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Preventing Cisplatin-Induced Ototoxicity in Pediatrics: *What You Need to Know to Improve Patient Outcomes*

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Sponsored by Fennec Pharmaceuticals

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Learning Objectives

Following this educational program, participants will be able to:

1. Understand the incidence and mechanism of cisplatin-induced ototoxicity in children
2. Discuss the mechanism of action and safety and efficacy data of sodium thiosulfate in the prevention of cisplatin-induced ototoxicity
3. Describe the safety impact of select inactive ingredients in pharmaceutical products in pediatric patients

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Faculty

- **Noah Federman, MD**
  Professor of Pediatrics and Orthopaedic Surgery
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- **Rita K. Jew, PharmD, MBA, BCPPS, FASHP**
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Prevention of Cisplatin-Induced Ototoxicity

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Disclosures

- Honoraria for speaking, ad hoc advisory boards: Bayer AG, Springworks, Fennec
- Company co-founder: Icona BioDx

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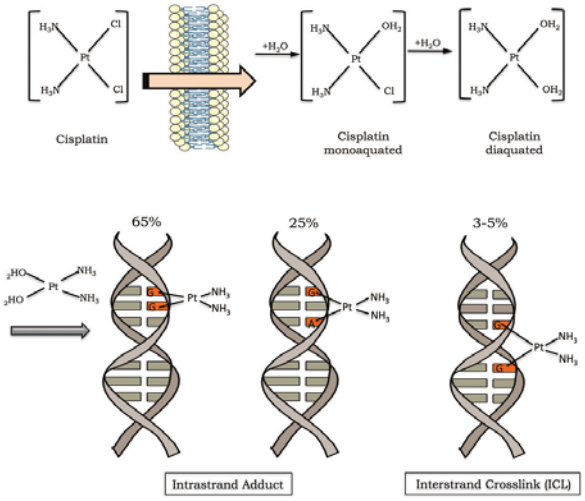
History of Cisplatin: An "accidental discovery"

Barnett Rosenberg, Ph.D, Biophysicist Michigan State, 1965

serendipitously discovers cisplatin "by accident" as platinum compound (thought to be biologically inactive) on electrodes was blocking cell division not the electrical currents themselves



Rocha, Silva et al. DNA repair pathways and cisplatin resistance. *Clinics*. 2018; 73.

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Cisplatin is an Established Option for Solid Tumors in Children[1,2]

- Cisplatin-based therapy is an indispensable component of treatment for several common cancers in children, including:
  - Germ cell tumors[1]
  - Hepatoblastoma[1]
  - Medulloblastoma[1]
  - Neuroblastoma[1]
  - Osteosarcoma[1]
- An estimated 2000 children* are treated with cisplatin in the United States every year[2]

*Aged 1-15.

An analysis of outcomes for one series of pediatric patients receiving cisplatin-based chemotherapy for solid tumors reported an overall survival rate of about **70% to 75%**[3]

References: 1. Gold JM, Raja A. Cisplatin (Cisplatinum). NCBI Bookshelf. Accessed June 10, 2022. https://www.ncbi.nlm.nih.gov/books/NBK547695/ **2.** Varan A, et al. *Pediatr Hematol Oncol*. 2012;29:529-537. **3.** Bhandari R, et al. *Pediatr Hematol Oncol*. 2021;38(3):239-250.

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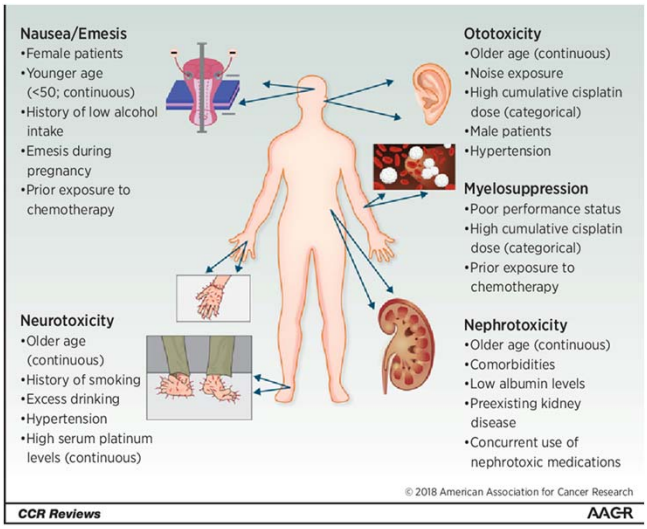
Cisplatin is Associated with Significant Toxicities



Trendowski, Matthew R et al. *Clinical Cancer Research* 25 (2018): 1147 - 1155.

