Etirinotecan Pegol in the Treatment of High-Grade Glioma: A Phase 2 Trial

Seema Nagpal, Cathy Kahn Recht, Urooj Imtiaz, Sophie Bertrand, Reena Parada Thomas, Abdulrazag Ajlan, Justine Pena, Megan Gershon, Pamela L. Kunz, Gordon Li, Lawrence David Recht
Stanford Cancer Institute, Stanford, CA; Stanford University, School of Medicine, Stanford, CA

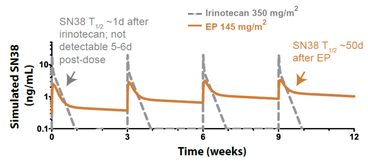
Background

- High-grade gliomas (HGGs), including anaplastic astrocytomas, anaplastic oligodendrogliomas, and glioblastomas (GBMs), are the most common and most aggressive primary brain tumors.
- Prognosis for patients with HGG remains poor, with near universal recurrence after initial therapy with temozolomide and radiation, and an estimated median survival from initial diagnosis between 12–18 months.
- Since May 2009, the majority of patients in the US with an initial recurrence of HGG received bevacizumab (BEV), a monoclonal antibody against vascular endothelial growth factor, which is thought to prevent angiogenesis in these highly vascular tumors.
- Response to BEV occurs in 32-62% [4]; however, the response is short-lived, and patients eventually progress.
- No chemotherapeutic agent administered following progression through BEV has made a significant impact on survival [5,6].
- Patients progress to death within 1-5 months after resistance develops; objective responses are rarely seen or durable [6,7].

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 (IRN) with an elimination half-life of 50 days compared to 2 days; peak SN38 concentrations are at least 5-10 times less [1].

Model-Predicted Plasma SN38 Concentration Time Profiles After Dosing with Etirinotecan Pegol or Irinotecan



Etirinotecan Pegol Showed Promising Efficacy in Phase 1–2 Trials

	Tumor Types	n	Response Rate (%)	PFS (months)	OS (months)	Reference
Phase 1	Advanced solid tumors	76	11	-	-	Jameson 2013 [1]
Phase 2	Metastatic breast	70	28.6	4.7	10.3	Awada 2013 [2]
Phase 2	Metastatic ovarian	69	20*	4.1	11.1	Vergote 2013 [3]

*based on 66 evaluable patients

- Enrollment in BEACON, a Phase 3 open-label, randomized, multicenter study of etirinotecan pegol vs. treatment of physician's choice in patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine, was completed in Q3/2013.

Methods

- **Statistical Methods**:
  - The null hypothesis is that the 6-week PFS rate is less than 25%. A sample size of 20 patients provides 88% power to reject a 6-week PFS rate of 5% at a one-sided significance level of 10%, if the true 6-week PFS rate is 25% or better.
  - Response and disease progression will be assessed by RANO criteria. Time-to-event endpoints are estimated using Kaplan-Meier estimates 95% confidence intervals (CI) are based on the Grenwood formula.

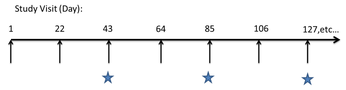
Objectives

Primary:
- To estimate the 6-week progression-free survival (PFS) rate of NKTR-102 in mono-therapy in patients with BEV-resistant HGG.

Secondary:
- To determine survival of patients receiving NKTR-102 for BEV-resistant HGG assessed from time of first NKTR-102 infusion to date of death
- To determine overall survival from date of pathologic diagnosis or confirmation of HGG
- To determine the safety profiles of NKTR-102

Study Design

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



- **Key Eligibility Criteria**:
  - Age >18 with histologically proven anaplastic astrocytoma or GBM who previously received standard chemo-radiation and recurred after BEV.
  - A predicted life expectancy > 6 wks, KPS ≥ 50, and adequate organ and bone marrow functions were required.
- **Treatment Summary**:
  - All patients received 145 mg/m² of NKTR-102 intravenously (IV) on a q21 day dosing schedule as monotherapy. Patients did not receive BEV while on study. Response was assessed by RANO criteria.

