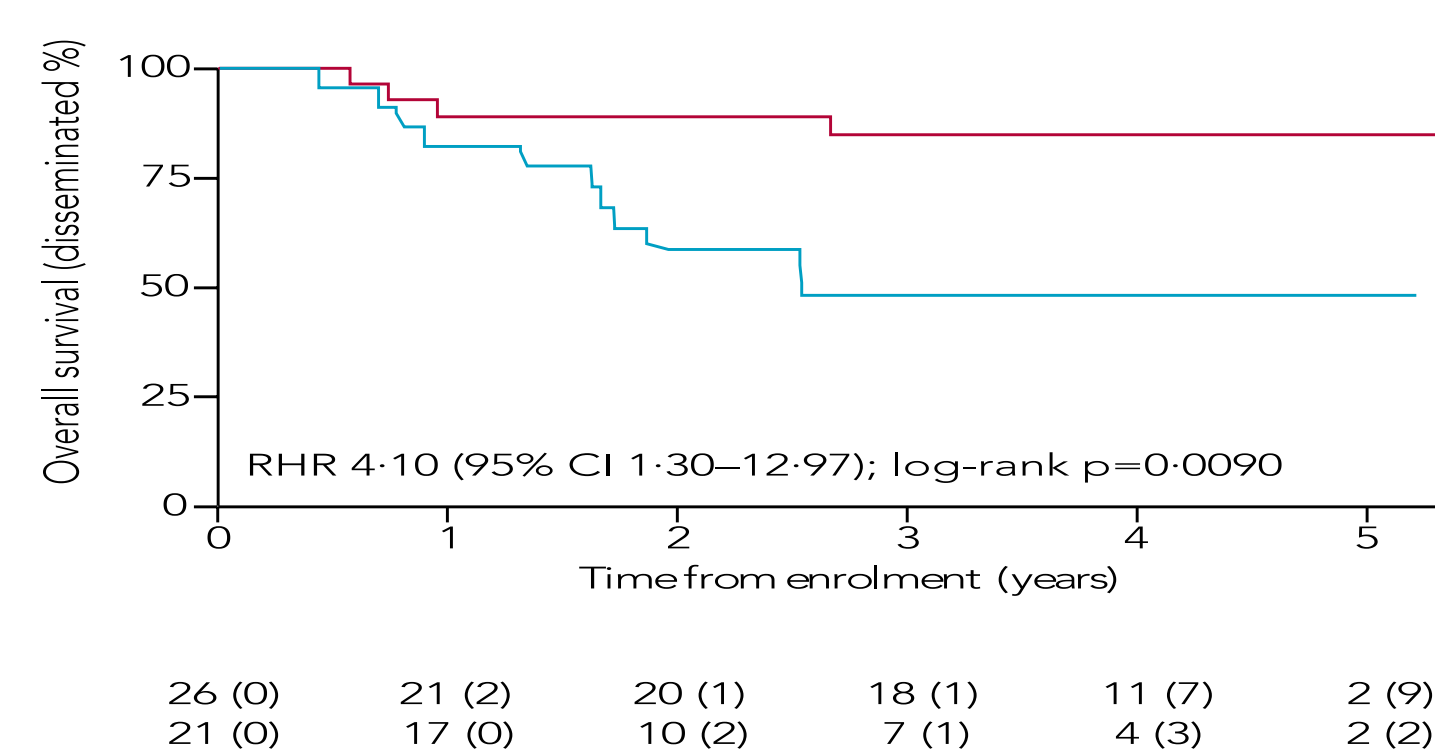