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Cisplatin Treatment is Associated with Ototoxicity in Children[1,2]

- Cisplatin-based chemotherapy has been widely associated with irreversible, bilateral, progressive hearing loss[1,2]
- This cisplatin-induced ototoxicity (CIO) can have a **dose-limiting effect**[3]
- Factors that significantly increase the risk of hearing loss following cisplatin treatment include[4]:
  - Younger age
  - Prior treatment with radiotherapy
  - Larger amount of cisplatin infused per dose
  - Larger cumulative cisplatin dose

Permanent hearing loss may occur in 60% to 70% of children treated with cisplatin.[4,5]
Incidence is impacted by factors such as age, type and number of treatments, and disease characteristics.

References: 1. Langer T, et al. *Trends Pharmacol Sci.* 2013;34(8):458-469. **2.** Hennegan K, et al. ISPOR Annual Meeting 2020. May 18-20, 2020 [Virtual]. Poster PIH67. **3.** Paken J, et al. *J Toxicol.* 2016;2016:1809394. **4.** Camet ML, et al. *Front Oncol.* 2021;11:673080. **5.** Hudson MM, et al. *JAMA.* 2013;309(22):2371-2381.

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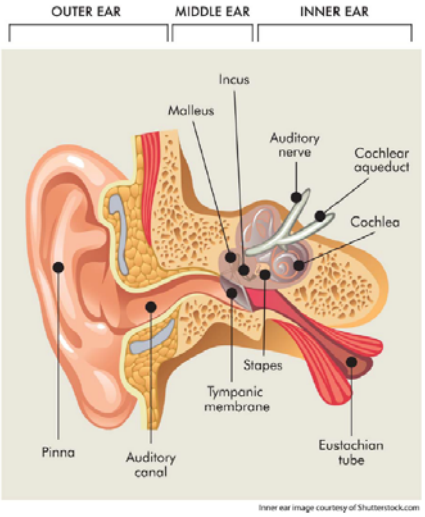
Mechanisms of Cisplatin-Induced Ototoxicity[1]

- Treatment with cisplatin causes toxic levels of reactive oxygen species to be produced in the cochlea
- The reactive oxygen species destroy the cochlear hair cells and damage the stria vascularis and spiral ganglion cells
- Damage begins at the base of the cochlea and additional drug exposure causes the damage to spread towards the cochlear apex
- Cochlear hair cells cannot regenerate, meaning hearing loss is irreversible



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Reference: Landier W. *Cancer.* 2016;122(11):1647-1658.

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What is the Clinical Impact of Cisplatin-Induced Ototoxicity?

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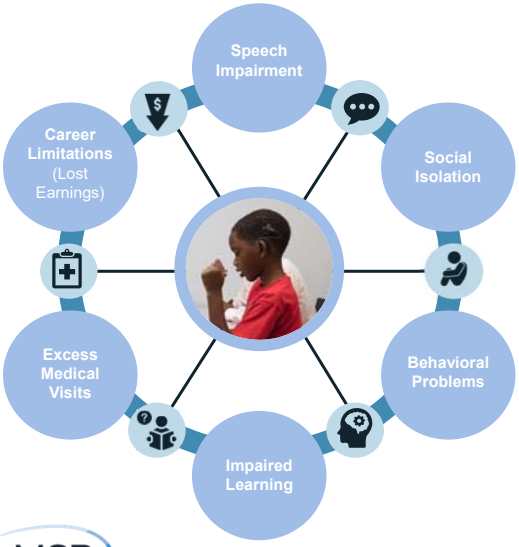
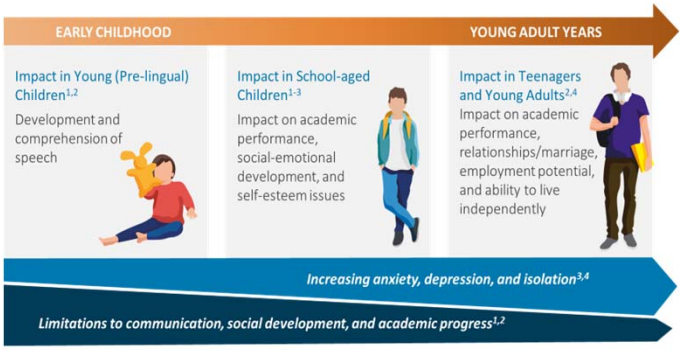
Acquired Hearing Loss Can Have Profound, Multi-faceted, Long-term Impact on Children[1-3]





