A Phase 2 Study of BPM31510 (a lipid nanodispersion of oxidized CoQ10) with Vitamin K in combination with Standard of Care (SOC) RT and TMZ in Glioblastoma Multiforme (GBM) patients without prior therapy

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Background

- CoQ10 deficiency is a common feature of glioblastoma (Biomolecules. 2022 Feb; 12(2): 336). **BPM31510** is a novel drug-lipid conjugate nanodispersion that achieves 10,000X supraphysiological levels of oxidized CoQ10. In preclinical studies, supraphysiological concentrations of oxidized CoQ10 induce a metabolic shift accompanied by Reactive Oxygen Species (ROS) generation leading to apoptosis in cancer cells. Main AEs in phase 1 were hepatotoxicity and coagulopathy. DLT was not achieved even at the highest dose level. Coagulopathy (prolonged PT/INR, PTT/aPTT) was alleviated by prophylactic administration of Vitamin K. Starting at phase 1, RP2D dose has remained at 110 mg/kg/week.
- **BPM31510IV-11 (NCT04752813):** A single-arm, non-randomized, open-label, phase 2 study of BPM31510 + Vitamin K1 with standard chemoradiation and TMZ in newly diagnosed GBM patients. The study is currently recruiting patients in the US.

FIGURE 1: BPM31510 Mechanism of Action

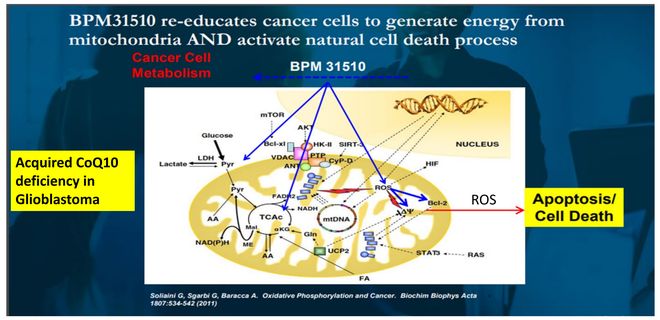

FIGURE 2: Phase 1 Overview and Results

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Dose Cohort	Dose (mg/kg)
-1	88
Starting	110
+ 1	137
+ 2	171

Phase 1 Patient Population: Subjects with glioblastoma that has recurred on a bevacizumab-containing regimen

Trial Design
- mTPI adaptive clinical trial design to determine maximum-tolerated dose (MTD) up to maximum 10 subjects
- **The MTD in this study was 171 mg/kg**

Treatment Dose	# Patients
100 mg/kg	6
137 mg/kg	1
171 mg/kg	5

Study Details
- Investigator Sponsored Study
- Clinical Site: Stanford University
- Clinical Investigators: Dr. Lawrence Recht, Dr. Seem Nagpal, Dr. Reena Thomas

Clinical Summary
- No dose limiting adverse events reported to date and drug is well tolerated

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Survival Data
- The median OS was 128 d (95% [CI]:48-209)
- The median PFS for eligible and evaluable patients was 34 d (CI of mean 8.9).
- No patients on this study showed PR or CR

Pharmacokinetics
- BPM31510 dose proportional PK was observed

TEAE
- Most common TEAEs were fatigue, increased ALT, increased AST and increased GGT. Elevated LFT were the main TEAE related cause for study drug withdrawal (2 patients).
- Decreased levels of platelets and lymphocytes, and increased BUN, potassium and cholesterol and prolonged aPTT compared to baseline were observed.
- ECG results showed an increased P wave axis angle, decreased PR, QPRD and RR intervals and consistently decreased QRS axis angle and T wave axis angle.

FIGURE LEGEND: A. Phase 1 study in GBM established MTD for phase 2. B. Phase 1 Study Results in recurrent GBM

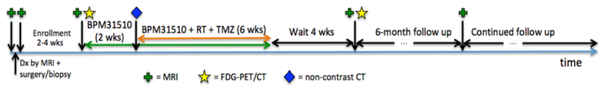
FIGURE 3: Phase 2 BPM31510IV-11 Study Design, Endpoints, and Treatment

Study Design:
- A single-arm, non-randomized, open-label Phase 2 therapeutic study to assess the effects of adding BPM31510 onto a conventional treatment framework of RT and concurrent TMZ chemotherapy for subjects with newly diagnosed GB.
- Study initiated with a dose-confirmation phase establishing safety of BPM31510 in combination with RT and TMZ. Following a standard 3+3 dose design, with 1 potential dose de-escalation in the event of a DLT.
- The efficacy phase of the study will begin after the recommended Phase 2 dose (RP2D) being confirmed.
- The study will enroll approximate 50 subjects for ~90% power in rejecting the null hypothesis of PFS6 of ≤ 30%.

