Etirinotecan Pegol in the Treatment of High-Grade Glioma: A Phase 2 Trial
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Introduction
- Etirinotecan pegol (EP, NKTR-102) is the first long-acting topoisomerase 1 inhibitor designed to concentrate in the tumor and provide continuous tumor exposure.
- In patients, etirinotecan pegol leads to greatly prolonged plasma SN38 exposure compared to irinotecan (IRI) with an elimination half-life of 56 days compared to 2 days; peak SN38 concentrations are at least 5-10 times less [2].

Key Eligibility Criteria
- Age ≥18 with histologically proven anaplastic astrocytoma or GBM who previously received standard chemotherapy and recurred after BEV.
- A predicted life expectancy > 6 weeks.
- Adequate organ system reserves, i.e., normal hematopoietic function was required.

Treatment Summary
- All patients received 145 mg/m² of NKTR-102 intravenously (IV) on a 21-day dosing schedule as monotherapy. Patients did not receive BEV while on study. Response was assessed by RANO criteria.

Study Design
- Phase 2: single-arm, open-label, non-randomized study
- 20 patients with recurrent BEV-resistant high-grade glioma
- NKTR-102 given as single-agent every 21 days

Study Demographics
- 20 subjects were enrolled from Aug 2012 to May 2013 at Stanford University Hospital.

Results
- Efficacy: Overall Response Rate
- Progression-Free Survival
- Overall Survival

SAFETY

Conclusion
- Etirinotecan pegol is well tolerated in patients with recurrent, bevacizumab-refractory high-grade gliomas. Only 1 patient (5%) had a Grade 3 toxicity (diarrhea with dehydration) attributable to EP.

Results in Context
- Though participants in this trial were heavily pre-treated and more neurologically symptomatic than many clinical trial patients, we observed low toxicity and 3 PRs.
- Patients had few options after BEV. Activity was demonstrated by both PR by RANO criteria (15%) and an additional six patients who had stable disease at their 1st and 2nd imaging assessment.
- The slow-release, large molecule is intriguing for use in combination with an agent such as BEV, which could theoretically trap the large molecule in the tumor and further extend activity.
- We believe follow-up study of EP in high-grade glioma patients is warranted.

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References

Abbreviations
HGG: High-grade glioma; GBM: glioblastoma; BEV: bevacizumab; EP: NKTR-102; irinotecan; SN38: 7-ethyl-10-carboxamido camptothecin; MGMT: O6-alkylguanine-DNA methyltransferase; KPS: Karnofsky Performance Status; NR: not recorded; PD: progression; CI: confidence interval; TKI: tyrosine kinase inhibitor; OS: overall survival; PFS: progression-free survival; IV: intravenous; S: standard; SD: stable disease; PR: partial response; AE: adverse event