References: 1. Clemens E, et al. *Lancet Oncol.* 2019;20(1):e29-e41. **2.** Bass JK, et al. *Pediatr Blood Cancer.* 2016;63(7):1152-1162. **3.** U.S. Food and Drug Administration. Childhood cancer hearing loss. Accessed June 13, 2022. https://www.childhoodcancerpfdd.org/hearing-loss

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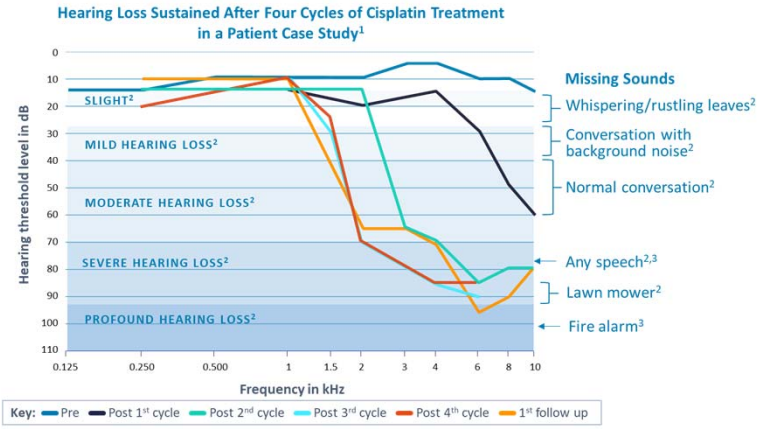
Symptoms of Cisplatin-Induced Ototoxicity

- Symptoms of cisplatin-induced ototoxicity in children include[1,2]:
  - Bilateral and irreversible hearing loss which is usually symmetric and can be progressive
  - Tinnitus
  - Vertigo
- Hearing loss initially affects higher frequencies (≥4 kHz) before progressing to involve the lower frequencies associated with speech (<4 kHz)[1]
- Hearing can be affected from first treatment w/cisplatin and worsens with successive exposure
- Cisplatin can persist in the cochlea for months and years and exacerbate further deterioration



Left ear audiogram of a single patient at baseline before cisplatin treatment, after 4 cycles of cisplatin, and during follow-up. Adapted from Langer T, et al. *Trends Pharmacol Sci.* 2013.

References: 1. Langer T, et al. *Trends Pharmacol Sci.* 2013;34(8):458-469. **2.** Paken J, et al. *J Toxicol.* 2016;2016:1809394.

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Recommended Interventions for Childhood Cancer Survivors Vary by Degree of Hearing Loss[1]

- General recommendations for childhood cancer survivors with permanent hearing loss:
  - Referral to audiologist
  - Counseling for child and their family to discuss impact of hearing loss
  - Compensatory communication strategies
  - Speech and language therapy
  - Accommodations and support at school, college, and in the workplace

Hearing loss ≥6 kHz:

Remote microphone technology

Hearing loss ≥3 kHz:

Personal hearing aids

Consideration of remote microphone technology

Hearing loss affecting speech understanding (not helped with hearing aids):

Electroacoustic stimulation device (e.g., cochlear implant)

Remote microphone technology

Reference: 1. Clemens E, et al. *Lancet Oncol.* 2019;20(1):e29-e41.

