

LDH kinetics as a biomarker of disease activity in glioblastoma treated with porphyrin metabolite activation (PoMA)

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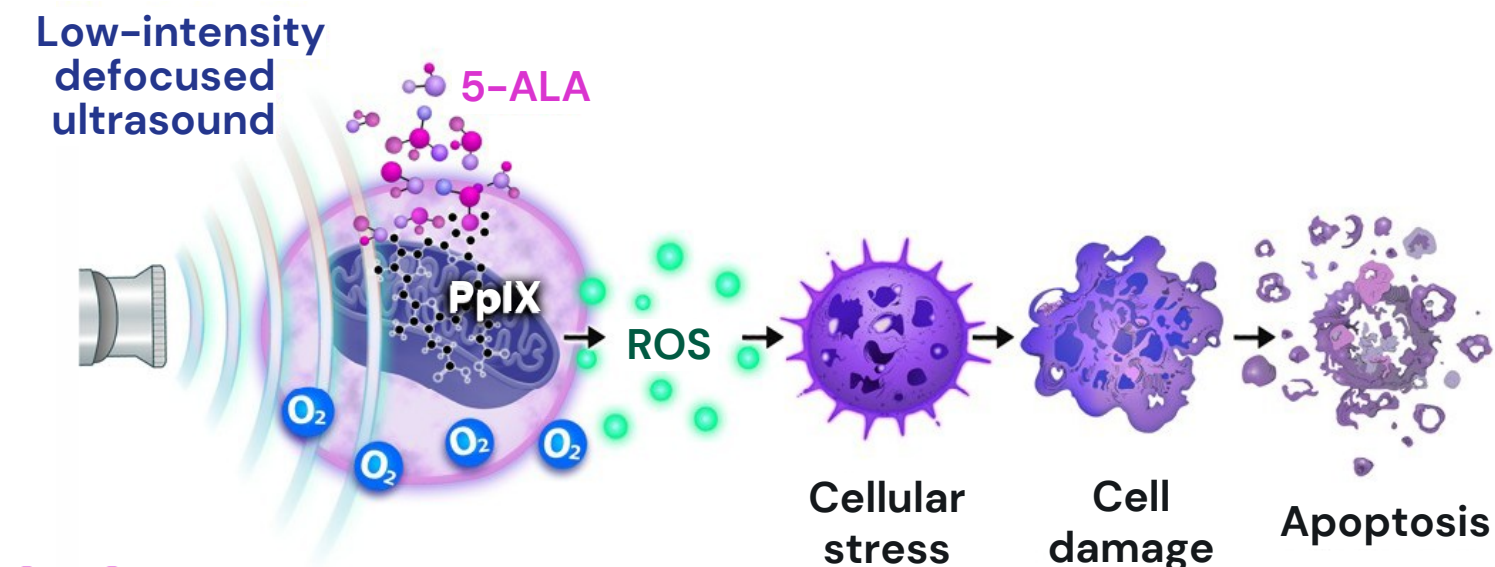
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Background

- GBM is an aggressive, infiltrative brain tumor characterized by profound heterogeneity and complex microenvironment, with poor OS (12-16 months) based on current management strategies¹
 - Treatment of patients with MGMT-unmethylated GBM, as well as those with multiple tumor lesions or recurrent GBM remain an unmet need²⁻⁴
- Current GBM therapies primarily target a single pathway or mechanism and may be associated with off-target toxicities¹
- PoMA is a drug-led therapeutic approach designed to achieve antitumor activity by exploiting the natural pathophysiology of GBM and biology of PpIX
 - PpIX derived from exogenous 5-ALA accumulates within tumor cells and is activated by low-intensity ultrasound, enabling treatment of the entire cerebral hemisphere in a single treatment session (Figure 1)⁵
- A previous Phase 1 study in 12 patients with recurrent (any level), inoperable HGG showed that PoMA was well-tolerated, with no serious TEAEs, and extension in both PFS and OS⁶
- The efficacy and safety of PoMA is currently being investigated in patients with both recurrent (NCT05362409) and newly diagnosed GBM (NCT07225621)^{7,8}
- Assessing disease progression in GBM is challenging because treatment-related imaging changes can mimic disease progression, potentially leading to premature treatment discontinuation^{9,10}
- LDH, a key enzyme involved in tumor glycolysis, may reflect tumor metabolic activity and serve as a blood-based biomarker, which has shown promise in other solid tumor types¹¹
- In this analysis of the phase 1 first-in-human study (NCT05362409), we evaluated whether serial LDH kinetics could inform disease trajectory in patients with recurrent GBM treated with PoMA