Study Demographics

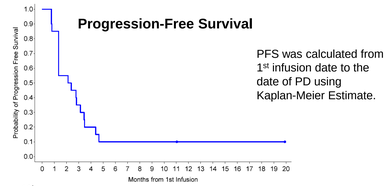
- 20 subjects were enrolled from Aug 2012 to May 2013 at Stanford University Hospital.

Characteristic	N=20
Median Age, yrs (Range)	49.5 (20–73)
Median KPS (0-100) (Range)	70 (50–100)
Primary Histology:	
GBM	17 (75%)
II or III → GBM	3 (15%)
Highest Grade III	2 (10%)
Resection:	
Biopsy	7 (35%)
Sub-Total Resection	2 (20%)
Gross Total Resection	9 (45%)
Median Prior Lines of Therapy (Range)	3 (2–5)
Median Time Since HGG Diagnosis, months (Range)	12.5 (3.1–53.0)
Median Time Since Primary Diagnosis, months (Range)	19.1 (7.0–140.0)

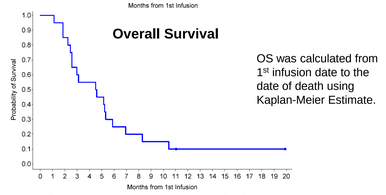
Results

EFFICACY: OVERALL RESPONSE RATE

Parameter	N=20
Median No. of Cycles (Range)	3 (1-22)
Best Overall Response:	
Partial Response	3 (15%)
SD	8 (40%)
PD or Clinical Decline	9 (45%)
Progression-Free Survival:	
No. of Patients Censored (%)	2 (10%)
Median PFS, months (95% CI)	2.2 (1.4-3.4)
Probability of PFS at 6 wks, % (95% CI)	55.0 (31.3-73.5)
Probability of PFS at 6 months, % (95% CI)	10 (1.7-27.2)
Overall Survival, months	
No. of Patients Censored (%)	2 (10%)
Median OS from 1st NKTR-102 Infusion (95% CI)	4.5 (2.4-5.9)
Median OS from HGG Diagnosis (95% CI)	17.1 (10.0-36.3)



PFS was calculated from 1st infusion date to the date of PD using Kaplan-Meier Estimate.

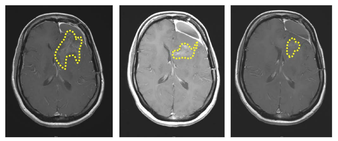


OS was calculated from 1st infusion date to the date of death using Kaplan-Meier Estimate.

- Dots indicate censored subjects as of 22-Apr-14.
- Note: Patient at 22 cycles progressed in May 2014

EFFICACY: PARTIAL RESPONSES

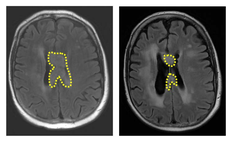
Case #1



Progression on BEV	6 wks	12 wks
53.3 x 37.2 mm	32.8 x 22.7 mm	17.8 x 15.4 mm
% Change in Tumor Area	**-62%**	**-86%**

33-year-old woman with a prior diagnosis of low-grade glioma that transformed into an MGMT-negative glioblastoma after 4 years. At recurrence, she received bevacizumab and an experimental agent for 3 months. When she progressed, she received EP monotherapy. She required Neupogen because of prior treatment toxicity, but tolerated EP without worsening myelosuppression. Her first and second MRIs (6 & 12 weeks) demonstrated PR.

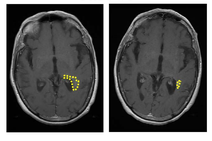
Case #2



Progression on BEV	~ 32 wks
23.3 x 45.9 mm	18.9 x 12.2 mm 19.8 x 10.5 mm
% Change in Tumor Area	**-59%**

54-year-old woman with a n MGMT-positive glioblastoma who underwent a gross total resection then received the standard chemo-radiation and an experimental agent. She had recurrence 20 months after her initial diagnosis, which was treated with bevacizumab alone because she had significant fatigue with previous treatment. She received bevacizumab for 4 months, but then developed disease that expanded and crossed the corpus callosum. She has received 15 cycles of EP. Imaging demonstrates continued shrinkage of the midline masses. She has maintained her KPS during treatment.