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Prevention of Cisplatin-Induced Ototoxicity with PEDMARK (Sodium thiosulfate-anhydrous)

PEDMARK (STS-anhydrous)

- Putative mechanism of action
- First/Only FDA approved STS formulation
- Clinical trial data: Efficacy and Safety

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PEDMARK (Sodium thiosulfate [STS]-anhydrous) Can Protect Hearing by Reducing Risk of Ototoxicity from Cisplatin

PEDMARK is a novel form of STS-anhydrous designed to treat ototoxicity in children[1]

- The mechanism of action is currently unknown but may include[2]:
  - Increasing levels of endogenous antioxidants
  - Scavenging reactive oxygen species
  - Direct interaction between cisplatin and the thiol group in STS
- PEDMARK can enter cells at least partially through the sodium sulfate cotransporter 2 and can cause intracellular effects including[1]:
  - Increase in antioxidant glutathione levels
  - Inhibition of intracellular oxidative stress
  - Does not contain KCl and minimal boric acid in excipient

References: 1. PEDMARK [package insert]. Hoboken, NJ: Fennec Pharmaceuticals, Inc.; September 2022. **2.** Data on file. Fennec Pharmaceuticals.

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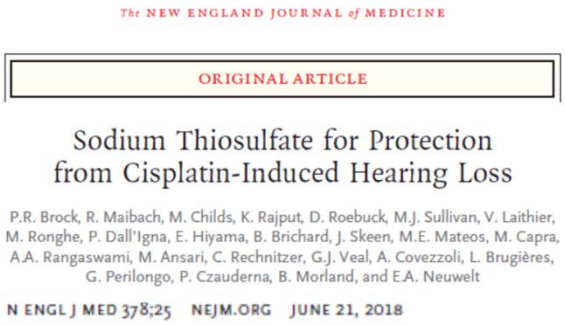
Clinical Data from Two Landmark Clinical Trials in North America and Europe: PEDMARK (STS-anhydrous) Can Prevent Cisplatin-Induced Ototoxicity


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss

P.R. Brock, R. Maibach, M. Childs, K. Rajput, D. Roebuck, M.J. Sullivan, V. Laithier, M. Ronghe, P. Dall'Igna, E. Hiyama, B. Brichard, J. Skeen, M.E. Mateos, M. Capra, A.A. Rangaswami, M. Ansari, C. Rechnitzer, G.J. Veal, A. Covezzoli, L. Brugières, G. Perilongo, P. Czauderna, B. Morland, and E.A. Neuwelt

N ENGL J MED 378;25 NEJM.ORG JUNE 21, 2018


THE LANCET
Oncology

Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial

David R Freyer, Lu Chen, Mark D Krailo, Kristin Knight, Doojduen Villaluna, Bonnie Bliss, Brad H Pollock, Jagadeesh Ramdas, Beverly Lange, David Van Hoff, Michele L VanSoelen, John Wiernikowski, Edward A Neuwelt*, Lillian Sung*

www.thelancet.com/oncology Vol 18 January 2017

September 20, 2022, **FDA approves sodium thiosulfate** to reduce the risk of ototoxicity associated with cisplatin in pediatric patients with localized, non-metastatic solid tumors

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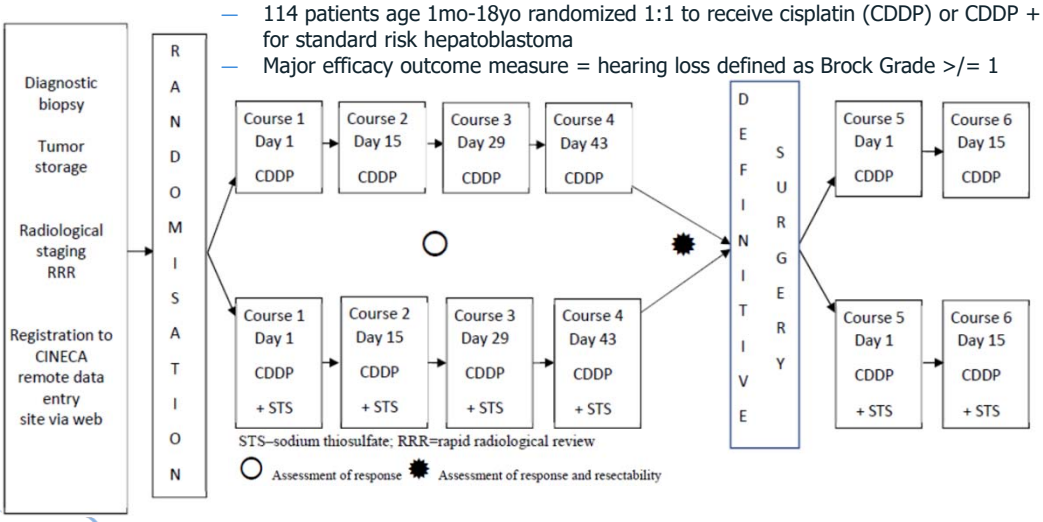
SIOPEL 6 (NCT00652132) Multicenter, Randomized, Controlled, Open-Label Study Conducted by the International Childhood Liver Tumor Strategy Group (2007-2018)

