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# Pharmacological Protection against Cisplatin-Induced Hearing Loss

Year 9 CTR-IN Pilot Grant

Gabe Bargaen (PI) & Chris Sanford (Co-I)  
Associate Professor, Communication Sciences & Disorders, Audiology

Danny Xu (Co-I)  
Associate Professor, Biomedical & Pharmaceutical Sciences

Meridian Health Sciences Center, Idaho State University

**ROAR**



# Cisplatin (CIS)

- Among the most widely-used and effective anti-cancer drugs
- Used to treat testicular, bladder, lung, stomach, head & neck, ovarian, and other cancers
- The most ototoxic drug in clinical use
- Incidence of hearing loss varies widely (20-90%). Highest in children treated for medulloblastoma (88%), osteosarcoma (75%), and neuroblastoma (68%)
- Cisplatin-induced hearing loss (CIHL) is sensorineural, bilateral, progressive, and irreversible
- Mechanisms of CIHL are poorly understood, Mostly involve inner ear hair cell death as a result of the activation of inflammation and oxidative stress pathways
- No FDA approved drugs to prevent or mitigate CIHL (Hozlitt et al. 2018; Müller et al. 2015)



# Esomeprazole (ESO)

- OTC proton pump inhibitor for acid reflux/GERD
- ESO prevents systemic inflammatory and stress responses in mice (Balza et al., 2016)
- ESO reduces onset of cisplatin-induced nephrotoxicity in cancer patients (Ikemura et al., 2017)
- ESO combined with cisplatin leads to increase in antitumor effect (Oral et al., 2013)
- Preclinical data from the Xu lab demonstrated ESO mitigates cisplatin-induced ototoxicity in animal models (unpublished)



# Hypothesis and Approach

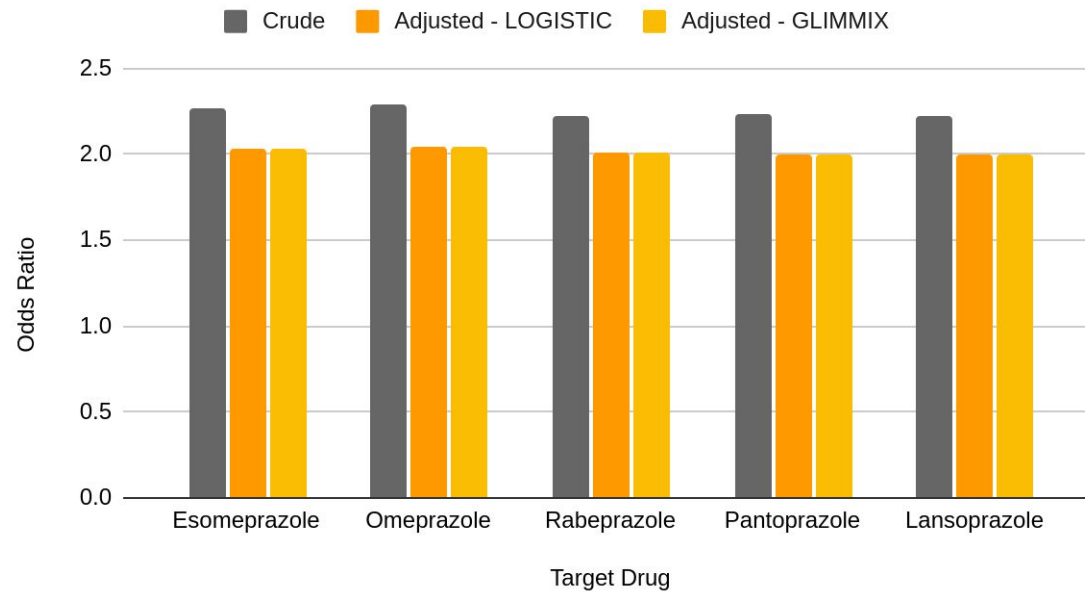
- Hypothesis – ESO may protect against CIHL.
- Approach – Combined retrospective and prospective study design



