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Supplemental Tables:

sTable 1: Representativeness of Study Participants

Cancer types	Cisplatin is used to treat tumors in both children and adults. In children, this includes osteosarcoma, hepatoblastoma and hepatocellular carcinomas, medulloblastoma, atypical teratoid/rhabdoid tumors (AT/RT), neuroblastoma, germ cell tumors, and other sarcomas. In adults, common cisplatin-treated tumors include germ cell tumors as well as non–small-cell lung, bladder, and head and neck cancers. It is estimated that over 500,000 patients annually in the United States are diagnosed with cisplatin-treated tumors.
Demographic Considerations	
Age	Cisplatin is used to treat tumors across all ages, including infants, children, adolescents, young adults, and older adults. After accounting for cisplatin dosing and multimodal treatment, younger children less than five years of age at cisplatin exposure appear to be at greatest risk for developing hearing loss.
Sex	Cisplatin is used to treat tumors that occur in both sexes. There is a slight male predominance reported in data from cisplatin-treated trials (In the Children's Oncology Group ACCL0431 trial[1] [60% male] and SIOPEl-6 trial[2] [54% male]) and in cohort studies, such as the landmark study from Moke et al[3] (56% male).
Race/Ethnicity	Patients of all races and ethnicities develop tumors treated with cisplatin. There are no known differences among races and ethnicities in risk of developing cisplatin-induced hearing loss.
Geographic Considerations	Cisplatin-based regimens vary considerably based on geography, with differences in cisplatin dosing and infusion schedules, including within the United States and internationally. However, hearing loss due to cisplatin is related to dosing and administration schedules independent of geography. Multiple grading systems for cisplatin-induced hearing loss endpoints are in use internationally; in children, a consensus system from the International Society of Pediatric Oncology (SIOP Ototoxicity Scale) offers a uniform international grading scale.
Incidence of Hearing Loss	Hearing loss from cisplatin occurs in ~40% of children across all tumor types, with increased prevalence in some tumor subtypes (brain tumors, hepatoblastoma, neuroblastoma) and in younger children (less than five years old at exposure).
Other Considerations	Data from the COG ACCL0431 trial raised concern for a potential adverse impact on survival from use of thiol agents in patients with metastatic tumors at presentation. As such, use of systemic thiol agents is not recommended in this population.
Overall Representativeness	**The population in this trial is therefore broadly representative of the pediatric oncology population being treated with cisplatin-based regimens, including for ages (i.e., children and adolescents) and tumor types enrolled. Patients receiving NAC in the intervention arm of this trial are similarly broadly representative of patients recommended to receive thiol-based systemic otoprotection. Use of an international consensus ototoxicity grading system, and incorporation of detailed cisplatin dosing into all analyses, further augmented the representativeness of the data internationally and across cisplatin regimens.**

[1]Freyer et al Lancet Oncol, 2017; [2]Brock et al N Engl J Med, 2018; [3]Moke et al Lancet Child Adolesc Health 2021

sTable 2: Comparison of dose-escalation and dose-expansion cohorts

Variable	Dose-Escalation n (%)	Dose-Expansion n (%)	p-value
Total	15	9	
Age at first Cisplatin dose			
0-5	6 (40)	3 (33)	0.504
6-10	3 (20)	4 (44)	
≥11	6 (40)	2 (22)	
Sex			
Male	8 (53)	6 (67)	0.678
Female	7 (47)	3 (33)	
Race			
White	12 (80)	8 (89)	0.442
Black or African American	1 (7)	0 (0)	
Asian & Pacific Islander	2 (13)	0 (0)	
Other/Not Reported	0 (0)	1 (11)	
Ethnicity			
Hispanic/Latinx	8 (53)	5 (56)	1.000
Not Hispanic/Latinx	7 (47)	4 (44)	
Tumor type			
Hepatic tumor	5 (33)	0 (0)	0.190
CNS tumor	5 (33)	4 (44)	
Osteosarcoma	5 (33)	5 (56)	
Starting cisplatin dose/day, mg/m2			
Median (range)	108.60 (75.2, 142.0)	104.30 (90.8, 131.4)	0.655
Cumulative Cisplatin dose, mg/m2			
Median (range)	457.70 (202.2, 619.7)	469.00 (210.4, 952.8)	0.929
Reduction in cisplatin dose			
No	11 (73)	8 (89)	0.615
Yes	4 (27)	1 (11)	
Pretreatment Cranial radiation			
No	11 (73)	8 (89)	0.614
Yes	4 (27)	1 (11)	
Autologous stem cell transplant			
No	14	8	1.000
Yes	1	1	
VPS prior to cisplatin			
No	12 (80)	6 (67)	0.635
Yes	3 (20)	3 (33)	

CNS = central nervous system; VPS = ventriculoperitoneal shunt.

sTable 3: Dose-based univariable and multivariable Cox model analyses for time to SIOP ≥2 hearing loss

Covariable	# event/total	Univariable analysis		Multivariable analysis	
	n/n	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, years					
0-5	14/19	7.020 (1.928, 45.029)	0.037	3.494 (0.573, 29.263)	0.102
6-10	6/11	4.871 (1.114, 33.390)		6.083 (1.294, 43.277)	
≥11	2/14	Reference group		Reference group	
Cisplatin Dosing		1.025 (1.006, 1.048)	0.018	1.021 (0.994, 1.057)	0.162
NAC Otoprotection					
Yes	8/18	0.645 (0.255, 1.535)	0.331	0.342 (0.123, 0.897)	0.032
No	14/26	Reference group		Reference group	
NAC = N-acetylcysteine; HR = Hazard Ratio; 95% CI = 95% Confidence Interval					

sTable 4: Diagnosis-based univariable and multivariable Cox model for time to SIOP ≥2 hearing loss