SIOPEL 6 Study Design:

- 114 patients age 1mo-18yo randomized 1:1 to receive cisplatin (CDDP) or CDDP + PEDMARK(STS) for standard risk hepatoblastoma
- Major efficacy outcome measure = hearing loss defined as Brock Grade >/= 1



Brock et al. *N Engl J Med.* 2018;378:2376-2385.

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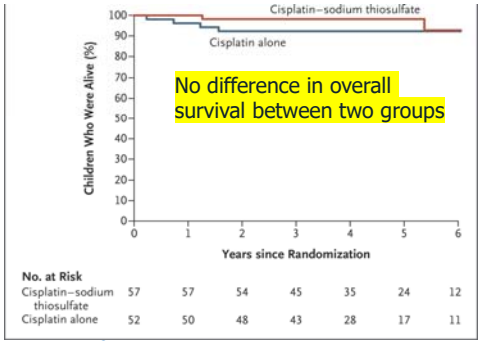
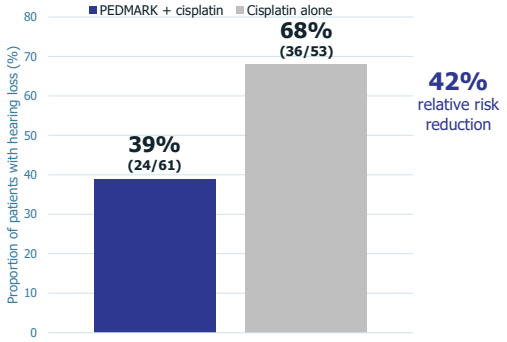
PEDMARK Reduced Relative Risk of Hearing Loss in Children with Standard Risk Hepatoblastoma

PEDMARK reduced the relative risk of hearing loss by 42% compared with cisplatin alone[1]

- In the evaluable population with available hearing assessment (n=101), PEDMARK demonstrated a **48%** relative risk reduction in hearing loss (33%; n=18/55) vs cisplatin alone (63%; n=29/46)



Hearing loss in the intent-to-treat population (N=114)[1]



8 patients in the PEDMARK + cisplatin arm and 5 patients in the cisplatin alone arm did not have hearing data available for evaluation and were assumed to have hearing loss in the analysis.

Brock, et al. *N Engl J Med.* 2018;378:2376-2385

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SIOPEL 6: Safety Results

- **PEDMARK safety profile in children with standard risk hepatoblastoma**
  - Patients receiving PEDMARK were treated for a median of 6 cycles (range 2 to 8 cycles) over a median of 94 days of chemotherapy
  - Serious adverse reactions occurred in 40% of patients who received PEDMARK in combination with cisplatin-based chemotherapy
  - Serious adverse reactions in >5% of patients who received PEDMARK included infection, decreased neutrophil count, and pyrexia
  - PEDMARK was permanently discontinued due to an adverse reaction in 1 patient; this patient discontinued PEDMARK for Grade 2 hypersensitivity

Adverse reactions occurring in ≥10 of patients receiving PEDMARK, with a >5% difference from cisplatin alone

Adverse Reaction	PEDMARK + cisplatin (n=53)		Cisplatin alone (n=56)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Vomiting	85	8	54	3.6
Nausea	40	3.8	30	5
Investigations				
Decreased hemoglobin	34	19	29	16
Metabolism and nutrition disorders				
Hypernatremia	26	1.9	3.6	0
Hypokalemia	15	9	1.8	0
Hypophosphatemia	15	9	1.8	0
Hypermagnesemia	11	9	5	3.6
General disorders				
Pyrexia	15	0	9	0

References: 1. PEDMARK [package insert]. Hoboken, NJ: Fennec Pharmaceuticals, Inc.; September 2022. **2.** Brock PR, et al. *N Engl J Med.* 2018;378(25):2376-2385.