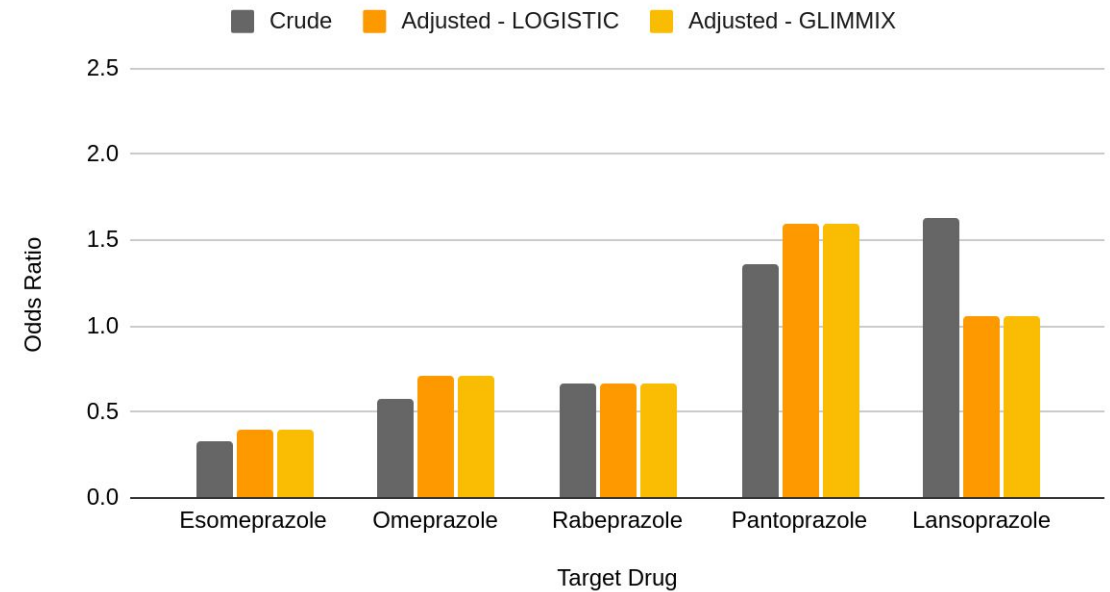
# Aim 1. Retrospective Study

- FAERS Cross-Sectional Data Mining