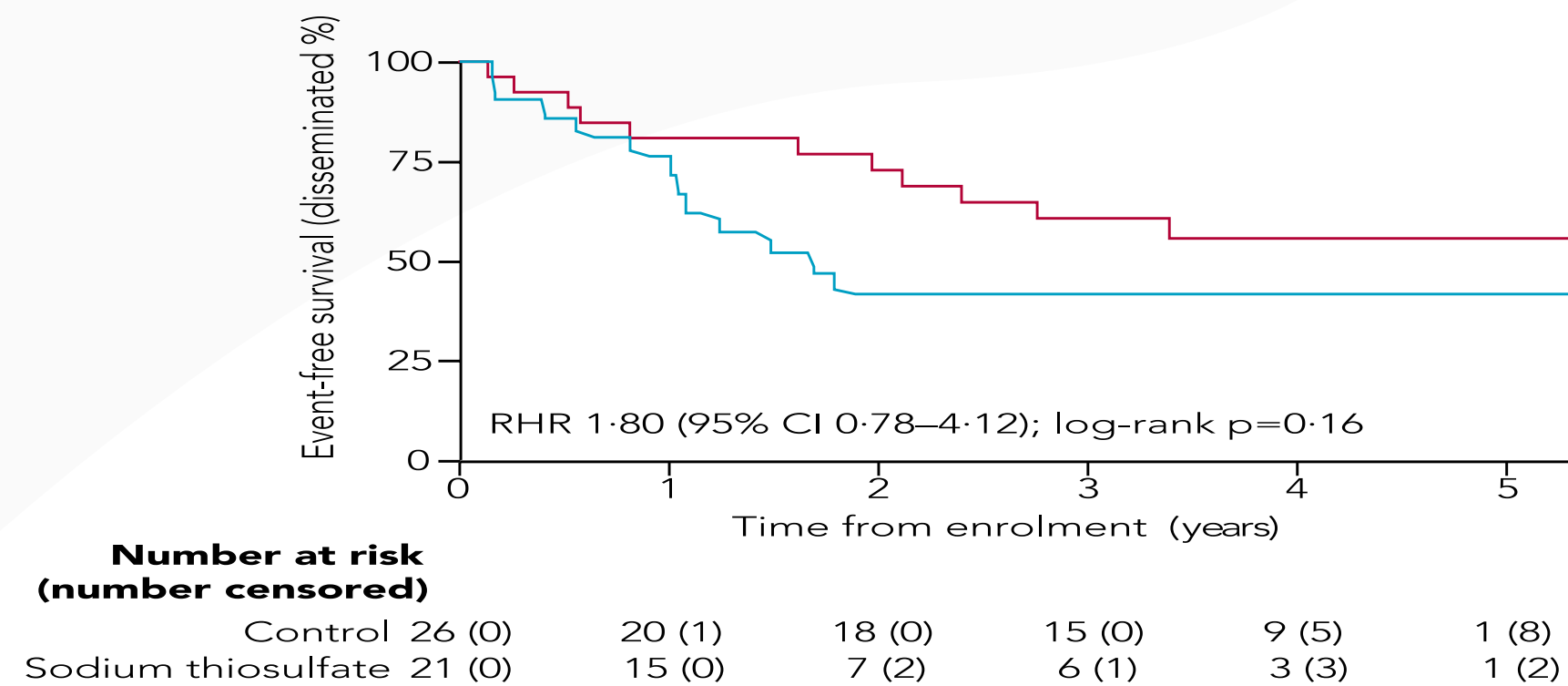
COG ACCL0431 | Lancet Oncology 2016