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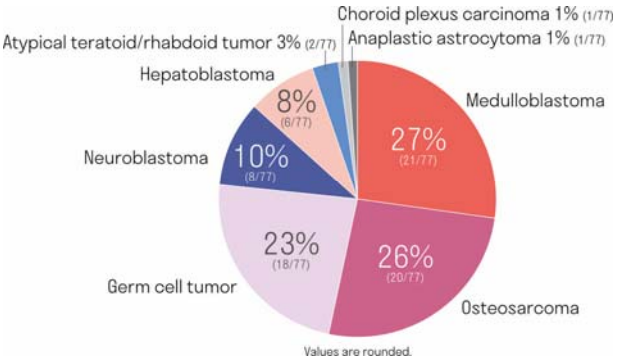
Children's Oncology Group (COG) ACCL0431 Study: Multicenter, Randomized Controlled, Open-Label Study of STS (PEDMARK) in Children with Solid Tumors Receiving Cisplatin Chemotherapy (Years 2008-2021)

Study design:

- Multicenter, randomized, controlled, open-label study of 125 patients aged 1 to 18 years with solid tumors receiving platinum-based chemotherapy for any stage disease that included a cisplatin dose of 200 mg/m^2
- Patients were randomized 1:1 to receive 6 cycles of perioperative cisplatin-based therapy with PEDMARK + cisplatin (n=61) or cisplatin alone (n=64); individual doses of cisplatin to be infused over 6 hours or less
- Efficacy analysis was performed on the ITT population included only patients with localized disease PEDMARK (n=77) + cisplatin arm (n=39) or cisplatin alone arm (n=38)
- Major efficacy outcome measure was hearing loss defined by ASHA criteria. Hearing loss was assessed at baseline and 4 weeks after the final dose of cisplatin



Freyer DR, et al. *Lancet Oncol.* 2017;18(1):63-74.

ASHA, American Speech-Language-Hearing Association; ITT, intent-to-treat; mITT, modified intent-to-treat.

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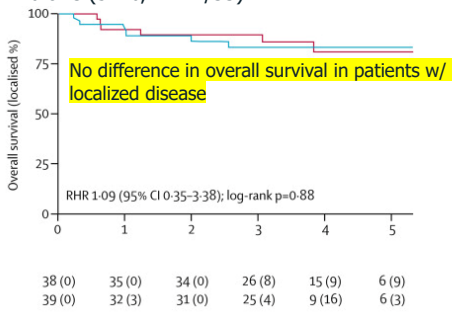
COG ACCL0413 Efficacy Results: PEDMARK (STS) Reduced Risk of Hearing Loss

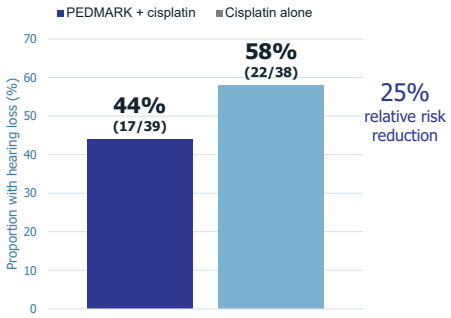
PEDMARK reduced relative risk of hearing loss by 25% compared with cisplatin alone

- In the evaluable population with available hearing assessment and localized disease (mITT [n=64]), PEDMARK demonstrated a **44%** relative risk reduction in hearing loss (29%, n=9/31) vs cisplatin alone (52%, n=17/33)



No difference in overall survival in patients w/ localized disease

Hearing loss in patients with localized disease (ITT population [N=77])



8 patients in the PEDMARK + cisplatin arm and 5 patients in the cisplatin alone arm did not have hearing data available for evaluation and were assumed to have hearing loss in the analysis.

Freyer DR, et al. *Lancet Oncol.* 2017;18(1):63-74.

