Precision Radiotherapy for Incurable Brain Tumors: Phase 1b Dose & Regimen Optimization Study of Iopofosine I 131 in Inoperable Relapsed or Refractory Pediatric High-Grade Glioma, Interim Data Assessment

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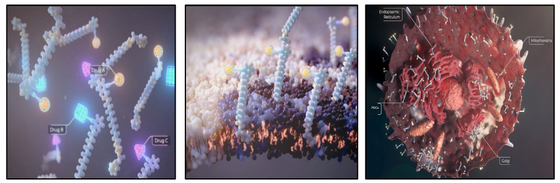
Introduction

- Pediatric high-grade gliomas (HGG) represent about 8-12% of all pediatric brain tumors, demonstrate molecular heterogeneity, and are associated with a poor prognosis (5 year survival rates <20%)[1,2]
- Iopofosine I 131 is a novel radiopharmaceutical composed of a lipid raft-targeting phospholipid ether covalently bound to ^{131}I, a beta-emitting radioisotope resulting in a phospholipid drug conjugate (PDC) (**Figure 1**)
  - Designed to provide targeted delivery of iodoine-131 directly to cancer cells, while limiting exposure to healthy cells
  - Crosses the blood-brain barrier[3]
  - Has shown antitumor activity in murine models of neuroblastoma[4]
- Iopofosine I 131 is currently being assessed in the CLOVER-2 study (NCT05610891) evaluating its activity in children, adolescents, and young adults with relapsed, refractory, recurrent HGGs and ependymoma
- The CLOVER-2 study enrolled patients with solid tumors, lymphomas, and brain tumors; this poster focuses on those enrolled with brain tumors.

Figure 1: PDC Mechanism of Action

Universal Targeting With Diverse Payloads



(1) PDC containing desired payload with tumor-targeting phospholipid ether

(2) Specific targeting of lipid raft on cancer cell membrane

(3) Intercellular delivery of payload by transmembrane flipping of lipid raft

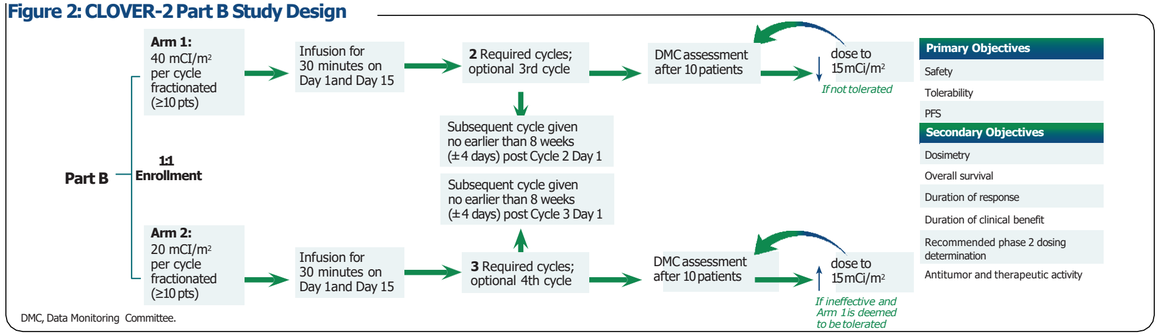
Study Summary

- The primary objective of Part A of this study was to determine the safety and tolerability of iopofosine I 131 in children, adolescents, and young adults with relapsed or refractory malignant solid tumors and lymphoma and recurrent or refractory malignant brain tumors
- Patient received either a single dose (15-30 mCi/m^2) on Day 1 or a fractionated dose (total dose 45-75 mCi/m^2) on Day 1 and 15 in a 12-week cycle. Additional cycles allowed at investigator discretion.
- Part B is an expansion cohort, and the primary objective of Part B of this study is to determine the safety, tolerability, and preliminary efficacy based on progression-free survival (PFS) of iopofosine I 131 in children, adolescents, and young adults with relapsed or refractory malignant HGG and ependymoma (Figure 2)
- Part B aims to assess two dosing regimens in parallel with patients enrolled 1:1 into two treatment arms:
  - **Arm 1:** Iopofosine I 131 administered as 40 mCi/m^2 per cycle fractionated into two 20 mCi/m^2 doses 14 days apart (± 1 Day) in two planned cycles, with an optional third cycle. Cycles are defined as two doses 14 days apart (± 1 Day). Cycle 2 will be given 8 weeks (± 4 Days) post initial infusion
  - **Arm 2:** Iopofosine I 131 administered as 20 mCi/m^2 per cycle fractionated into two 10 mCi/m^2 doses 14 days apart (± 1 Day). Cycles are defined as two doses 14 days apart (± 1 Day). Cycle 2 will be given 8 weeks (± 4 Days) post initial infusion. The third cycle will be initiated 8 weeks (± 4 days) post Cycle 2 Day 1

References

1. Funakoshi Y, Hata N, Kuga D, et al. Pediatric Glioma: An Update of Diagnosis, Biology, and Treatment. *Cancers* (Basel). 2021;13(4):758. 2. Hall CP, Cronk JC, Rubens JA. STINGing the immune system: lessons learned through a model of G34-mutant pediatric high-grade glioma. *J Clin Invest.* 2022;132(22):e164420

Figure 2: CLOVER-2 Part B Study Design



DMC, Data Monitoring Committee.