Odds Ratio Comparisons for Cisplatin Only



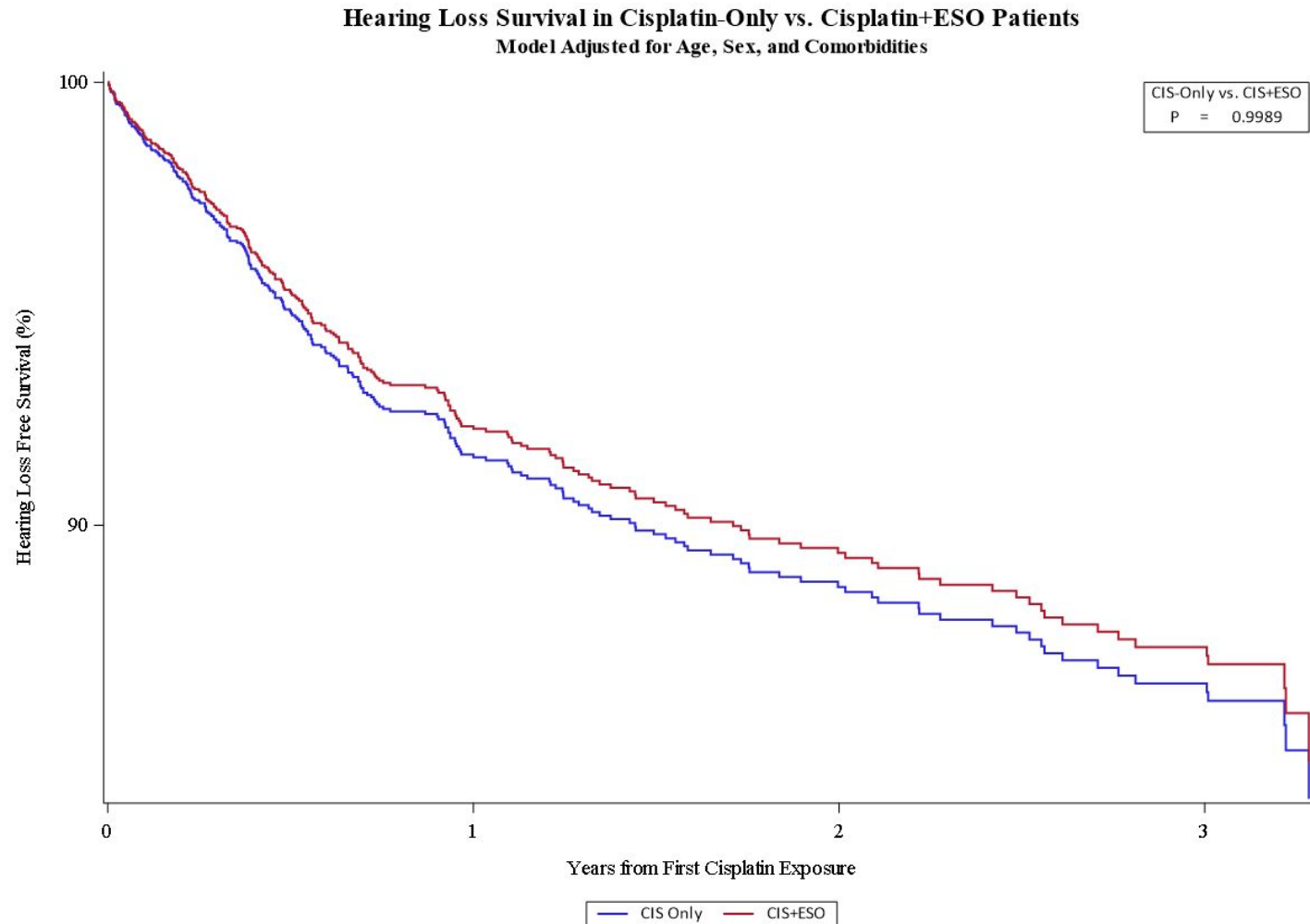
Odds Ratio Comparisons for Cisplatin And Target





