PEDMARK® (sodium thiosulfate injection) Prevents Cisplatin-Induced Hearing Loss in Children and Young People Without Impact on Survival: A Pooled Analysis

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Background

HEARING LOSS IS A COMMON SIDE EFFECT OF CHEMOTHERAPY, PARTICULARLY IN CHILDREN AND YOUNG PEOPLE

Platinum-based chemotherapy is effective in treating cancer but is highly ototoxic. It has been shown to cause permanent and irreversible hearing loss, particularly in children and young adults.[1,2]

- Cisplatin causes dose-dependent damage of cochlear outer hair cells[3]
- Hearing loss has been documented as early as following the first platinum chemotherapy dose and as late as 50 months after cessation of chemotherapy[4,5]
- Hearing loss typically begins in the high frequency (4 to 8 kHz) and very high frequency (9 to 20 kHz) ranges and affects progressively lower frequencies in a cumulative fashion[5]

PEDMARK® (sodium thiosulfate injection) has been approved by the Federal Drug Administration (2022), European Medicines Authority (2023), and the Medicines and Health Regulatory Authority UK (2023) for prevention of cisplatin-induced hearing loss (CIHL) based on 2 pivotal studies ACCL04316 and SIOPEL [6,7]

Objective

Investigate survival and response in children and young people undergoing cisplatin chemotherapy with and without PEDMARK 6 hours after each cisplatin infusion by pooling the data from 2 pivotal studies.

References

1. Brock PR et al. *J Clin Oncol*. 2012;30(19):2408-2417; 2. Knight KR et al. *J Clin Oncol*. 2005;23(34):8588-8596; 3. Laurell G, Bagger-Sjöbäck D. *Acta Otolaryngol*. 1991;111(5):891-898; 4. Berg AL et al. *Laryngoscope*. 1999;109(11):1806-1814; 5. Bertolini P et al. *J Pediatr Hematol Oncol*. 2004;26(10):649-655; 6. Freyer DR et al. *Lancet Oncol*. 2017;18(1):63-74; 7. Brock PR et al. *N Engl J Med*. 2018;378(25):2376-2385.

Disclosures

James Long and Pierre Sayad are Fennec Pharmaceuticals employees; Donna Lockhart received a consulting fee from Fennec Pharmaceuticals

Methods

Data from ACCL04316 and SIOPEL 67 databases were pooled and analyzed.

234 participants (age 1 month to 18 years) with new solid tumor diagnoses; 116 were randomized to the no-PEDMARK arm and 118 to the PEDMARK arm.

There were no statistical differences between arms in relation to age, weight, age category (<5 years, ≥5 years), sex distribution, race, or tumor category.

Discussion / Conclusion

Results confirmed PEDMARK's efficacy in reducing cisplatin-induced hearing loss:

- **39% of patients experienced hearing loss in the PEDMARK arm compared to 65% in the no-PEDMARK arm, (P<0.0001)**
- There was **no significant difference in overall survival** or best overall response rate to chemotherapy between treatment arms
- PEDMARK did not alter the effectiveness of cisplatin-based chemotherapy

Results

Figure 1: Hearing Loss in Pooled Analysis Group (Intent-to-Treat Population)

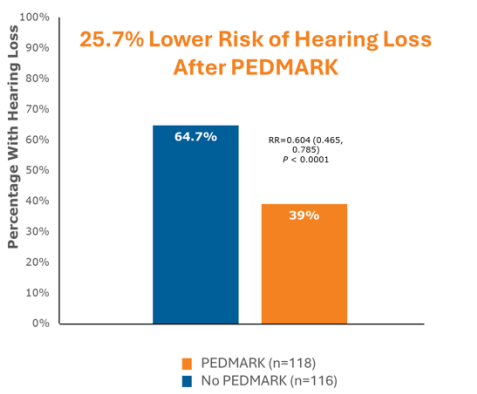

Table 1: Summary of Overall Survival and Best Overall Response Rate to Chemotherapy in Pooled Analysis Set (Including Subgroups) – Intent-to-Treat Population

Analysis Group	Analysis Parameter	No PEDMARK Arm	PEDMARK Arm
Overall Survival	n	116	118
	Subjects with event, n (%)	16 (13.8)	20 (16.9)
	Subjects censored, n (%)	100 (86.2)	98 (83.1)
	Treatment comparison		
	Hazard ratio	1.29	
	95% CI	(0.67, 2.53)	
	log-rank *P* value	0.4464	
Overall Survival (excluding diagnosis of 'Other' tumour)	N	114	115
	Subjects with event, n (%)	16 (14.0)	17 (14.8)
	Subjects censored, n (%)	98 (86.0)	98 (85.2)
	Treatment comparison		
	Hazard ratio	1.08	
	95% CI	(0.55, 2.17)	
	log-rank *P* value	0.8172	
All Patients With Any Recorded Response to Chemotherapy	n	111	106
	CR, n (%)	69 (62.2%)	69 (65.1%)
	PR, n (%)	27 (24.3%)	28 (26.4%)
	ORR, n (%)	96 (86.5%)	97 (91.5%)
	95% CI	80.1%, 92.8%	86.2%, 96.8%
	ORR treatment difference in favor of PEDMARK (95% CI)	5.0% (-3.3%, 13.3%)	
Patients (Excluding Diagnosis of 'Other' Tumour) With Any Recorded Response to Chemotherapy	n	109	103
	CR, n (%)	68 (62.4%)	69 (67.0%)
	PR, n (%)	27 (24.8%)	27 (26.2%)
	ORR, n (%)	95 (87.2%)	96 (93.2%)
	95% CI	80.9%, 93.4%	88.3%, 98.1%
	ORR treatment difference in favor of PEDMARK (95% CI)	6.0% (-1.9%, 14.0%)	

CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response.
Note: Time to event was calculated from the time of randomization to death. Subjects alive were censored at the time of last known follow-up visit. 'Other' includes localised astrocytoma (n=1; No PEDMARK arm), localised choroid plexus carcinoma (n=1; No PEDMARK arm), disseminated carcinoma of unknown origin (n=1; PEDMARK arm), and localised glycosaminoid-mediated tumours (n=2; PEDMARK arm).

Figure 2: Overall Survival (Excluding 5 Subjects With Diagnosis of 'Other' Tumour) – Intent-to-Treat Population