Primary Endpoint:
- Progression free survival at 6 month, defined as the proportion of subjects who have met Response Assessment in Neuro-Oncology criteria for complete response, partial response, or stable disease at 6 month following initiation of BPM31510.

Secondary Endpoints:
- Overall survival as determined by measuring from start date of BPM31510 to the date of death or date of last follow-up (for subjects who have not died).
- To assess safety and tolerability of BPM31510 and Vitamin K1 administered neo-adjuvantly and concurrently with standard RT and TMZ in subjects with newly diagnosed GB.

- Subjects will receive **a weekly, 96-h infusion of BPM31510 110 mg/kg/wk from Day 1 through Day 54**.
- Prophylactic Vitamin K1 at a recommended dose of 10 mg will be given subcutaneous (s.c.) to all subjects prior to the beginning of each week of therapy
- Subjects will start **concurrent treatment with standard RT and TMZ from Day 15 through Day 54**
  TMZ 75 mg/m² once daily (qd) × **42 days (d)** (ie, until Day 54).
- Subjects will receive the **standard TMZ treatment for additional 6 cycles post BPM31510 treatment**.
- During the **dose confirmation phase** of the study, subjects will be assessed for DLTs for 30 d (± 5 d) after the end of RT/TMZ .
- During the **efficacy phase of the trial**, subjects will have a Safety Follow-up (FU) visit 28 d (± 5 d) after the last RT/TMZ treatment.
- Blood samples will be collected at each visit during the treatment period (ie, Days 1, 2, 8, 15, 22, 29, 36, 43, 50, and 54) for pharmacokinetics and pharmacodynamics assessments.



Abbreviations: CT = computerized tomography; Dx = diagnosis; FDG-PET = fluorodeoxyglucose-positron emission tomography; MRI = magnetic resonance imaging; RT = radiation therapy; TMZ = temozolomide; wks = weeks

Note: Subjects will receive the standard TMZ treatment for additional 6 cycles post BPM31510 treatment, as per standard institutional guidelines.

FIGURE 4: Patient Recruitment Criteria

Inclusion Criteria:

- Subjects with newly diagnosed pathologically verified GB (by the World Health Organization 2021 criteria or using molecular features defined in C-IMPACT, update 6) with any evidence of residual disease (enhancing or fast fluid-attenuated inversion-recovery [FLAIR]).
- No prior RT, chemotherapy, immunotherapy, or targeted agents administered specifically for the lesion being treated.
- Age ≥18 y.
- Life expectancy ≥3 mo and in the opinion of the investigator is expected to complete the concurrent phase of chemoradiation without the use of bevacizumab or its biosimilars.
- Karnofsky performance score ≥60.
- Adequate organ and marrow function as follows (all required):
  - a. ANC ≥1.5 K/µL
  - b. Platelets ≥100 k/µL
  - c. Hemoglobin ≥9 g/dL
  - d. Serum creatinine ≤1.8 mg/dL or creatinine clearance >50 mL/min
  - e. Bilirubin ≤1.5 mg/dL
  - f. ALT ≤3.0 × upper limit of normal (ULN)
  - g. AST ≤3.0 × ULN
  - h. PT ≤1.5 × ULN
  - i. INR ≤1.5 × ULN
  - j. PTT ≤1.5 × ULN
- Ability for subject to understand and the willingness to sign a written ICF.
- Subjects of childbearing potential must agree to use hormonal or barrier birth control with spermicidal gel to avoid pregnancy during the study.
- Be at least 15 d and not more than 50 d from surgery definitive surgical resection.

Exclusion Criteria:

- Subjects History of clinically significant tumor-related cerebral hemorrhage.
- Patients who are not eligible for definitive surgical resection
- Any of the following cardiac history:
  - a. Active heart disease including myocardial infarction within previous 3 mo
  - b. Symptomatic coronary artery disease
  - c. Clinically significant arrhythmias not controlled by medication
  - d. Unstable angina pectoris
  - e. Uncontrolled or symptomatic congestive heart failure (New York Heart Association Class III and IV)
- Uncontrolled or severe coagulopathies or a history of clinically significant bleeding within the past 6 mo, including any of the following, but not limited to:
  - a. Severe epistaxis
  - b. Hemoptysis
  - c. Hematochezia
  - d. Hematuria
  - e. GI bleeding
  - f. Spontaneous or tumor-related intracranial hemorrhage
- Known predisposition for bleeding such as von Willebrand's disease or other such condition(s)
- Uncontrolled concurrent illness that would limit compliance with study requirements, including any of the following, but limited to:
  - a. Uncontrolled infection
  - b. Psychiatric illness/social situations
- Prior malignancy except for non-melanoma skin cancer and carcinoma in situ (of the cervix or bladder), unless diagnosed and definitively treated more than 3 y prior to first dose of study drug.
- Receiving any of the following medications:
  - a. Therapeutic doses of any anticoagulant, including low-molecular weight heparin. Concomitant use of warfarin, even at prophylactic doses, is prohibited.
  - b. Digoxin, digitoxin, lanatoside C, or any type of digitalis alkaloids.
  - c. Antiangiogenic drugs (ie, Avastin) either in the past 2 wk or if anticipated within the next 2 wk of informed consent.
  - d. Theophylline
- Known allergy to CoQ10.
- Known allergy or adverse reaction to oral, subcutaneous, or IV Vitamin K1.
- Pregnant or lactating.
- Known to be positive for the human immunodeficiency virus (HIV). Note: HIV testing is not required for eligibility, but if performed previously and was positive, the subject is ineligible.
- Subjects with a contraindication to radiation