Figure 1: Mechanism of Action of PoMA in GBM



Methods

- This exploratory analysis included 22 adults (≥18 years) with recurrent, inoperable supratentorial HGG (including multifocal/multicentric tumors in 1 hemisphere)
- Other key inclusion criteria included prior radiotherapy, WHO performance status of ≤2, and adequate organ function following washout from prior anticancer therapy
- Key exclusion criteria:
 - Infratentorial, brainstem, spinal cord, or bihemispheric disease
 - Contraindications to MRI or 5-ALA
 - Recent stroke/CNS bleeding or clinically significant edema
 - Significant uncontrolled comorbidities
 - IDH-mutant or MGMT-methylated tumors (allowing for homogenous analysis of patients with the poorest expected OS)
- Patients received 4 protocol-defined PoMA treatment sessions (120 minutes per cycle; Q4W), which included receiving 5-ALA administered as a sonosensitizer prior to CV01-delivered ultrasound (Alpheus Medical)
- LDH was assessed at prespecified cycle-based visits (screening/baseline; cycle days 1, 8, 15, and 22 in some patients; and end of treatment), with no fixed time interval between assessments
 - Sustained LDH increases were defined as consecutive increases of ≥25% from the preceding value, with an absolute increase of ≥40 U/L, or for patients with limited sampling, a single increase of ≥50%
- Associations between LDH kinetics and investigator-assessed clinical deterioration during treatment, as well as imaging-based suspected PD, were evaluated; radiographic responses were assessed using RANO criteria
- AEs were recorded and graded per National Cancer Institute CTCAE v5.0, with attribution to study treatment determined by the treating investigator at the local site
 - DuLTs were prospectively defined as any grade ≥3 non-hematologic toxicity, considered at least possibly related to study intervention, occurring during the cycle 1 DuLT period (first 4 weeks of treatment)

Results

Baseline Clinical Characteristics

- LDH kinetics were assessed in 15/22 patients with MGMT-unmethylated recurrent GBM
 - Overall, 67% (n=10) patients were male and 33% (n=5) were female, with a median (min-max) age of 61 (31-75) years
 - Patients exhibited a median (min-max) LDH level of 182 (134-310) U/L at baseline

Clinical and Radiographic Disease Status

- Patients received a median (min-max) of 2 (1-8) POMA treatment cycles; repeat dosing of 5-ALA and PoMA resulted in extension of both PFS and OS (Table 1)
- Following 4 POMA treatment cycles, median OS for all patients was 13.6 months
 - Despite 6 patients demonstrating imaging-based progression, 100% (6/6) of these patients also had stable LDH levels and exhibited an increased median OS compared to the overall group
 - Additionally, of 6 patients with stable imaging and clinical status following treatment, 83% (5/6) had higher than or similar to overall median OS; LDH levels were not elevated, non-interpretable, or discordant in these patients
 - In 3 patients that demonstrated clinical deterioration and a poor OS, LDH levels were consistently increased

