DSP-0390, an oral emopamil binding protein (EBP) inhibitor, in patients with recurrent high-grade glioma: a first-in-human, phase 1 study

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Introduction

- Unlike other organs, cholesterol in the brain is derived wholly from de novo biosynthesis (because the blood–brain barrier is impermeable to systemic cholesterol)[1]
- At high cell density, normal astrocytes downregulate genes related to cholesterol biosynthesis, resulting in low cholesterol levels; in contrast, glioblastoma (GBM) cells keep this pathway activated, leading to high cholesterol levels[2]
- The overexpression of cholesterol synthesis genes is associated with decreased survival in patients with GBM, suggesting that gliomas may be sensitive to the inhibition of cholesterol biosynthesis[2]
- EBP is an endoplasmic reticulum membrane protein involved in the final steps of cholesterol biosynthesis[3,4]
- De novo cholesterol synthesis is integral to cell membrane structure and signaling[5]
- High expression of EBP and upregulation of the cholesterol metabolism pathway have been observed in solid tumors[6]
- Inhibition of EBP has been associated with an upregulation of its substrates zymostenol and zymosterol[7,8]
  - This, in turn, can contribute to lethal autophagy in cancer[9,10] and efficient cellular cholesterol depletion via secondary liver X receptor activation[11]
- DSP-0390 is an investigational, small molecule inhibitor of EBP **(Figure 1)**
- Here, we describe the design of an ongoing phase 1 study of DSP-0390 monotherapy in patients with recurrent high-grade glioma

Figure 1. Mechanism of action of DSP-0390

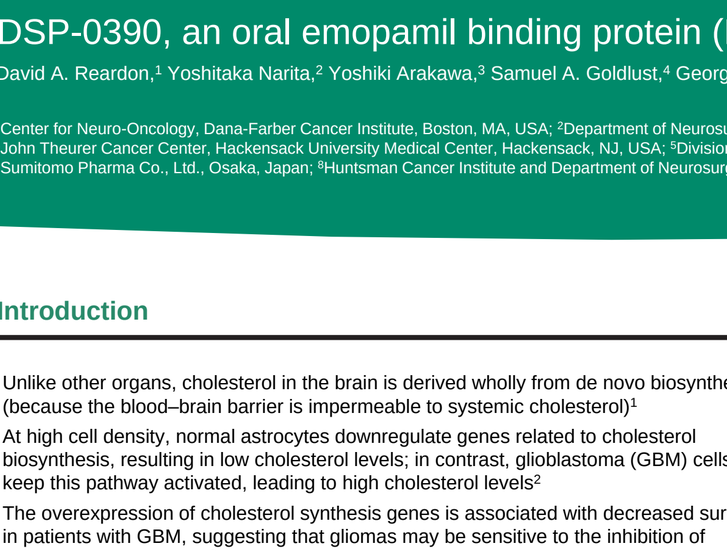


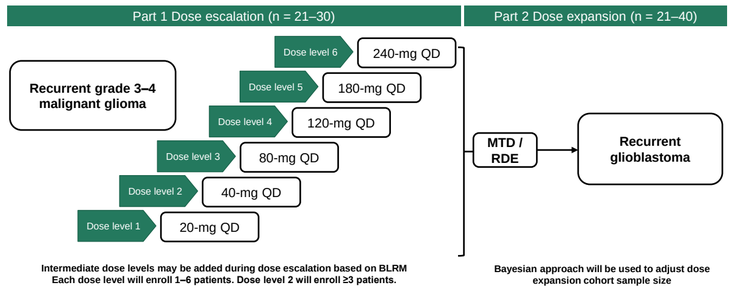
Figure from: Sumitomo Pharma Oncology, Inc., Available at: https://oncology.sumitomo-pharma.com/pipeline/?gclid=EAIaIQobChMIfeEsqPd9gIV1O2zCh20uQETEAAYASABEgLT4_D_BwE#DSP-0390_background Accessed April 1, 2022.

Methods

Study Design

- NCT05023551 is an open-label, phase 1 study of oral DSP-0390 consisting of 2 parts (**Figure 2**):
  - A dose-escalation part, which will evaluate increasing doses of DSP-0390 to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) in patients with recurrent World Health Organization (WHO) grade 3–4 malignant glioma
  - A dose-expansion part, which will assess the preliminary antitumor activity and safety of DSP-0390 at the MTD/RDE identified during dose escalation in patients with recurrent GBM

Figure 2. Study Design



BLRM, Bayesian Logistic Regression Model; MTD, maximum tolerated dose; RDE, recommended dose for expansion; QD, once daily.

