T-cell infiltration after linoserpaturev reveals a VEGFA-high hypoxic resistance niche in glioblastoma

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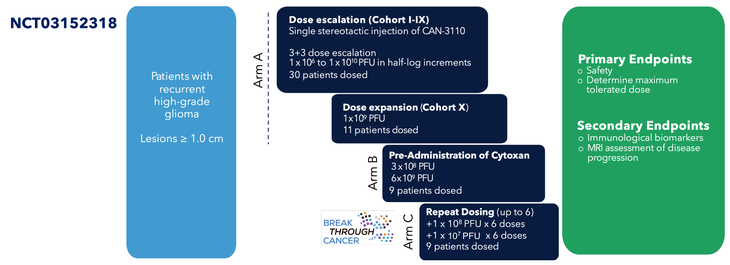
Background and objective

Linoserpaturev (CAN-3110) is an investigational oncolytic HSV-1 designed for tumor-selective replication in nestin-expressing, p16-defective glioblastoma cells. The vector deletes both native ICP34.5 genes and reintroduces one ICP34.5 copy under a nestin enhancer–HSP68 promoter in the disrupted UL39/ICP6 locus. This design supports tumor-cell lysis and antitumor immune activation while limiting replication in normal tissue.

A single intratumoral administration was associated with persistent T-cell infiltration, clonotype expansion, and tumor-proximal cytotoxic activity linked to clinical outcomes (1).

- **We evaluated overall survival in the 3 cohorts**
- **We assessed associations between changes in TME occurring after linoserpaturev treatment to identify potential correlations between biological changes and clinical outcomes**
- **We evaluated OS post additional treatment exposure in cohort A+B to assess potential contribution to observed survival**

Clinical trial design



NCT03152318 is a phase 1b trial of linoserpaturev in recurrent high-grade glioma.

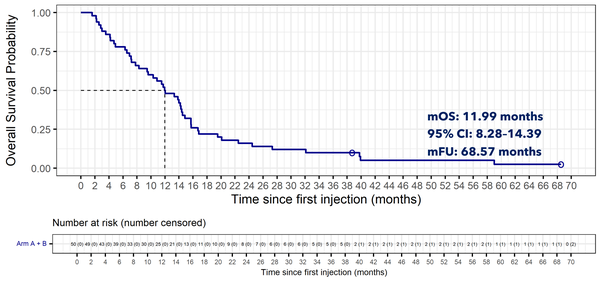
Arms A+B primarily evaluated single-administration treatment; 50 unique patients received 51 injections, including one Arm A patient who received two injections.

Arm C evaluates repeated administrations of linoserpaturev.

Overall survival after linoserpaturev in recurrent glioma

At the 14 August 2026 data cutoff, 50 patients in Arms A+B had received 51 intratumoral injections of linoserpaturev, including two injections in a single Arm A patient. Median OS was 11.99 months (95% CI, 8.28–14.39). Reported median follow-up was 68.57 months (Figure 1A).

Figure 1A. Overall survival, Arms A+B



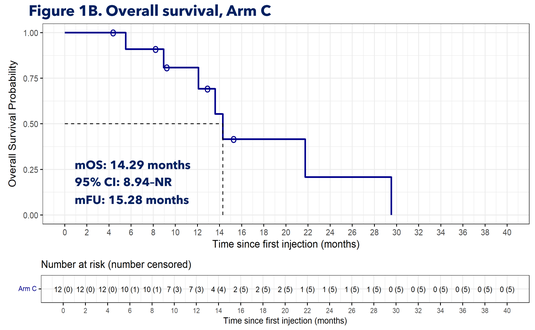
Patient documented alive at specific timepoints

Time from treatment	Patients alive, n/N (%)
18 months	11/50 (22)
24 months	8/50 (16)
36 months	5/50 (10)
48 months	2/50 (4)

Arm C included 12 patients with recurrent glioblastoma treated at 10^8 or 10^7 PFU, with up to 6 administrations and serial tumor biopsies.

At the July 13, 2026 efficacy cutoff, mOS was 14.29 months, with a 95% CI of 8.94 months to not reached (Figure 1B).

Figure 1B. Overall survival, Arm C



Abbreviations: OS, overall survival. mOS, median overall survival. PFS, progression-free survival. CI, confidence interval. TCR, T-cell receptor. PFU, plaque-forming units. GBM, glioblastoma.

Single injection of linoserpaturev induces persistent T-cell infiltration

CODEX analysis demonstrated dense CD4+ and CD8+ T-cell infiltration in post-treatment biopsies/tumor resection/autopsies) collected 6–25 months after a single intratumoral administration of linoserpaturev.

T-cell infiltration and lymphoid aggregate formation

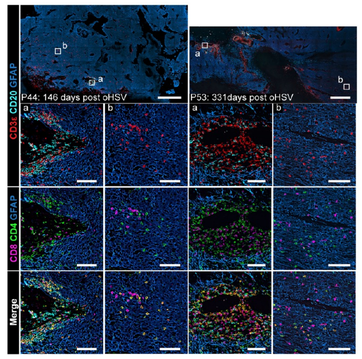


Figure 2. CD4+ and CD8+ T-cell infiltration in GFAP+ tumor regions.

Immune-cell density before and after treatment

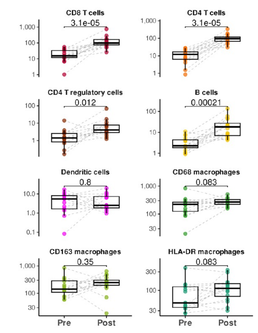


Figure 3. Paired immune-cell densities before and after linoserpaturev treatment. From Meylan et al., Cell 2026.