# Aim 1. Retrospective Study

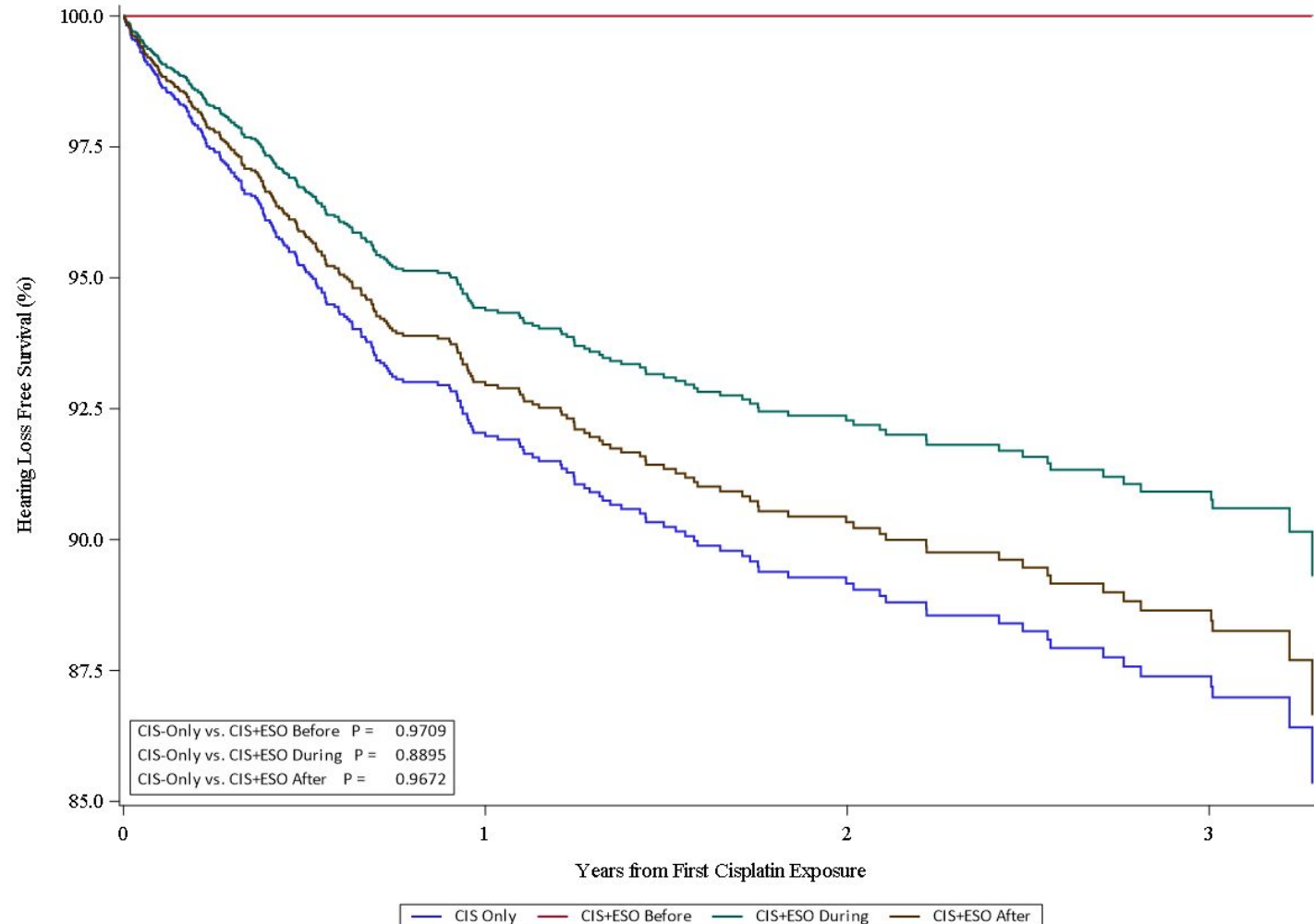
- PharMetrics Longitudinal Data Mining