# EFS/OS: EXTENT OF DISEASE\*

## Localized Disease (n=77)



## Disseminated Disease (n=47)



\*Determined post hoc (ie, retrospectively during the preliminary data analysis after completion of accrual).

# PIVOTAL STUDY

**SIOPEL 6 | New England Journal of Medicine 2018**

## Objectives

Assess the efficacy of STS to reduce the hearing impairment caused by Cisplatin in SR-HB

Monitor any potential impact of STS on response (protocol pre-specified IDMC tumor response review 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 I, II or III, serum AFP > 100 µg/L

First patient in the study enrolled in 2007, last patient in Dec 2014

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## 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

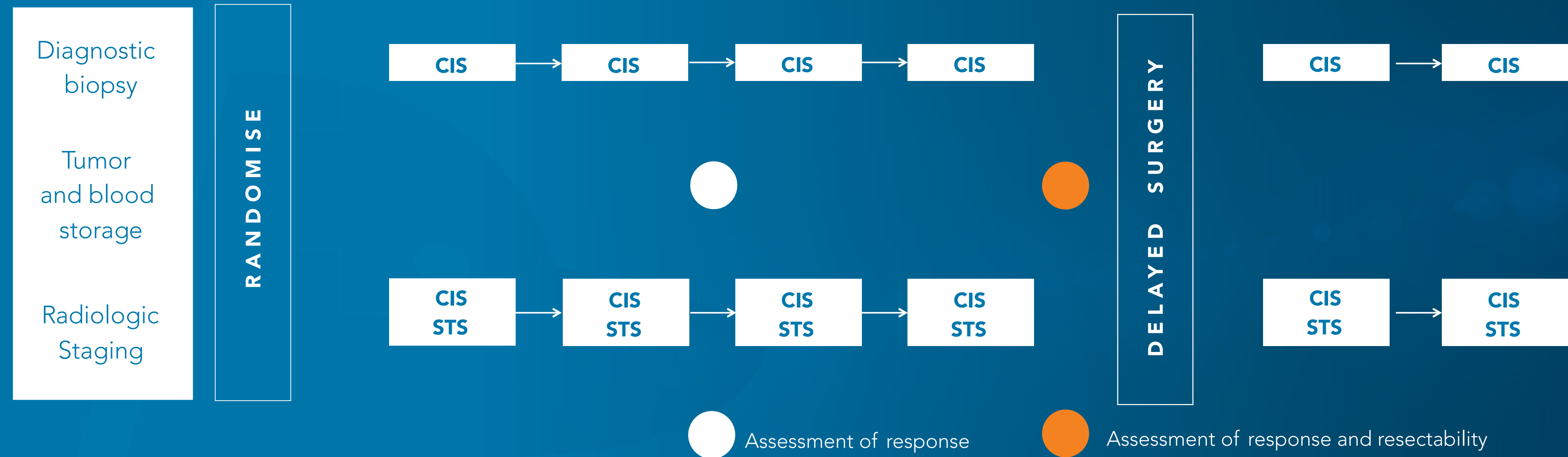
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## Secondary Endpoints

Response, resection, EFS, OS and long term renal function



# SIOPEL 6 METHODS & DESIGN



Cisplatin alone : IV infusion over 6 hrs (80 mg/m<sup>2</sup> for children > 10kg, 2.7 mg/kg for infants and children 5-10kg or 1.8 mg/kg for infants < 5kg)

**OR**

Cisplatin (same dose) and STS administered IV exactly 6 hours after stop of cisplatin over 15 minutes at 20 g/m<sup>2</sup> for children > 10kg, 15 g/m<sup>2</sup> for infants and children of 5-10 kg or 10 g/m<sup>2</sup> for infants < 5kg

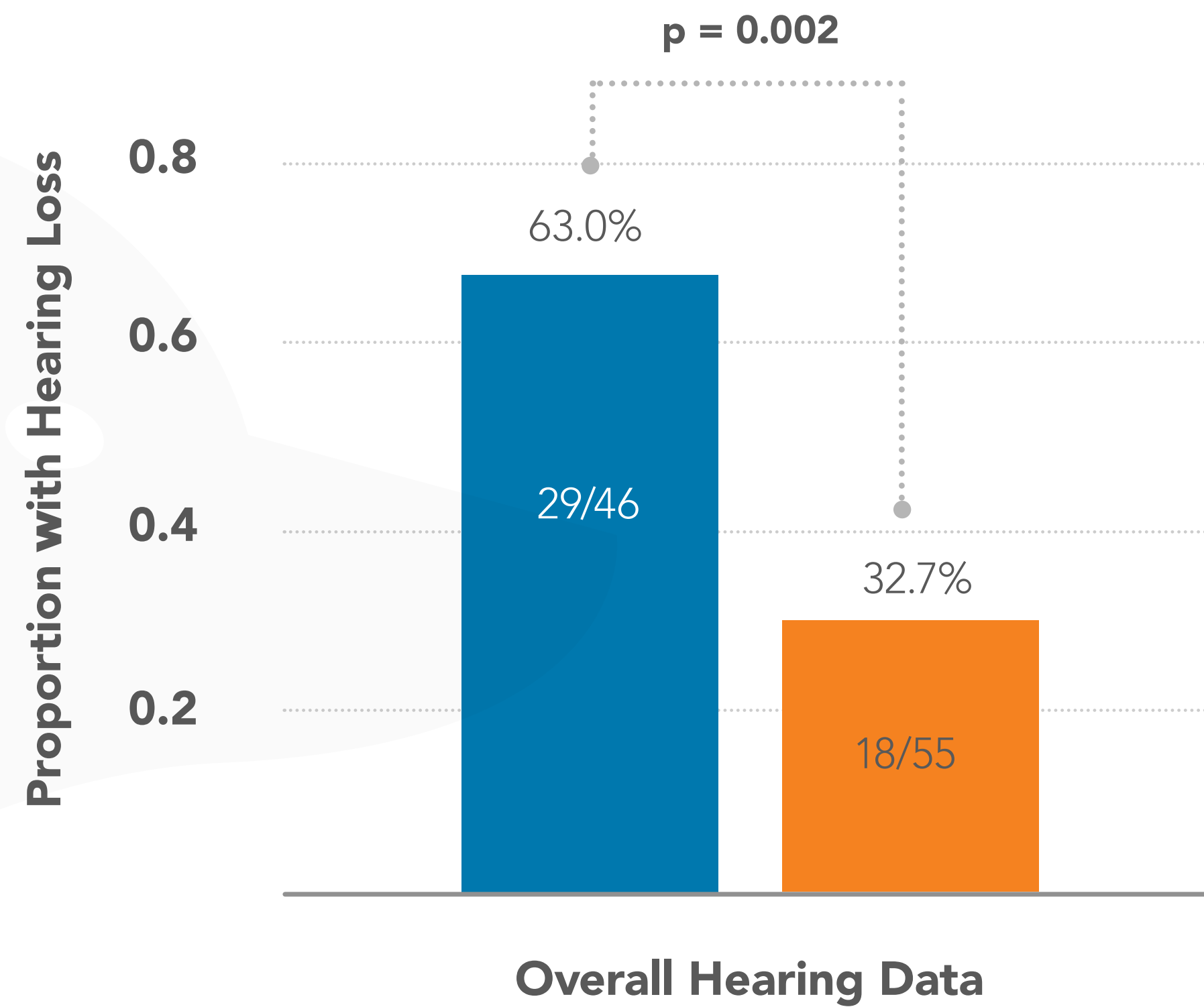
Stratification by Country, age (above and below 15 months), PRETEXT (I and II vs III)