T-cell responses correlate with clinical outcomes in single injection cohorts

Patients with expanded shared tumor TCR clonotypes had longer median OS than those without expansion: 445 versus 235 days (log-rank p=0.033).

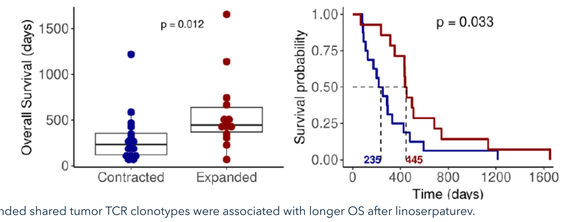
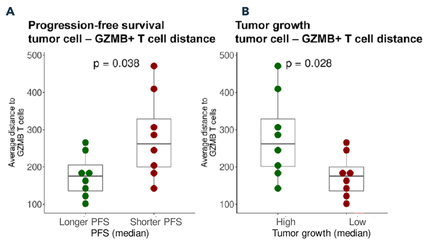


Figure 4. Expanded shared tumor TCR clonotypes were associated with longer OS after linoserpaturev.



Longer PFS (>1.9 months) correlated with shorter tumor-to-GZMB+ T-cell distances (175 versus 262 µm, p=0.038). Shorter distances also correlated with slower tumor growth (p=0.028).

Figure 5. Tumor-to-GZMB+ T-cell distance by PFS (A) and tumor growth (B). From Meylan et al., Cell 2026.

Persistent T-cell infiltration after linoserpaturev coexists with VEGFA-high hypoxic, T-cell-low regions in glioblastoma: rationale for prospective VEGF-blockade studies

VEGFA-high hypoxic regions showed relative exclusion of the T-cell signature. Greater tumor-to-T-cell distance within these regions suggests areas of relative T-cell exclusion and provides a rationale for prospective combination testing with bevacizumab.

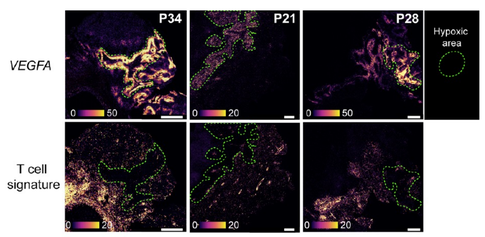
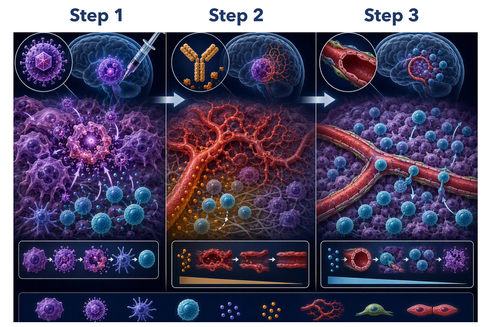


Figure 6. Xenium maps show VEGFA expression (top) and the T-cell signature (bottom) in post-treatment tumors from P34, P21, and P28. Green dotted outlines mark VEGFA-high hypoxic regions with reduced T-cell signal. Scale bars, 1 mm. From Meylan et al., Cell 2026.

Combination rationale: a hypothesis for prospective testing

- Linoserpaturev promotes sustained T-cell infiltration, but VEGFA-high hypoxic regions remain relatively T-cell excluded.
- Bevacizumab inhibits VEGF signaling and reduces angiogenesis and vascular permeability.
- The combination could reduce VEGF-associated T-cell exclusion after viral immune priming.



Step 1: Linoserpaturev activates antitumor immunity
Step 2: Bevacizumab inhibits VEGF signaling
Hypothesis: VEGF inhibition may improve T-cell access

Exploratory analysis on bevacizumab exposure and overall survival

Among 41 patients in the single-injection cohort, 34 received additional therapies, including bevacizumab, pembrolizumab, radiation, or surgical resection, at or after disease progression. The naïve ever-versus-never analysis was not designed to estimate a bevacizumab treatment effect as treatment was not protocol defined and patients received treatment at different time points post treatment and for different length of time.

Exploratory overall survival by post-treatment bevacizumab exposure*

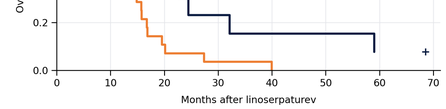


Figure 7. Overall survival by post-treatment bevacizumab exposure (28 exposed, 13 unexposed).

The curves cross. Treatment selection, timing, and indication bias limit this retrospective comparison and prevent causal conclusions. Analysis does not provide reliable evidence for or against an OS difference

Conclusions

- Linoserpaturev administration was followed by persistent CD4⁺ and CD8⁺ T-cell infiltration and exploratory immune features associated with clinical outcomes.
- VEGFA-high hypoxic regions remained relatively T-cell-poor, identifying a candidate spatial immune-evasion niche.
- The findings support prospective biomarker-informed evaluation of linoserpaturev with scheduled VEGF blockade; they do not establish combination efficacy or superiority of repeated administration.
- Durable long-term survival was observed in a subset of patients after a single linoserpaturev administration, with 8/50 patients alive at 24 months and 2/50 at 48 months, an uncommon outcome in recurrent glioblastoma.
- Repeated administration in Arm C was feasible, with a median OS of 14.3 months (95% CI, 8.94 months to not reached); 5 of 12 patients in Arm C were still alive at the data cutoff.

References and acknowledgments

1. 1. Ling AL, et al. Nature. 2023.
2. Meylan M, et al. Cell. 2026;189:1287–1304.e18.

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