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COG ACCL0431: Safety Results

PEDMARK safety profile in children with various types of cancer

- Patients receiving PEDMARK were treated for a median of 3 cycles (range 1 to 6 cycles) over a median of 15 weeks of cisplatin-based chemotherapy
- Serious adverse reactions occurred in 36% of patients who received PEDMARK in combination with cisplatin-based chemotherapy
- Serious adverse reactions in >5% of patients who received PEDMARK included febrile neutropenia, decreased neutrophil count, decreased platelet count, decreased white blood cell count, anemia, stomatitis, infections, decreased lymphocyte count, and increased alanine aminotransferase (ALT)
- PEDMARK was permanently discontinued due to an adverse reaction in 1 patient; this patient discontinued PEDMARK for Grade 2 hypersensitivity

Adverse reactions occurring in ≥10% of patients receiving PEDMARK, with a >5% difference from cisplatin alone

Adverse Reaction	PEDMARK + cisplatin (n=59)		Cisplatin alone (n=64)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Metabolism and nutrition disorders				
Hypokalemia	27	27	20	20
Hypophosphatemia	20	20	11	11
Hyponatremia	14	12	6	6
Hypernatremia	12	0	6	0
Gastrointestinal disorders				
Stomatitis	14	14	6	6

PEDMARK [package insert]. Hoboken, NJ: Fennec Pharmaceuticals, Inc.; September 2022

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Summary

- Cisplatin is a cornerstone therapy for a variety of pediatric cancers
- Ototoxicity is a very common short- and long-term side effect of cisplatin exposure
- The symptom burden of cisplatin ototoxicity is high and permanent leading to long term functional, emotional, social, cognitive and other problems
- PEDMARK (STS) is the first and only FDA approved STS formulation to prevent cisplatin-induced ototoxicity. The FDA does not permit substitution of PEDMARK with other STS formulations.
- In two randomized clinical trials, PEDMARK (STS) showed a significant reduction in relative risk of hearing loss
- Common adverse reactions include electrolyte disturbances (hyponatremia, hypokalemia, hypophosphatemia, hypermagnesemia) as well as nausea, vomiting, pyrexia and stomatitis

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Inactive Ingredients: Impact in Pediatric Patients

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Benzyl Alcohol

- Gasping Baby Syndrome
  - Metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (convulsion, intracranial hemorrhage), hypotension, cardiovascular collapse, death
- ≥99 mg/kg/day
- Examples: Heparin flushes, midazolam

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Sodium Benzoate

- Displaces bilirubin
- May cause kernicterus
- ?? Critical amount
- Example: IV caffeine, doxapram

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Propylene Glycol

- Hyperosmolality, lactic acidosis, hemolysis, hemoglobinuria, neurological disturbances
- ?? Critical amount
- Examples: lorazepam, etomidate

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Thimerosal

- Ethylmercury used as preservative in some vaccines
- Fetal exposure to methylmercury causes neurological symptoms
- FDA attempt to eliminate thimerosal from all vaccines
- Examples: Hepatitis B vaccine, influenza vaccine

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Aluminum

- Leaches from glass containers of IV products
- Accumulates in bone & CNS
- Causes fractures & neurotoxicity
- FDA mandates: < 5 mcg/kg/day
- Examples: Potassium phosphate, IV multivitamins

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Potassium Chloride

- Rapid infusion of potassium chloride
  - Cardiac conduction disturbances (bradycardia, heart block, asystole, ventricular tachycardia, ventricular fibrillation)
- Example: Sodium thiosulfate 250 mg/mL contains potassium chloride 4.4 mg/mL
  - 1 month old, 4.5 kg infant, BSA = 0.25 m^2
    - Sodium thiosulfate dose: 10 g/m^2 = 2.5 g/10 mL to infuse over 15 minutes
    - Potassium dose: 44 mg or 0.59 mEq
    - Potassium infusion rate: 0.52 mEq/kg/hr (continuous cardiac monitoring required)
  - 1 year old, 10.5 kg toddler, BSA = 0.5 m^2
    - Sodium thiosulfate dose: 20 g/m^2 = 10 g/40 mL to infuse over 15 minutes
    - Potassium dose: 176 mg or 2.35 mEq
    - Potassium infusion rate: 0.89 mEq/kg/hr (continuous cardiac monitoring required)

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Other Inactive Ingredients

- Alcohol
- Carbohydrates: ketogenic diet
- Gluten: Celiac disease

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Questions?

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