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

# HEARING LOSS: RANDOMIZED ARM



N = 101 evaluable patients

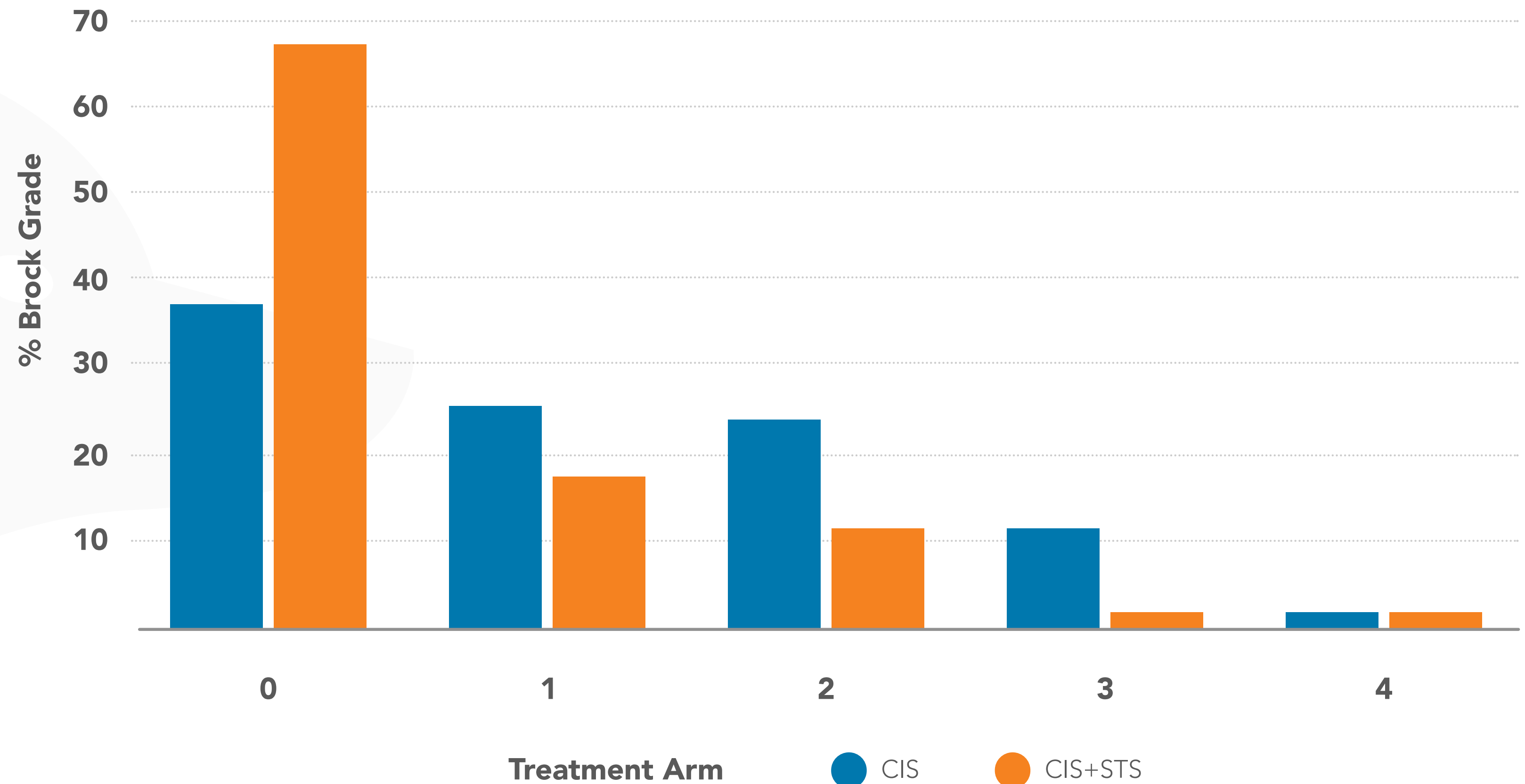
● CIS ● CIS+STS

SIOPEL 6 | New England Journal of Medicine 2018

# SENSITIVITY OF HEARING LOSS BY BROCK GRADE

Bilateral Hearing Loss	Grade	Designation
< 40 dB at all frequencies	0	Minimal
>= 40 dB at 8kHz only	1	Mild
>= 40 dB at 4kHz and above	2	Moderate
>= 40 dB at 2kHz and above	3	Marked
>= 40 dB at 1Khz and above	4	Severe

\* A Brock grade of 0 indicates hearing at less than 40 dB at all frequencies and does not necessarily equate to completely normal hearing. Grades 1, 2, 3, and 4 indicate hearing levels at 40 dB or higher at 8 kHz, 4 kHz, 2 kHz, and 1 kHz and above, respectively. The grade was determined according to the hearing level in the child's better ear.