FIGURE 5: GBM Phase II Study Sites and RP2D Assessment by DSMC

Active Study Site	Investigator
Stanford University Cancer Center	Seema Nagpal, MD
Cedars-Sinai Medical Center	Chirag Patil, MD, MS
Mount Sinai Hospital	Rebecca M Brown, MD, PhD
Inova Schar Cancer Institute	Adam Cohen, MD
Valley Health Hospital	Rupa Juthani, MD
Study Site in Start-up	**Investigator**
Sansum Clinic, Santa Barbara	Ryan Kendle, MD
Virginia Cancer Specialists	Alexander Spira, MD, PhD, FACP
Virginia Oncology Associates	Shaker George Shaman, MD
Texas Oncology, Austin	Brian Vaillant, MD

Safety committee summary:
- DSMC made determinations after 4th patient completed PFS6.
- Recommended dose by DSMC was 110 mg/kg.
- **DSMC members had unanimous agreement to proceed with enrollment per protocol given no DLTs.**

Voting Committee Members:
- Priya Kumthekar, MD (Chair) Neuro-Oncology at Northwestern Memorial Hospital
- Mustafa Khasraw, MD Neuro-Oncology at Duke University Hospital
- Mahua Dey, MD Neurological Surgery at University of Chicago Medicine
- Thomas Fleming, PhD Biostatistics Professor at University of Washington

FIGURE 6: GBM Phase II Patient Study Status (Sept 3, 2024)

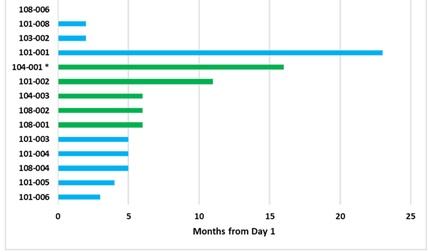
A **Subjects in Trial:**

Subject	MGMT status	Disease Progression @ 6-Month	Estimated 6-Month Visit Window	Time to Progression (month)	From Day 1 to Death or Present for Patient Alive (month)
101-006	Unmethylated	NA	11/08/2024-11/22/2024	NA	3
101-005	Unmethylated	NA	10/2/2024-10/16/2024	NA	4
108-004	Unmethylated	NA	9/16/2024-10/14/2024	NA	5
101-004	Unmethylated	NA	9/25/2024-10/09/2024	NA	5
101-003	Unmethylated	NA	9/4/2024-09/18/2024	NA	5
108-001	Methylated	No		NA	6
108-002	Methylated	NA	08/26/2024-09/23/2024	NA	6
104-003	Methylated	NA	8/05/2024-09/02/2024	NA	6
101-002	Methylated	No		NA	11
104-001 *	Methylated	Yes		5	16
101-001	Unmethylated	No		18	23
103-002	Unmethylated	NA	12/10/2024-12/24/2024	NA	2
101-008	Unmethylated	NA	12/20/2024-01/03/2025	NA	2
108-006	NA	NA	1/29/2025-02/12/2025	NA	0
101-010	Unmethylated	NA	1/29/2025-02/12/2025	NA	1
103-003	Unmethylated	NA	2/03/2025-02/17/2025	NA	0

* Death

MGMT= O6-methylguanine-DNA methyltransferase

B **Patient Follow Up Status:**



High MGMT promoter methylation rate is associated with improved progression-free survival (PFS) and overall survival (OS)

CONCLUSIONS AND NEXT STEPS

Summary of safety and any efficacy:

- BPM31510 is well-tolerated and does not exacerbate toxicity of chemoradiation with no new drug related SAEs encountered in treatment naïve patients in a front-line setting.
- Prophylactic Vit K has greatly reduced any grade 1 increases in PTT/INR and has improved safety profile vis-à-vis bleeding risk.
- One CR was achieved and remains in follow-up.
- A PFS of 18 months has been achieved in a patient with unmethylated MGMT status.
- The Trial is actively recruiting.
- A contemporaneous control arm is being built with HER data and discussions are ongoing with several sites to develop a case-control comparison

- **Corresponding author email address Dr. Seema Nagpal, snagpal@stanford.edu**

The safety and efficacy of BPM31510 has not been determined yet by the FDA.