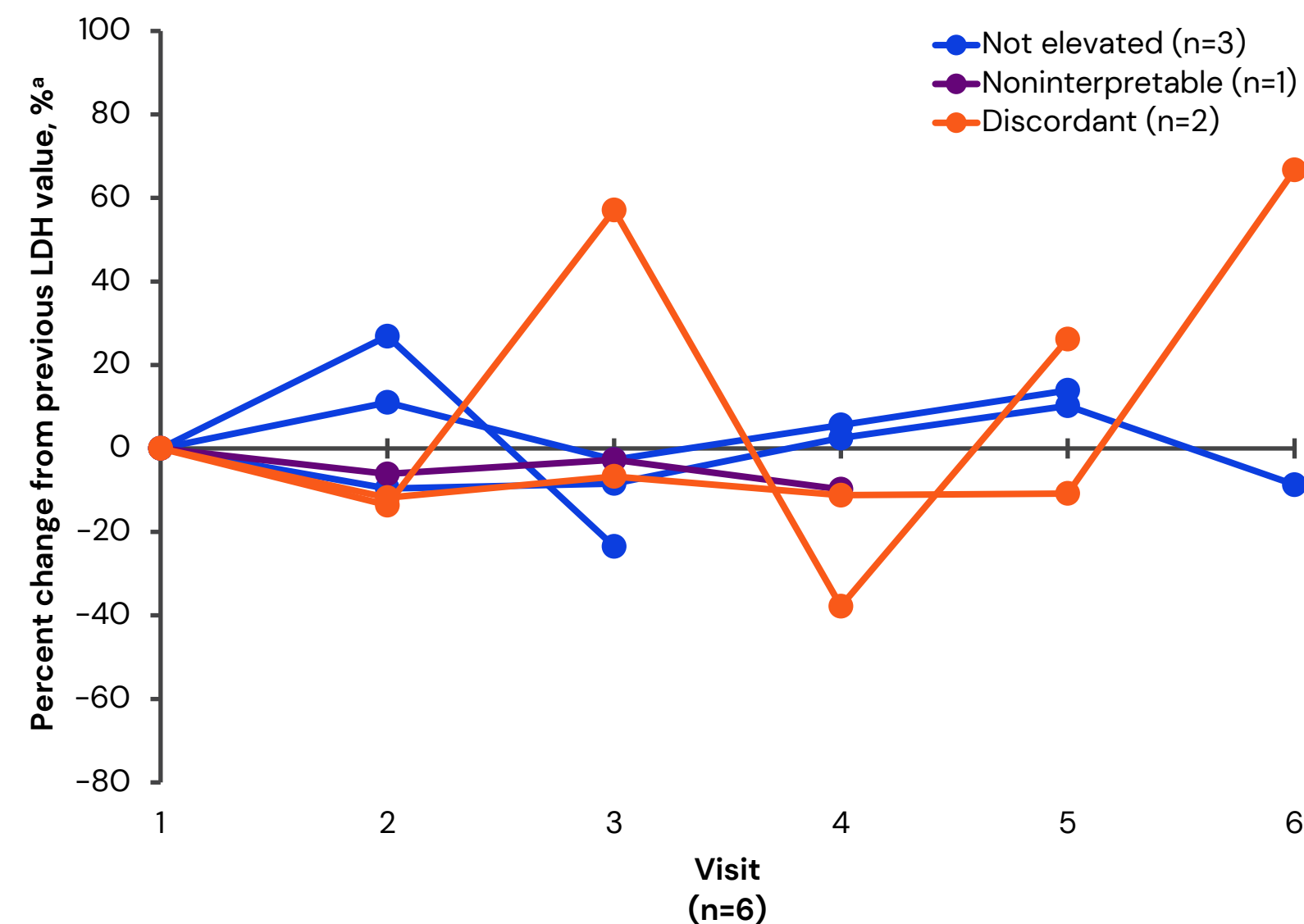
Table 1: Summary of Clinical and Radiographic Disease Status

Category	LDH finding (n/N)	OS (median, days)	OS (median, months)	PFS (median, days)	PFS (median, months)
Imaging-based progression	Stable (6/6)	479	15.7	51	1.7
Stable LDH, imaging, and clinical status	Not elevated (3/6)	383	12.6	203	6.7
	Non-interpretable (1/6)	62	2.0	37	1.2
	Discordant (2/6)	485	15.9	201	6.6
Clinical deterioration	Increase (3/3)	111	3.6	56	1.8
Overall	–	414	13.6	56	1.8