SIOPEL 6 | New England Journal of Medicine 2018

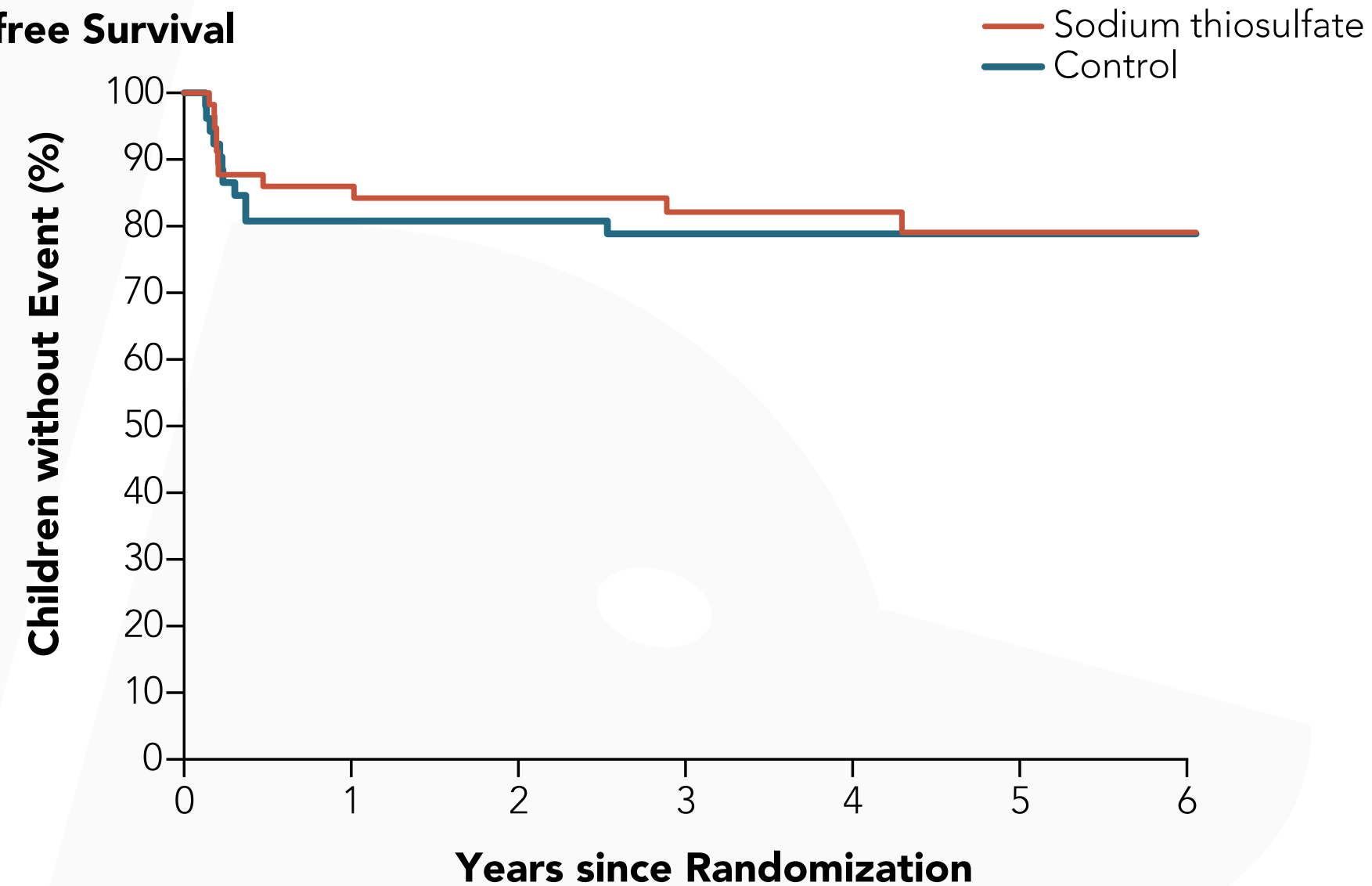
# EFS/OS: RANDOMIZED ARM

Median Follow-Up 52 months

3yr-EFS Cis 78.8% | CIS+STS 82.1%

3yr-OS Cis 92.3% | CIS+STS 98.2%

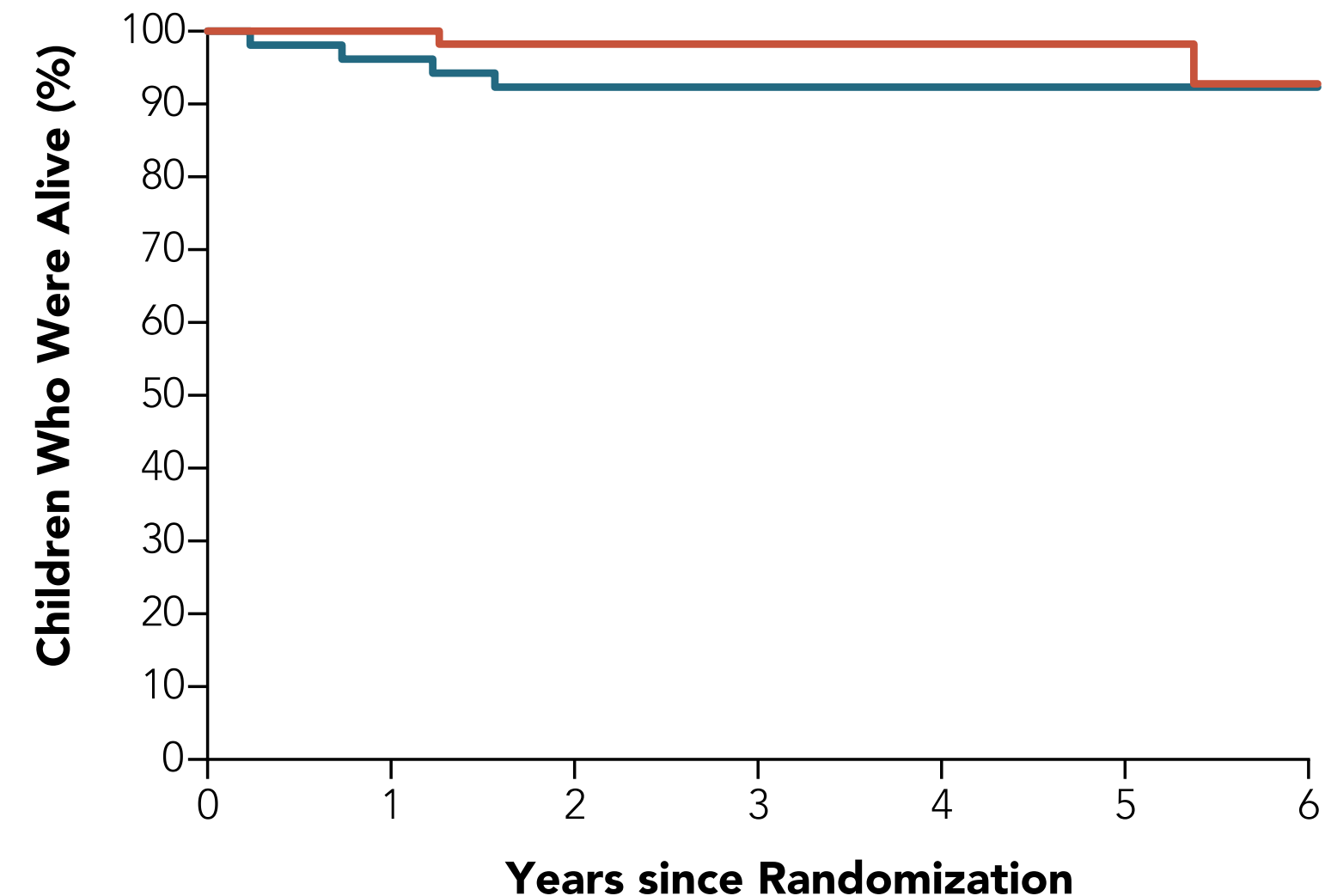
Event-free Survival



No. at Risk

	0	1	2	3	4	5	6
Cisplatin-sodium thiosulfate	57	49	46	37	29	19	9
Cisplatin alone	52	42	42	37	22	13	8

Overall Survival



No. at Risk

	0	1	2	3	4	5	6
Cisplatin-sodium thiosulfate	57	57	54	45	35	24	12
Cisplatin alone	52	50	48	43	28	17	11

SIOPEL 6 | New England Journal of Medicine 2018

# SODIUM THIOSULFATE AND CISPLATIN INDUCED HEARING LOSS | NEJM EDITORIAL

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“Taken together, these trials provide definitive evidence that sodium thiosulfate reduces the incidence of cisplatin-induced hearing loss and suggest that sodium thiosulfate is safe to use in patients with standard-risk hepatoblastoma and probably in those with other localized cancers. However, the use of sodium thiosulfate in patients with disseminated disease may affect survival, and caution is warranted in that context.”\*

\*David R. Freyer, D.O. | A. Lindsay Frazier, M.D. | Lillian Sung, M.D., Ph.D.

“We agree with Freyer et al. that drawing conclusions for clinical practice from our trial and ACCL04311 would support the use of sodium thiosulfate for protection from cisplatin-induced hearing loss in patients with any localized solid tumor and encourage careful further clinical assessment in patients with metastatic disease. No definitive conclusion or therapeutic direction should be drawn from any post hoc analysis, particularly in ACCL0431, in which children were not randomly assigned according to disease-specific key prognostic factors that are important in determining outcome in metastatic disease.”\*

\*Penelope R. Brock, M.D., Ph.D. | Rudolf Maibach, Ph.D. | Edward A. Neuwelt, M.D.

# PATIENT FOCUSED DRUG DEVELOPMENT (PFDD) MEETING - SEPTEMBER 13, 2018

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The PFDD meeting was organized by several patient advocacy groups to help regulators understand the burden of platinum induced hearing loss in children and establish the benefits and risks as expressed by patients and their caregivers