- Study participants will receive single-agent DSP-0390 daily in 28-day cycles until unacceptable toxicity, withdrawal of consent, loss to follow-up, or discontinuation of the patient by the investigator and/or Sponsor
  - Patients who experience disease progression may continue with study treatment based on the investigator's decision, if they are adequately tolerating study therapy and appear to be deriving clinical benefit
  - In the dose-escalation part of the study, DSP-0390 will be administered at a starting dose of 20 mg once daily; additional dose levels ranging from 40–240 mg once daily will be opened, as appropriate

Patients

- Key eligibility criteria for this phase 1 trial are summarized in **Table 1**

Table 1. Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Histologically confirmed recurrent[a] WHO grade 3–4 malignant glioma[b]; ≥1 prior line of therapy **(dose escalation only)** • Histologically confirmed recurrent[c] GBM (primary; IDH-wildtype) and measurable disease per RANO 2010 criteria **(dose expansion only)** • Age ≥18 years (or ≥20 years per local laws) • Karnofsky performance status score of ≥70 • Adequate renal, hepatic, and hematologic function	• Prior treatment with a VEGF inhibitor ≤3 months of Day 1 • Multifocal disease, leptomeningeal metastasis, or extracranial metastasis • Abnormal ECG that is clinically significant • LVEF <40% per ECHO or MUGA • Active infection (acute or chronic) • Significant CV disease, including NYHA class III–IV CHF and MI, ≤6 months of day 1 • Major surgery, chemotherapy, or investigational therapy ≤4 weeks[d] of day 1 and radiotherapy ≤12 weeks of day 1 • Concurrent treatment with tumor-treating fields

For a comprehensive list of eligibility criteria, please refer to ClinicalTrials.gov (NCT05023551).
[a]Defined as radiographic evidence of progression per RANO 2010 criteria.
[b]Includes anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed glioma, and GBM.
[c]Defined as radiographic evidence of progression following primary therapy with surgery and radiation ± chemotherapy.
[d]Except 6 weeks for nitrosoureas and immunotherapy or 8 weeks for an implanted nitrosoureas wafer.
CHF, congestive heart failure; CV, cardiovascular; ECG, electrocardiogram; ECHO, echocardiogram; GBM, glioblastoma; IDH, isocitrate dehydrogenase isozyme; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MUGA, multiple-gated acquisition; NYHA, New York Heart Association; RANO, Response Assessment in Neuro-Oncology; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

Endpoints

- Study endpoints are summarized in **Table 2**

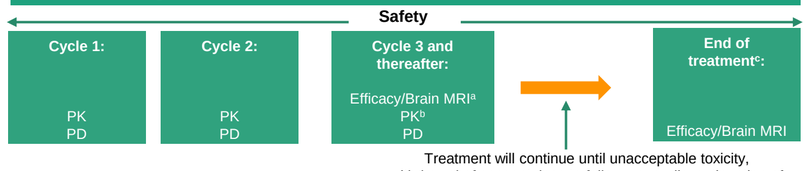
Table 2. Study endpoints

Endpoint	Dose escalation	Dose expansion
Primary	• TEAEs and SAEs • DLTs	• PFS rate at 6 months[a]
Secondary	• AUC, C_{max}, t_{max}, $t_{1/2}$, R_{acc} • ORR[b] and DOR[c]	• ORR[b] • PFS[d] • DOR[c] • OS rate at 12 months[e] • TEAEs and SAEs
Exploratory	• Biomarkers in blood[f] • Correlation of steady-state trough concentrations with AEs, response, and PD markers	
	• Detection of metabolites from DSP-0390 • Biomarkers in tumor tissue[g]	• Biomarkers in tumor tissue and/or blood[g]