Case #3



Progression on BEV	~ 45 wks
8.69 x 17.38 mm	5.28 x 7.87 mm
% Change in Tumor Area	**-72%**

73-year-old woman who underwent biopsy only of a left temporal glioblastoma (MGMT unknown). She underwent chemo-radiation. Fourteen (14) months later, she developed progression posterior to the original tumor. She received single-agent bevacizumab for a total of 5 months and at progression enrolled in this trial. She received a total of 22 cycles of EP. Throughout her treatment, she maintained a KPS of 100 and reported minimal side effects.

SAFETY

Grade 3 or 4 Adverse Events	
CTCAE Category / Adverse Event	**N (%)**
Blood and lymphatic system disorders	1 (5%)
Gastrointestinal disorders	
Diarrhea	1 (5%)
Metabolism and nutrition disorders	
Dehydration	1 (5%)
Hypokalemia	1 (5%)
Hyponatremia	2 (10%)
Musculoskeletal and connective tissue disorders	
Muscle weakness lower limb	1 (5%)
Nervous system disorders	
Cognitive disturbance	1 (5%)
Peripheral motor neuropathy	1 (5%)
Seizure	2 (10%)
Psychiatric disorders	
Confusion	1 (5%)
Renal and urinary disorders	
Acute kidney injury	1 (5%)

Serious Adverse Events	
CTCAE Category / Adverse Event	**N (%)**
Blood and lymphatic system disorders	1 (5%)
Gastrointestinal disorders	
Diarrhea	1 (5%)
Nausea	2 (10%)
General disorders and administration site conditions	
Death NOS*	1 (5%)
Metabolism and nutrition disorders	
Dehydration	1 (5%)
Hypokalemia	1 (5%)
Hyponatremia	1 (5%)
Nervous system disorders	
Encephalopathy*	1 (5%)
Seizure	1 (5%)
Renal and urinary disorders	
Acute kidney injury	1 (5%)

* Grade 5 unrelated AEs

Conclusions

- 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. Hematologic toxicity was mild.
- There were 3 partial responses (PRs) in a group of 20 patients who had received a median of 3 prior regimens. Previous trials in this group have had few radiographic responses.
- Two patients with PR had sustained PR on etirinotecan pegol (14 and 20 months, respectively).

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 have 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.

Acknowledgements

We would like to acknowledge our patients and their families for their time and participation.

References

[1] Jameson et al., *Clin Cancer Res* 2013; 19:268-278.
[2] Awada et al., *Lancet Oncol* 2013; 14(12):1216-25.
[3] Vergote et al., *J Clin Oncol* 2013; 31(32):4060-6.
[4] Chamberlain MC. *Neurology* 2009; 72(8): 772-3; author reply 3-4.
[5] Quant EC, Norden AD, Drappatz J, Muzikansky A, Doherty L, Lafrankie D, et al. *Neuro Oncol* 2009; 11(5): 550-5.
[6] Iwamoto FM, Abrey LE, Beal K, Gutin PH, Rosenblum MK, Reuter VE, et al. *Neurology* 2009; 73(15): 1200-6.
[7] Nagpal S, Harsh G, Recht L. *Chemother Res Pract* 2011; 602812.

Abbreviations

HGG, high-grade glioma; GBM, glioblastoma; BEV, bevacizumab; EP, NKTR-102, etirinotecan pegol; IRN, irinotecan; CI, confidence interval; KPS, Karnofsky Performance Score; PFS, progression-free survival; IV, intravenously; OS, overall survival; SD, stable disease; PD, partial disease; PR, partial response; AE, adverse event

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2014. Central Nervous System Tumors. Saturday, May 31, 2014, 1:15 – 5 PM; S Hall A2; Poster Board 61.