Covariable	# event/total	Univariable Analysis		Multivariable Analysis	
	n/n	HR (95%CI)	p-value	HR (95%CI)	p-value
Age, years					
0-5	14/19	7.020 (1.928, 45.029)	0.037	5.269 (1.052, 41.647)	0.075
6-10	6/11	4.871 (1.114, 33.390)		6.675 (1.425, 47.326)	
≥11	2/14	Reference group		Reference group	
Tumor type					
CNS	9/16	0.622 (0.228, 1.698)	0.155	0.653 (0.199, 1.988)	0.617
OST	3/10	0.261 (0.057, 0.908)		0.505 (0.073, 3.121)	
Other	2/9	0.286 (0.043, 1.146)		0.282 (0.033, 1.571)	
Hepatic	8/9	Reference group		Reference group	
NAC Otoprotection					
Yes	8/18	0.645 (0.255, 1.535)	0.331	0.348 (0.127, 0.915)	0.034
No	14/26	Reference group		Reference group	
NAC = N-acetylcysteine; HR = Hazard Ratio; 95% CI = 95% Confidence Interval; CNS = central nervous system tumor, OST = osteosarcoma.					

sTable 5: Multivariate models of candidate gene analyses for trial endpoints

Gene	SNP	Chr:Position	Effect Allele	MODEL #1*		MODEL #2*		MODEL #3*		MODEL #4*	
				OR (95%CI)	p-value	OR (95%CI)	p-value	β Coefficient (95%CI)	p-value	β Coefficient (95%CI)	p-value
GSTP1	rs1695	11:67352689	G	1.634 (0.5641-4.732)	0.366	17.62 (1.525-203.6)	0.022	0.0218 (-0.0121-0.0557)	0.217	0.0067 (-0.0498-0.0633)	0.817
GSTM3	rs36120609	1:110280253-1:110280257	-	1.227 (0.3786-3.974)	0.733	0.8866 (0.2075-3.789)	0.871	-0.0127 (-0.0506-0.0252)	0.516	0.0082 (-0.0532-0.0695)	0.796
GSTP1	rs1138272	11:67353579	T	3.029 (0.1408-65.13)	0.479	4.995 (0.1525-163.6)	0.366	-0.0847 (-0.2200-0.0505)	0.229	-0.0800 (-0.2952-0.1352)	0.472
GSTA1	rs3957357	6:52668687	A	1.362 (0.491-3.778)	0.553	0.8362 (0.236-2.963)	0.782	-0.0056 (-0.0437-0.0326)	0.777	-0.0045 (-0.0644-0.0553)	0.883
GPX5	rs451774	6:28502550	G	2.6 (0.9317-7.258)	0.068	2.979 (0.7417-11.97)	0.124	-0.0035 (-0.0357-0.0286)	0.834	-0.0446 (-0.0969-0.0078)	0.107
GSTT1	Null versus 1-2 copies			1.365 (0.192-9.692)	0.756	1.340 (0.112-16.086)	0.818	-0.0603 (-0.1889-0.0682)	0.373	-0.0035 (-0.1928-0.1231)	0.669
GSTM1	Null versus 1-2 copies			0.649 (0.130-3.238)	0.598	0.518 (0.070-3.807)	0.518	-0.1168 (-0.1980-(-0.0355))	0.014	-0.0071 (-0.1142-0.0100)	0.897

* Model #1: Logistic regression, endpoint SIOP Grade ≥2 vs Grade <2 **at end of therapy**
Model #2: Logistic regression, endpoint SIOP Grade ≥2 vs Grade <2 **at latest follow-up**
Model #3: Linear regression, endpoint GSH at **+4 hours from completion of cisplatin (NAC peak)**
Model #4: Linear regression, endpoint GSH at **+6 hours from completion of cisplatin (delayed level)**
All models included covariates: age at diagnosis (in years), cisplatin dose, completed all planned NAC.
NAC = N-acetylcysteine, OR = Odds ratio, 95%CI= 95% Confidence Interval.

sTable 6: Multivariable linear and logistic models for renal and marrow toxicity

Covariable	Maximum Serum Creatinine log(Maximum creatinine, mg/dl)		Renal Tubular Damage (Electrolyte supplementation*)		Cycle Duration log(Median duration of phase)	
	Mean diff. (95% CI)	p-value	OR (95% CI)	p-value	Mean diff. (95% CI)	p-value
Age, years						
0-5 vs. ≥11	-0.610 (-0.888, 0.331)	<0.001	0.182 (0.021, 1.580)	0.044	-0.050 (-0.207, 0.107)	0.224
6-10 vs. ≥11	-0.120 (-0.397, 0.157)		3.021 (0.500, 18.256)		0.091 (-0.065, 0.247)	
Tumor type*						
CNS vs. Hepatic	0.156 (-0.139, 0.452)	0.039	0.211 (0.029, 1.552)	0.210	0.249 (0.082, 0.415)	0.001
OST vs. Hepatic	0.397 (0.030, 0.764)		0.137 (0.011, 1.769)		0.461 (0.255, 0.668)	
Other vs. Hepatic	0.499 (0.126, 0.871)		0.038 (0.002, 0.845)		0.188 (-0.022, 0.398)	
NAC Otoprotection						
Yes vs. No	-0.003 (-0.220, 0.215)	0.981	0.451 (0.113, 1.811)	0.262	-0.130 (-0.252, -0.008)	0.038

*Includes prescription for Magnesium, Calcium, Phosphorus, and/or Potassium supplementation. NAC = N-acetylcysteine, OR = Odds ratio, 95%CI= 95% Confidence Interval. CNS = central nervous system tumor, OST = osteosarcoma.