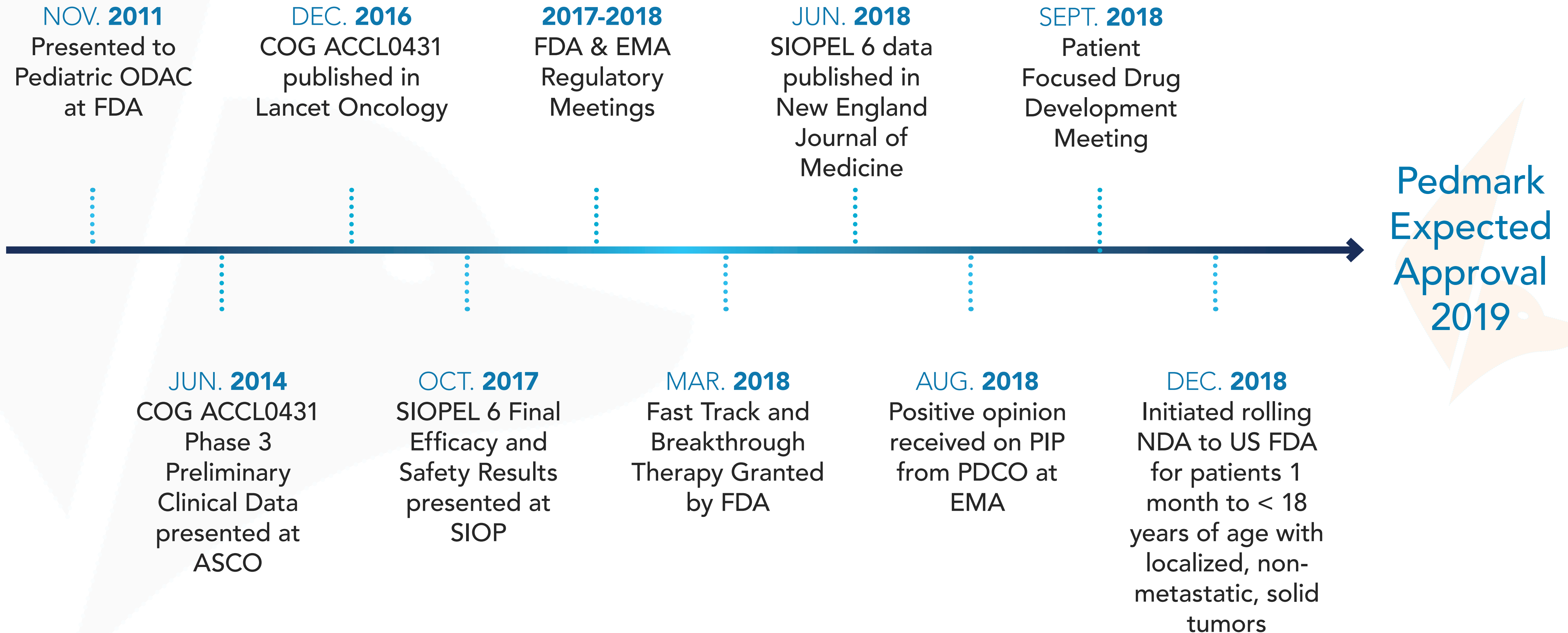
According to FDA, "Input can inform FDA's oversight both during drug development and during our review of a marketing application."

Over 30 long term survivors with various tumor types unanimously in agreement that hearing loss has a profound impact on their ability to live normal social lives, frequently citing loneliness, depression, lack of job opportunities and being a burden upon others

Several mothers requested that regulators put the choice back in the hands of patients and their families and make drugs like PEDMARK available to clinicians

Closing comment from Dr. Gregory Reaman, Associate Director for Oncology Sciences at the FDA, included: "assure you we heard you... we need to evaluate things differently as this is a very serious life altering toxicity that can and must be considered in risk benefit analysis of new therapies"

# PEDMARK™ DEVELOPMENT TIMELINE



# CAPITAL STRUCTURE | SHARE INFORMATION

<b>Stock Listings</b>	FENC – NASDAQ   FRX – TSX, Canada
<b>Current Share Price</b>	USD \$6.44
<b>Shares Outstanding</b>	19.729M
<b>Market Cap</b>	USD \$127.05M
<b>Insider Ownership</b>	Approx. 9% fully diluted
<b>Cash@ Sept. 30, 2018</b>	USD \$24.5M
<b>2017 Cash Burn</b>	USD \$4.0M
<b>Debt</b>	\$0 (\$12.5M facility available at Company's option to be funded upon NDA approval)

## INSTITUTIONAL OWNERSHIP

Southpoint Capital – 22%
Leadiant Bio – 19%
683 Capital – 6%
venBio Select Advisor – 6%
Opaleye Management – 5%
Eventide Funds – 4%



# BOARD OF DIRECTORS & MANAGEMENT

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## **Dr. Khalid Islam** | Chairman

Former Chairman & CEO at Gentium S.p.A. Sold to Jazz Pharma for \$1 billion.

## **Dr. Marco Brughera** | Director

Currently CEO & Global Head of Leadiant Bio (Sigma Tau Rare Disease). Successfully out licensed defibrotide US rights to Jazz Pharma and sold Oncaspar to Baxalta for \$1 billion.

## **Adrian Haigh** | Director

Currently SVP & General Manager PTC Therapeutics. Previously COO at Gentium S.p.A. Sold to Jazz Pharma for \$1 billion.

## **Chris Rallis** | Director

Previously President & COO of Triangle Pharmaceuticals. Sold to Gilead for \$500 million.

## **Rosty Raykov** | CEO & Board Member

## **Robert Andrade** | CFO

## **Mark Gowland** | Controller

## **Lei Fang** | Biostatistics

## **Anne McKay** | Regulatory

## **Ryan Aldridge** | Investor Relations



**FENNEC PHARMA**

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