Changes in LDH Over Time

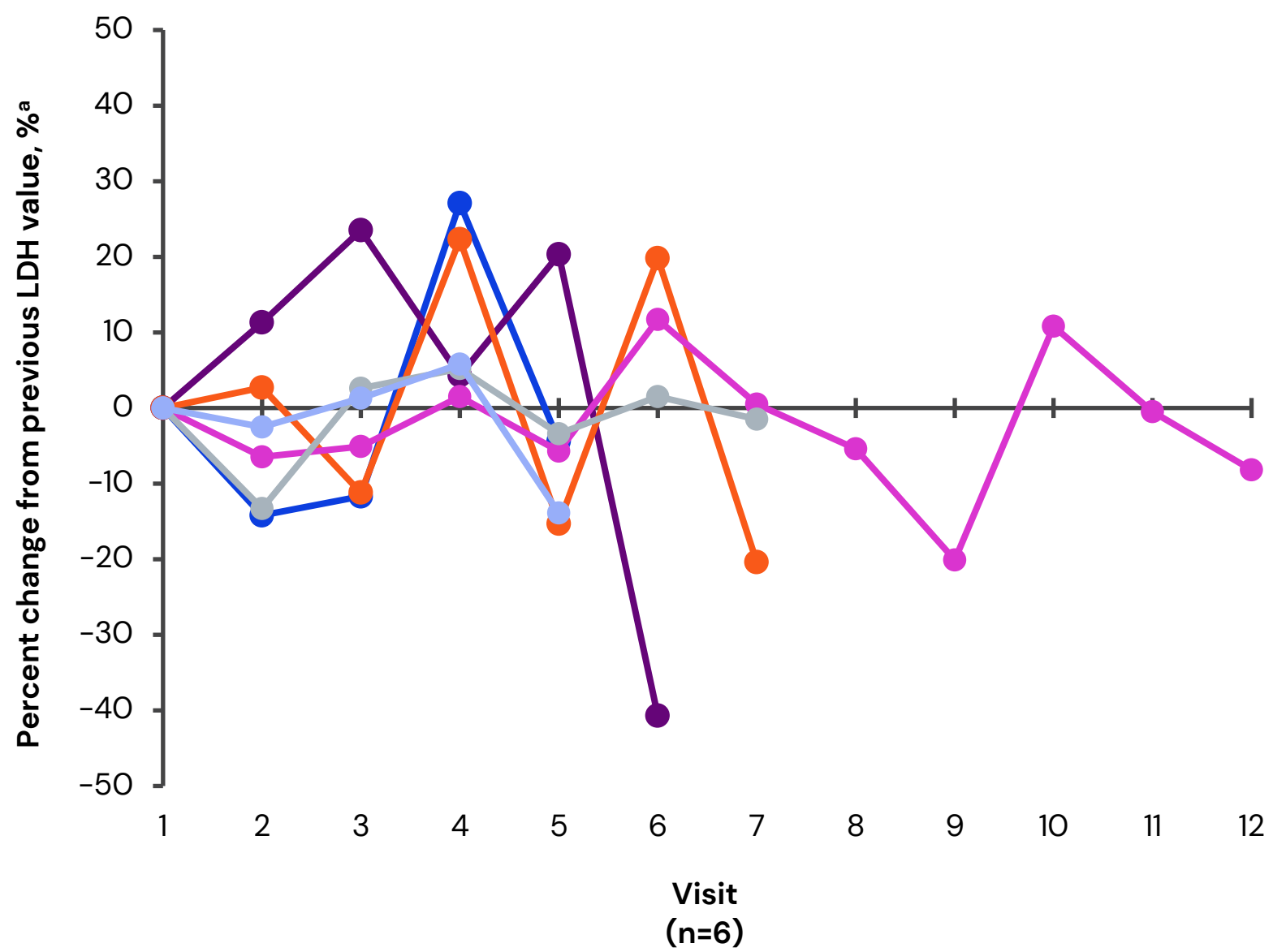
- Patients without evidence of disease progression generally demonstrated stable or declining LDH levels throughout treatment (Figure 2)
- Patients with imaging-based suspected disease progression generally maintained stable LDH levels despite radiographic progression (Figure 3)
- In contrast, all patients with investigator-assessed clinical deterioration exhibited sustained increases in LDH during treatment (Figure 4)

