Phase III Trial of SYN-408: Dual MET/EGFR Kinase Inhibition in Recurrent Glioblastoma

A Multi-Center, Randomized, Double-Blind Controlled Clinical Study (NEXA-GBM-03)

1. Introduction & Clinical Rationale

Unmet Need in Recurrent Glioblastoma (rGBM): Glioblastoma remains the most aggressive primary brain tumor in adults. Standard first-line therapy (resection, radiotherapy, and temozolomide) yields a median overall survival (OS) of 14.6 months. Upon recurrence, effective treatment options are severely limited, with historical median OS under 9 months.

Target Pathway: Dual MET & EGFR Co-Activation

- **EGFR Amplification / vIII Mutation:** Present in ∼50% of GBM tumors, driving hyperactive downstream MAPK and PI3K signaling.
- **MET Tyrosine Kinase Activation:** Serves as a primary bypass resistance mechanism under EGFR targeted monotherapy.
- **SYN-408 Mechanism:** A novel, orally bioavailable small-molecule dual inhibitor designed to concurrently block active ATP-binding domains of MET and EGFR.

2. Trial Objectives & Hypotheses

Primary Objective: To evaluate whether adding SYN-408 to standard salvage chemotherapy (lomustine) improves Overall Survival (OS) compared to placebo + lomustine in patients with first-recurrent glioblastoma.

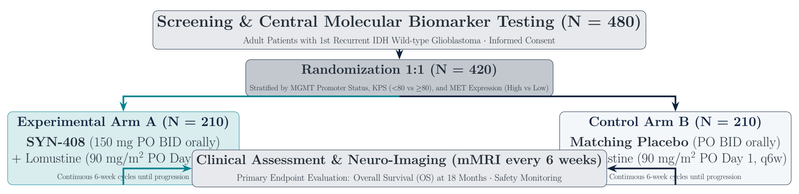
Secondary Objectives:

- Assess Progression-Free Survival (PFS) according to RANO 2.0 criteria.
- Determine Objective Response Rate (ORR) and Disease Control Rate (DCR).
- Characterize toxicity and safety profiles using NCI-CTCAE v5.0.
- Analyze biomarker subsets (MET high vs low expression; EGFRvIII mutant vs wild-type).

3. Patient Eligibility & Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Histologically confirmed IDH wild-type GBM at initial diagnosis.	• Prior systemic therapy with specific MET or EGFR targeted kinase inhibitors.
• First radiographically confirmed recurrence (RANO criteria).	• Active brainstem metastasis or leptomeningeal disease.
• Age ≥ 18 and ≤ 75 years; KPS score ≥ 70.	• Severe cardiac dysfunction (LVEF $< 50\%$ or QTc > 470 ms).
• Adequate hematologic, renal, and hepatic organ reserve.	• History of major surgical intervention within 28 days prior to Day 1.
• Archival tissue available for MET/EGFR biomarker assay.	• Concurrent investigational drug administration.