Figure 3: Patient Disposition

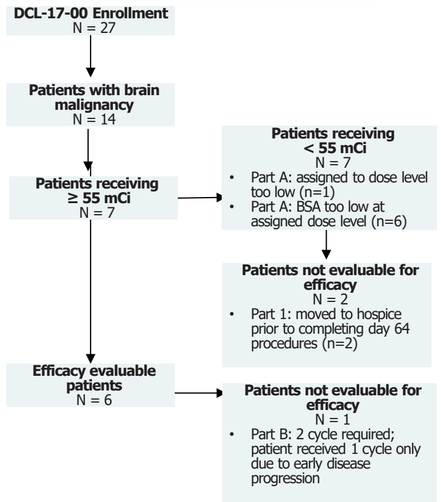


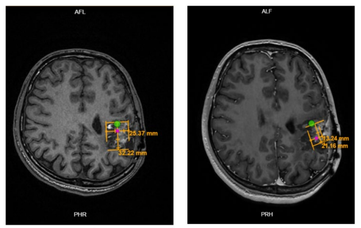
Table 1: Demographics

Characteristic	All patients with brain malignancy (n=14)	< 55 mCi TAD iopofosine I 131 (n=7)	≥ 55 mCi TAD iopofosine I 131 (N=7)
Diagnosis			
DHG	1	0	1
DIPG	4	3	1
DMG	1	0	1
Ependymoma	6	2	4
GBM	1	1	0
Medulloblastoma	1	1	0
Gender			
M	9	5	4
F	5	2	3
Median age (range) [years]	13 (5-25)	12 (5-14)	14 (11-25)
Mean prior interventions	4.4	4.7	4.1
Efficacy-evaluable			
Part A[1]	8	5	3
Part B[2]	3	0	3

Abbreviations: DHG: diffuse hemispheric glioma; DIPG: diffuse intrinsic pontine glioma; DMG: diffuse midline glioma; GBM: glioblastoma multiforme; TAD: total administered dose

1. Part A patients evaluable for efficacy if completed day 64 procedures following treatment
2. Part B patients evaluable for efficacy if completed 2 cycle of iopofosine I 131

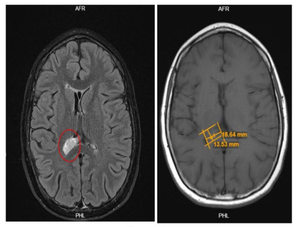
Figure 4: DHG patient



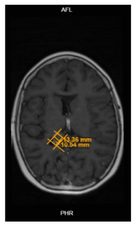
Screening

Day 327

Figure 5: Ependymoma patient



Screening



Day 270

One pt with DHG (Figure 4) experienced an initial 35% reduction in target lesions and a continued reduction to 50% at 8 months post-treatment representing a partial response but a new lesion was noted at the same time. A second pt with ependymoma (Figure 5) experienced a 31% reduction in the target lesion.

Table 2: Results

Table 2: Efficacy Results (evaluable patients)	< 55 mCi TAD iopofosine I 131 (n=5)	≥ 55 mCi TAD iopofosine I 131 (N=6)	Part B ≥ 55 mCi TAD iopofosine I 131 (N=3)
RAPNO Response			
Minor response; n (%)	0	2 (33.3)	2 (66.7)
Stable disease; n (%)	1 (20.0)	6 (100)	1 (33.3)
Mean duration of clinical benefit[1] (range) [months]	1.6 (0.9 – 2.8)	5.4 (1.9 – 11.0)	7.9 (1.9 – 11.0)
Mean progression free survival (range)[2] [months]	1.8 (1.2 – 2.8)	5.9 (2.1 – 11.2)	8.1 (2.1 – 11.2)
Mean overall survival (range) [months]	6.1 (3.2 – 7.7)	10.7 (6.2– 18.1)	Ongoing[3]

1. Duration of clinical benefit = time from first iopofosine I 131 dose to progressive disease or death
2. Progression free survival = time from arm assignment to progressive disease or death
3. Median follow up is 11.5 month (range 4.9 - 14.9 months)

Table 3: Treatment Related Adverse Events

Most common related TEAE (> 10% patients), n (%)	Any Grade (n=14)	Grade 3 (n=14)	Grade 4 (n=14)
Hematologic Toxicities			
Anemia	9 (64)	6 (43)	1 (7)
Febrile neutropenia	3 (21)	2 (14)	1 (7)
Lymphocyte count decreased	3 (21)	1 (7)	1 (7)
Neutropenia	9 (64)	1 (7)	8 (57)
Thrombocytopenia	11 (79)	2 (14)	8 (57)
White blood cell count decreased	9 (64)	1 (7)	8 (57)
Non-Hematologic Toxicities			
Constipation	2 (14)	0	0
Fatigue	5 (36)	0	0
Headache	3 (21)	0	0
Infusion-related reaction	2 (14)	0	0
Nausea	5 (36)	0	0
Rhinorrhea	2 (14)	1 (7)	0
Sepsis	2 (14)	2 (14)	0
Vomiting	4 (29)	0	0
Weight decreased	2 (14)	0	0

The safety profile was consistent with selective targeting of tumor sites with clinically negligible off-target effect outside the hematologic system. The most common treatment emergent adverse events (AE) are: thrombocytopenia (79%), anemia (64%), neutropenia (64%), and white blood cell count decreased (64%). The hematologic AEs are similar to those seen in other pts treated with iopofosine I 131 and are considered predictable and manageable.

Conclusions

- Less than 5% of infused activity accumulating in non-tumor tissue
- Heme AEs were considered predictable and manageable and consistent with previously observed AEs
- TADs of < 55 mCi and >55 mCi show clear dose response
  - Dosing regimen may need to be refined to provide higher TAD to achieve greater responses
- Preliminary data with iopofosine I 131 shows activity and warrants further investigation

For more information, please contact clinical@cellectar.com