[a]Defined as the proportion of patients alive 6 months after the first dose of DSP-0390 without disease progression per RANO 2010 criteria. [b]Defined as the percentage of patients with a complete or partial response per RANO 2010 criteria. [c]Defined as the time between the first documented response and disease progression or death (regardless of cause), whichever occurs first. [d]Defined as the time between the first dose of DSP-0390 and documented disease progression or death (regardless of cause), whichever occurs first. [e]Defined as the proportion of patients alive 12 months after the first dose of DSP-0390. [f]Eg, lathosterol/zymostenol ratio in serum. [g]Eg, gene mutation and gene expression analysis.
AE, adverse event; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; DLT, dose-limiting toxicity; DOR, duration of response; ORR, objective response rate; OS, overall survival; PD, pharmacodynamic; PFS, progression-free survival; RANO, Response Assessment in Neuro-Oncology; R_{acc}, ratio of accumulation; SAE, serious adverse event; TEAE, treatment-emergent adverse event; $t_{1/2}$, elimination half-life; t_{max}, time to achieve C_{max}.

- The timing of assessments for the primary, secondary, and exploratory endpoints is presented in **Figure 3**. Safety will be evaluated throughout the study

Figure 3. Schedule of select assessments by study visit



[a]Every 8 weeks (every 2 cycles) from Cycle 1 Day 1 cycle with a window of ±7 days. [b]PK blood collection will be made during cycle 3 (pre-dose) for the dose-expansion part only. [c]≤7 days of the last dose of DSP-0390.
MRI, magnetic resonance imaging; PD, pharmacodynamics; PK, pharmacokinetics.

Statistical Design and Analysis

- Approximately 21–30 patients will be enrolled in the dose-escalation part of the study
  - An adaptive Bayesian Logistic Regression Model (BLRM) with escalation with overdose control (EWOC) will be used to guide dose escalation and to estimate the MTD based on the occurrence of dose-limiting toxicities (DLTs), as defined in **Table 3**, during cycle 1
  - Each dose level will be evaluated in 1–6 patients, with the second and subsequent patients able to receive DSP-0390 after completion of all safety assessments on cycle 1/day 8 in the first patient
  - A minimum of 3 patients will be evaluated if a DLT is observed at a dose level
    - At dose level 2 (40 mg once daily), ≥3 patients will be evaluated before escalation to a higher dose

Table 3. Protocol-specified DLTs[a]

- Grade 4 neutropenia lasting >7 days
- Grade 4 anemia requiring RBC transfusion
- Grade 3–4 febrile neutropenia
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with clinically significant bleeding or requiring platelet transfusion
- Grade 2 retinopathy not resolved to grade ≤1 or baseline ≤7 days
- Any toxicity leading to treatment discontinuation
- Any toxicity leading to dose interruption lasting >7 days
- Any grade ≥3 non-hematologic toxicity, except for:
  - Grade 3 fatigue or asthenia
  - Grade 3 fever lasting <24 hours
  - Asymptomatic grade ≥3 electrolyte abnormalities not considered clinically significant by the investigator and that resolve to grade ≤1 ≤72 hours following withholding of study drug
  - Grade 3 nausea, anorexia, vomiting, constipation, or diarrhea lasting <72 hours

[a]Defined as an adverse event or abnormal laboratory value related to DSP-0390 that occurs during cycle 1 (equivalent to 4 weeks/28 days). Patients who experience a DLT will be discontinued from DSP-0390.
DLT, dose-limiting toxicity; RBC, red blood cell.

- Dose escalation will continue until identification of the MTD and/or RDE, which will occur when the following conditions are met:
  - ≥Six patients have been treated at this dose

  AND
  - The posterior probability of targeted toxicity at this dose is >50% and is the highest among potential doses **OR** ≥21 patients have been treated in the dose-escalation part of the study

  AND
  - It is the recommended dose based on the BLRM and a review of all available data
- Approximately 20–40 patients will be enrolled in the dose-expansion part of the study
  - A Bayesian approach will be used to continually assess the posterior probability of an objective response rate (ORR) of ≥15%
  - After ≥10 patients are evaluable for ORR, if the posterior probability is <5%, enrollment may be stopped due to lack of efficacy
- Data will be summarized primarily using descriptive statistics
- Progression-free survival at 6 months will be summarized via the Kaplan–Meier method

Conclusions

- A phase 1 trial of the oral EBP inhibitor DSP-0390 is currently recruiting patients with recurrent high-grade glioma in the United States and Japan
- For further information, please refer to ClinicalTrials.gov (NCT05023551)

References

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