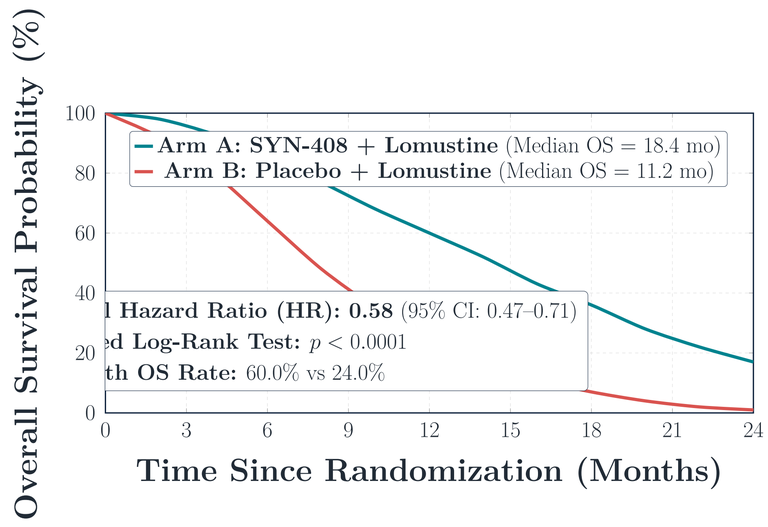
4. Study Design & Trial Schema



5. Patient Baseline Characteristics

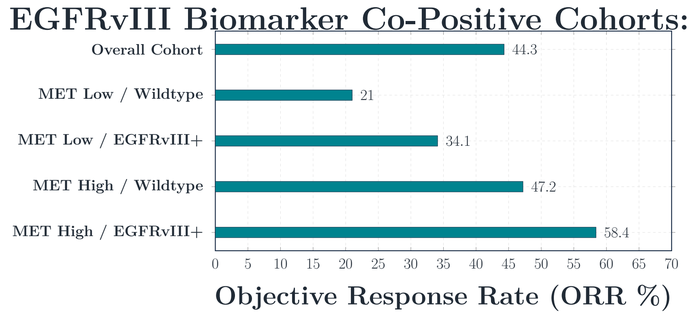
Characteristic	Arm A: SYN-408 (N=210)	Arm B: Placebo (N=210)	p
Median Age, years (IQR)	58.4 (49–66)	59.1 (50–67)	0.48
Male / Female, %	57.1 / 42.9	58.6 / 41.4	0.76
Karnofsky Performance Score $\geq$ 80, %	68.6	67.1	0.74
MGMT Promoter Methylated, %	38.1	37.6	0.92
EGFRvIII Mutation Positive, %	47.6	46.2	0.77
MET Overexpression High ($\geq$2+ IHC), %	52.4	53.8	0.77
Median Time from Resection, months	11.8	11.4	0.52
Prior Bevacizumab Exposure, %	14.3	15.2	0.79

6. Primary Efficacy: Kaplan-Meier Overall Survival



7. Biomarker Subgroup Analysis

Enhanced Response in MET-High / EGFRvIII Biomarker Co-Positive Cohorts:



8. Safety Profile & Adverse Events

Adverse Event (CTCAE v5.0)	Arm A: SYN-408 (%) Any Grade / Gr 3–4	Arm B: Placebo (%) Any Grade / Gr 3–4
Fatigue / Asthenia	54.2 / 4.3	48.1 / 3.8
Diarrhea	42.8 / 3.8	18.5 / 0.5
Acneiform Skin Rash	38.6 / 2.9	8.1 / 0.0
Nausea / Vomiting	33.1 / 1.9	31.4 / 1.4
ALT / AST Elevation	26.2 / 5.2	12.4 / 1.0
Thrombocytopenia	21.0 / 6.7	19.5 / 6.2
Neutropenia	18.6 / 5.7	17.1 / 5.2
AE Discontinuation Rate	**4.8%**	**3.3%**

9. Ethical Considerations & Regulatory Oversight

- **Institutional Review Board (IRB) Approval:** Protocol approved by Ethics Committees of Vertex Medical Institute (Ref: VMI-IRB-2024-88A) and Cambridge RECB-902.
- **Informed Consent:** Written informed consent was obtained from all patients or legal representatives prior to screening.
- **Data Safety Monitoring Board (DSMB):** Independent semi-annual safety reviews conducted. No unexpected safety signals or trial suspension criteria were met.
- **Declaration of Helsinki:** Conducted in strict accordance with ICH Good Clinical Practice (ICH-GCP) guidelines.

10. Conclusions & Clinical Impact

Key Takeaways

1. **Significant OS Benefit:** Adding SYN-408 to lomustine reduced the risk of death by 42% (HR = 0.58, $p < 0.0001$), extending median overall survival by 7.2 months.
2. **Robust Tumor Response:** ORR was three-fold higher in the SYN-408 arm (44.3% vs 14.8%), with maximum efficacy observed in MET-high/EGFRvIII+ co-positive patients.
3. **Manageable Safety Profile:** Adverse events were consistent with known EGFR/MET class effects and predominantly Grade 1–2. Discontinuation due to toxicity remained low (4.8%).
4. **Practice-Changing Potential:** SYN-408 represents a potential novel standard of care for biomarker-selected recurrent glioblastoma.

11. References &

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