# Aim 1. Retrospective Study

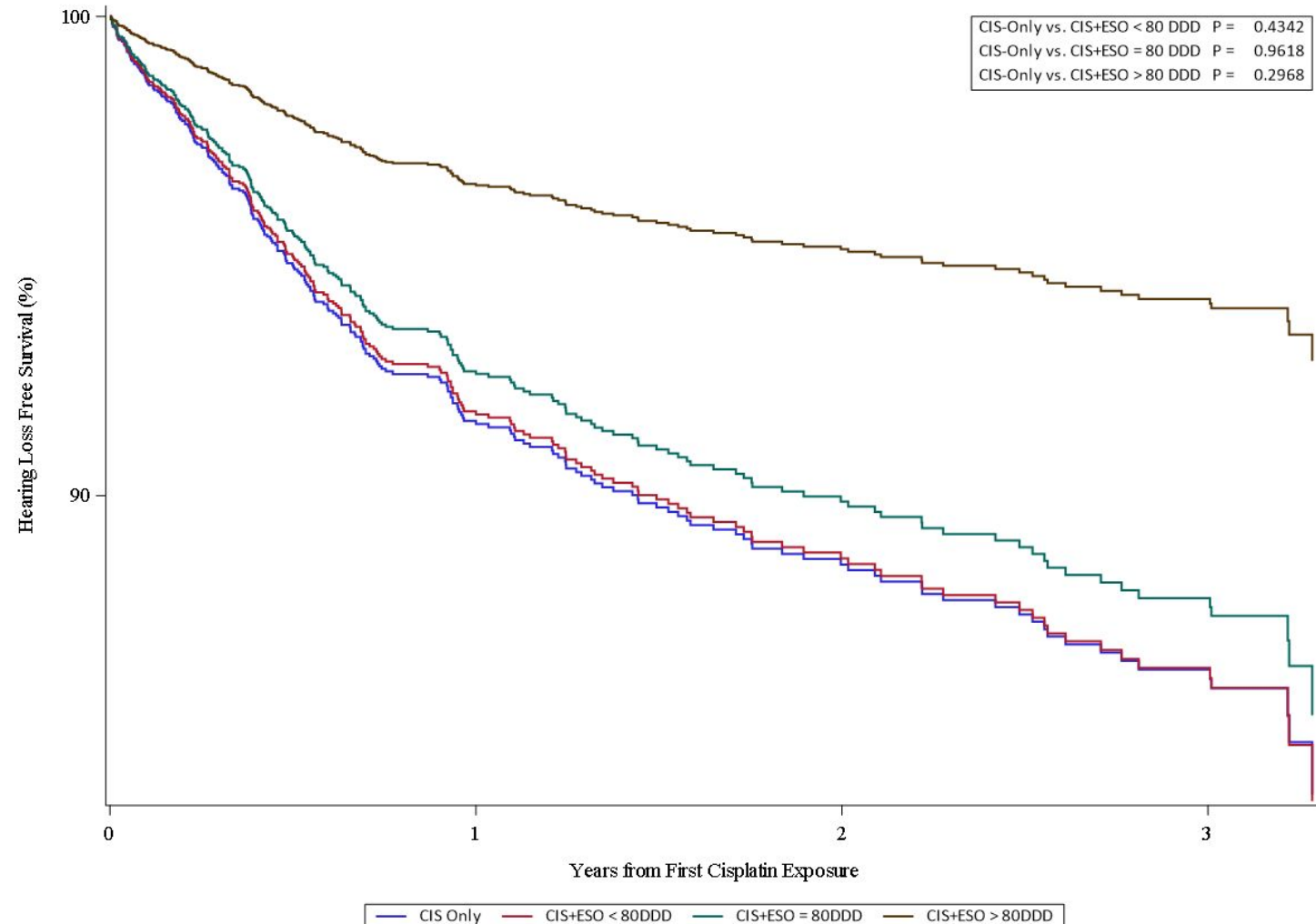
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# Aim 1. Retrospective Study

