# Case Study: Identifying Responder Populations in the Cilengitide CORE Study

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## ABSTRACT

**Background:** The CORE Study (NCT00813943) investigated cilengitide in newly diagnosed glioblastoma patients with unmethylated MGMT promoters. Traditional analysis showed no significant survival benefit. We reanalyzed this trial data to identify potential responder subpopulations.

**Methods:** We performed survival cluster analysis on 83 patients from the CORE Study using publicly available clinical trial data. Baseline characteristics were correlated with survival outcomes. Statistical methods included Kaplan-Meier survival estimation, effect size calculations, and biomarker correlation analysis.

**Results:** Four distinct survival clusters emerged (median survival range: 8.7-23.8 months). Approximately 11% achieved exceptional outcomes (median ~24 months), characterized by lower baseline neutrophil counts, elevated albumin, younger age, and predominantly male sex. These patients experienced fewer severe adverse events.

**Conclusions:** Statistical reanalysis revealed clinically meaningful heterogeneity within the CORE Study population. A subset of patients achieved substantial survival benefit, suggesting potential for biomarker-enriched trial design. Findings require prospective validation.

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## INTRODUCTION

Glioblastoma remains among the most lethal malignancies, with median survival of 12-15 months. For patients with unmethylated MGMT status (~45% of cases), outcomes are particularly poor.

Cilengitide, an integrin inhibitor, was investigated in the CORE Study based on promising preclinical data. The trial's overall analysis showed no significant survival improvement, leading to program discontinuation.

However, population-level analysis may obscure benefit in specific patient subgroups. We conducted a retrospective reanalysis to identify potential responder populations and their predictive characteristics.

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# METHODS

**Data Source:** CORE Study (NCT00813943) data obtained from public repositories (n=83 patients receiving cilengitide)

**Analytical Approach:**
We applied statistical clustering methods to identify distinct survival outcome groups. For each cluster, we systematically correlated baseline characteristics including:

- Hematologic parameters (CBC with differential)
- Metabolic markers (comprehensive metabolic panel)
- Demographics (age, sex)
- Performance status

Effect sizes (Cohen's d) were calculated to identify clinically meaningful differences between clusters. All analyses were exploratory and hypothesis-generating.

**Statistical Methods:** Kaplan-Meier survival estimation, log-rank tests, t-tests for continuous variables. No adjustments for multiple comparisons were applied given the exploratory nature of the analysis.

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# RESULTS

## Survival Heterogeneity

Four distinct outcome groups emerged:

- **Super-Responders (11%):** Median survival ~23.8 months
- **Good Responders (16%):** Median survival ~20.0 months
- **Moderate Responders (24%):** Median survival ~16.1 months
- **Poor Responders (49%):** Median survival ~8.7 months

The 2.7-fold survival difference between best and worst clusters indicates substantial heterogeneity.

### Biomarker Signatures

Super-responders versus poor responders showed:

**Inflammatory Markers:**

- Lower neutrophil counts (mean: 3.91 vs 5.93 × $10^9$/L, Cohen's d = 0.89)
- Lower alkaline phosphatase (mean: 63.6 vs 78.5 U/L, Cohen's d = 0.62)

**Metabolic Markers:**

- Higher albumin (mean: 44.0 vs 42.0 g/L, Cohen's d = 0.71)
- Higher hemoglobin (mean: 136.3 vs 132.4 g/L, Cohen's d = 0.43)

**Demographics:**

- Younger age (mean: 52.3 vs 54.7 years, Cohen's d = 0.38)
- Male predominance (89% vs 61%)

### Safety-Efficacy Relationship

Super-responders experienced 78% fewer severe adverse events (mean: 0.22 vs 1.0 per patient) compared to poor responders, despite identical dosing. This suggests baseline biology affects both efficacy and tolerability.

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# DISCUSSION

This reanalysis identified a patient subset (~11%) achieving exceptional cilengitide survival benefit (median ~24 months). These super-responders were characterized by baseline inflammatory suppression and preserved metabolic reserves.

**Mechanistic Hypothesis:**
Low-inflammation patients may maintain integrin-dependent tumor angiogenesis, making them sensitive to integrin inhibition. High-inflammation patients may exhibit integrin-independent angiogenesis pathways, rendering them resistant regardless of drug exposure. This hypothesis requires validation with tissue correlates.

**Clinical Implications:**
The identified biomarker signature comprises standard laboratory tests (CBC, CMP) available

universally without specialized assays. This accessibility could facilitate prospective validation studies.

**Limitations:**

- Small sample size (n=83)
- Retrospective exploratory analysis
- Lack of tissue-based validation
- Requires prospective confirmation before clinical application
- Sex disparity findings require equity analysis in future studies

**Future Directions:**
Prospective validation in a biomarker-enriched trial could test whether patient selection based on these characteristics improves outcomes. The identified signature provides testable hypotheses for mechanistic studies examining inflammation-angiogenesis interactions.

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# CONCLUSIONS

Reanalysis of the CORE Study reveals substantial outcome heterogeneity within the trial population. Approximately 11% of patients achieved exceptional survival with a distinct baseline biomarker profile. These findings suggest opportunities for refined patient selection in future trials.

Population-level analysis may obscure clinically meaningful benefit in specific subgroups. Systematic responder analysis of clinical trials could identify precision medicine opportunities that traditional approaches miss.

All findings are preliminary and hypothesis-generating, requiring prospective validation before influencing clinical decisions.

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# COMPETING INTERESTS

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# DATA AVAILABILITY

Analysis used publicly available data from NCT00813943 via https://data.projectdatasphere.org