Figure 2: Patients With Stable Disease and Stable/Declining LDH



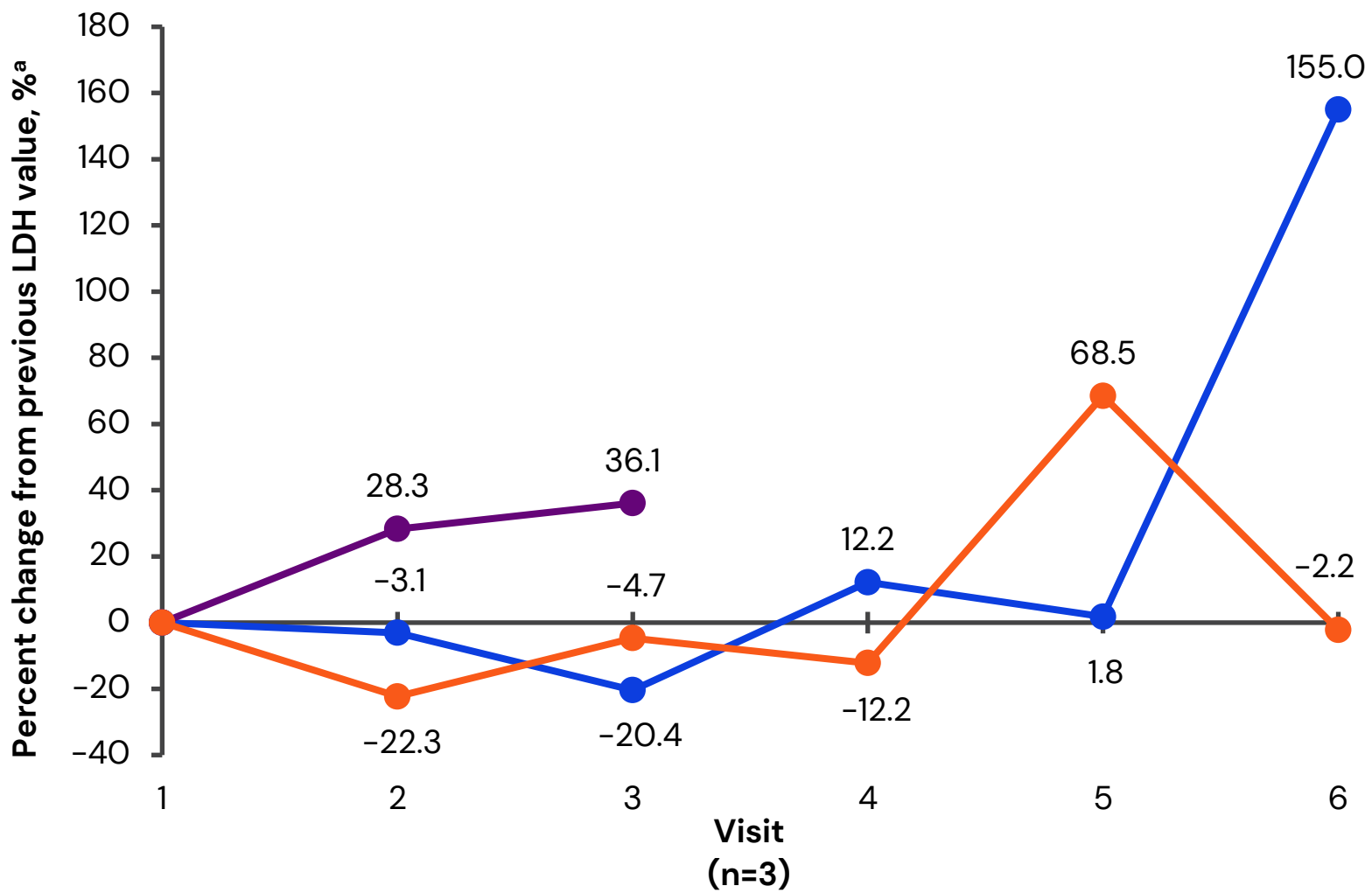
^a Baseline values were assessed at visit 1. Percent change at each visit was calculated from the LDH value of the previous visit. Each line color represents a different patient.