- PharMetrics Longitudinal Data Mining



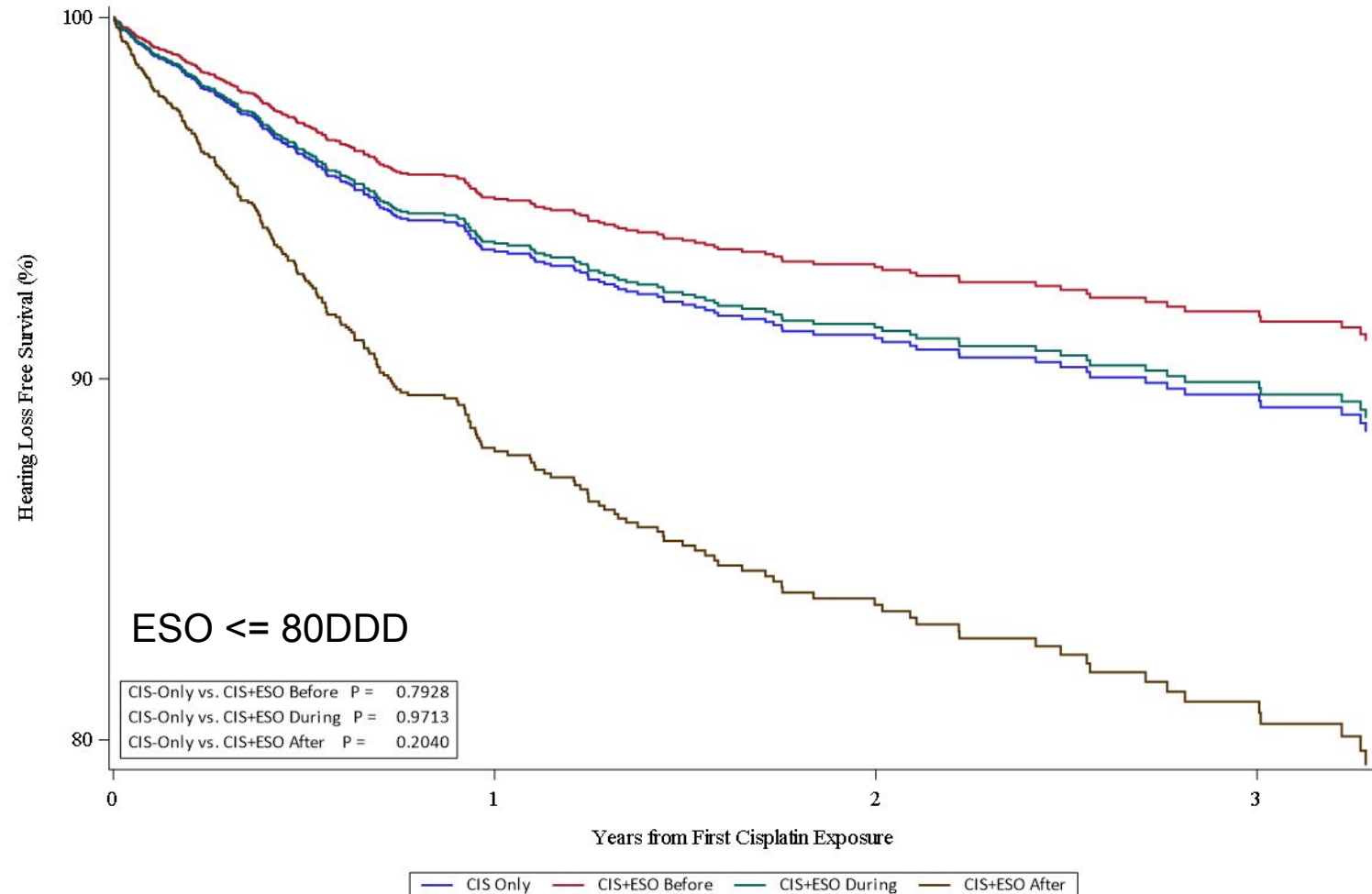




# Aim 1. Retrospective Study

- PharMetrics Longitudinal Data Mining

Hearing Loss Survival in Cisplatin-Only vs. ESO Timing Groups for DDD $\leq$ 80  
Model Adjusted for Age, Sex, and Comorbidities





## Aim 2. Prospective Study

- Evaluate changes in hearing ability between participants taking ESO prior to and while receiving cisplatin treatment (the experimental group) to participants receiving cisplatin treatment while not taking ESO (the control group) over an extended period of time (9-months)
- Auditory protocols: traditional pure-tone behavioral audiometry (standard and ultra-high frequencies), ABR, DPOAE, Word Recognition
- Recruitment external connections
  - Boise VA Oncology Clinic
  - Pocatello, ID Portneuf Cancer Center
  - 3 potential participants - Only 1 consented to participate