Figure 3: Patients With Progressive Disease on Imaging And Stable LDH Levels



^a Baseline values were assessed at visit 1. Percent change at each visit was calculated from the LDH value of the previous visit. Each color represents a different patient.

Figure 4: Patients With Clinical Deterioration And LDH Increases During PoMA treatment



^a Baseline values were assessed at visit 1. Percent change at each visit was calculated from the LDH value of the previous visit. Each color represents a different patient.

Safety

- Repeat dosing of 5-ALA and PoMA was safe and well tolerated, with no DuLTs observed, and promising extension in both progression-free survival and overall survival

5-ALA, 5-aminolevulinic acid; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DuLT, duration-limiting toxicity; GBM, glioblastoma multiforme; HGG, high-grade glioma; IDH, isocitrate dehydrogenase; LDH, lactate dehydrogenase; MGMT, O6-methylguanine-DNA-methyltransferase promoter; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PoMA, porphyrin metabolite activation; PpIX, protoporphyrin IX; ROS, reactive oxygen species; TEAE, treatment-emergent AE; WHO, World Health Organization.

Key Findings

- Together, these study findings support further prospective evaluation of the utility of LDH as a minimally invasive blood-based biomarker of disease activity during PoMA treatment
- In this exploratory analysis of a cohort of 15 patients with difficult-to-treat GBM and poor prognosis, patients without evidence of progressive disease generally demonstrated stable or declining LDH levels throughout PoMA treatment

Conclusions

- Sustained LDH elevations were generally concordant with investigator-assessed clinical deterioration during PoMA treatment; however, some patients with stable LDH levels and investigator-assessed clinical deterioration had long OS, suggesting pseudoprogression
- Discordant LDH findings in 2 patients may be explained by confounding from subsequent therapies (n=1) or transient aberrant readings (n=1), and do not appear to reflect sustained disease-related LDH elevation
- Serial LDH assessments may complement radiographic assessments by providing an additional non-invasive blood-based biomarker of clinically meaningful disease progression, warranting further evaluation in larger studies
- LDH kinetics had an expected natural variation; however, predefined consecutive increases or an initial large increase were more indicative of disease status than single smaller changes
- PoMA is currently under investigation in patients with recurrent and newly diagnosed GBM (NCT07225621 and NCT05362409) and has the potential to offer a repeatable, non-invasive treatment for patients with GBM, highlighting the need for potential complementary biomarkers to track disease progression^{7,8}

References

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Disclosures

T. Johanns reports serving on advisory boards for VelociTx and Servier; serving as a principal investigator for Compass; receipt of personal research funding from Lentigen; and serving as a local principal investigator for IDEAYA, BeOne, and AstraZeneca. M. Schulder reports stock ownership in Hyperfine, Inc. and SurgAL. L. Mechtler reports institutional research funding from AbbVie, Inc., Alpheus Medical, Inc., Axsome Therapeutics, Inc., Eli Lilly and Company, H. Lundbeck H/S, Hyperfine, Inc., Merz Therapeutics, Pfizer, Inc., ShiraTronics, Inc., Teva Pharmaceutical Industries, Ltd., and The Harry Dent Family Foundation, Inc.; service on advisory boards for Craniometrix, Inc., Hyperfine, Inc., and NeuroDiscovery AI, Inc.; and an ownership interest in NeuroNet GPO, Inc. V. Agarwal and A. M. Hulstine report financial interests with Alpheus Medical, Inc.