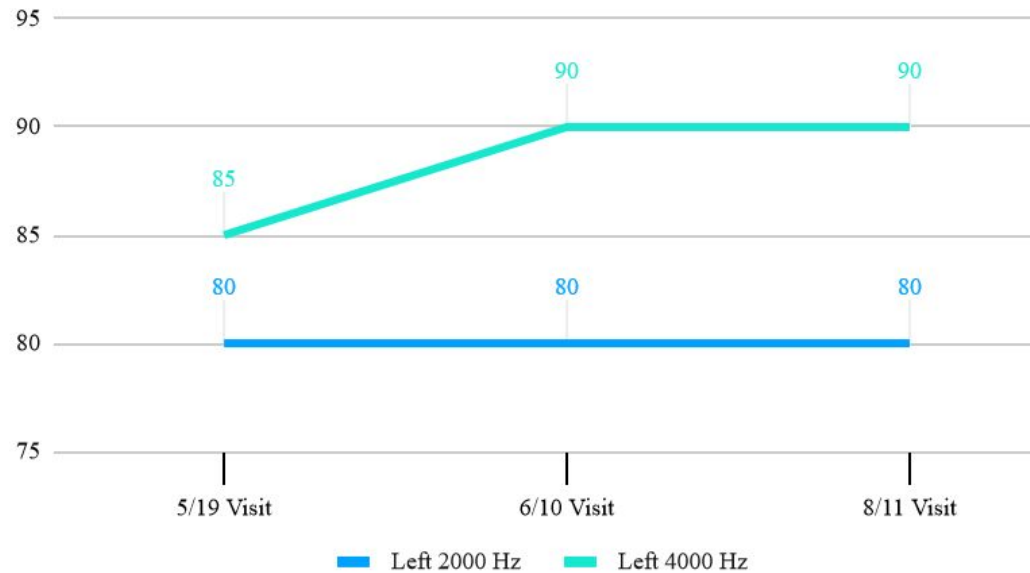
## Aim 2. Prospective Study

- 68-yo male completed 3 visits
- Occupation: farmer
- Considerable noise exposure: farm equipment, guns, recreation
- Significant medical history
  - Tinnitus: bilateral, constant
  - Dizziness: intermittent, generalized
  - Worn bilateral hearing aids for 2+ years
  - Tonsillar cancer diagnosed spring 2021
  - Taken omeprazole (acid reflux) for 2 years prior to study enrollment
  - Began taking Nexium 11 days prior to initial study visit

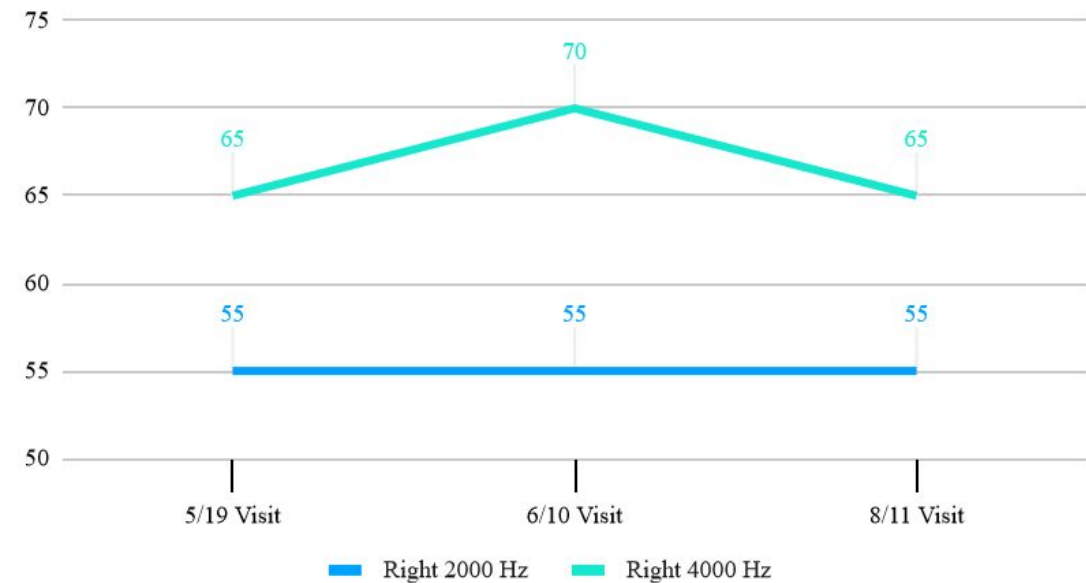


# Aim 2. Prospective Study

Left Ear: Tone Burst  
ABR Thresholds (dbnHL)



Right Ear: Tone Burst  
ABR Thresholds (dBnHL)



- No change in
- ABR thresholds
  - DPOAE response
  - Word recognition scores



# Conclusion

- Promising results from Aim 1 suggest that ESO may have a potential to protect against CIHL especially when taken before the initiation of CIS and higher ESO doses may offer better protection.
- The retrospective study was somewhat limited by the available clinical data, e.g. imbalanced sample size for CIS vs CIS+ESO groups; lack of CIS dosage info, etc.
- Aim 2 did not generate meaningful results due to difficulty with patient recruitment during COVID.



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# Acknowledgement

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- Idaho INBRE
- Idaho State University

**ROAR**