Phase 2 safety and efficacy of AR-67 (7-t-butyldimethylsiltyl-10-hydroxycamptothecin) in patients with recurrent Glioblastoma Multiforme (GBM) or Gliosarcoma

Abstract # ACTR-40

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ABSTRACT

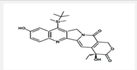
BACKGROUND: AR-67 (formerly DB-67) is a novel 3rd generation camptothecin with improved safety and lipophilicity than current drugs in this class. Safety and efficacy of AR-67 were evaluated in a Phase 2 study in recurrent GBM/gliosarcoma in adult patients. **METHODS:** AR-67 (7.5 mg/m2) was administered once daily by IV infusion for 5 consecutive days on a 21-day cycle. Cohort 1 patients (N=31/46 enrolled) had not received (or had not recently failed) bevacizumab. Cohort 2 patients (N=13/46 enrolled) had failed bevacizumab within 90 days before screening. Cohort assignments for 2/46 patients were undetermined. Tumor response was assessed ≥14d after every second cycle and before every third cycle using MRI. Primary endpoints were 6-month PFS (Cohort 1), and 2-month PFS (Cohort 2). **RESULTS:** 45/46 patients received ≥ one dose of AR-67; one patient (Cohort 1) died prior to dosing. Efficacy: 6/30 (Cohort 1) and 2/13 (Cohort 2) treated patients achieved the primary endpoints of 6- and 2-month PFS, respectively. Across the study, PR was the best overall response in 3/45 treated patients, all in Cohort 1. SD was the best overall disease response in 7/45 treated patients (5 in Cohort 1 and 2 in Cohort 2). Safety: AR-67 was well tolerated; 17 patients (38%) exhibited serious adverse events (SAEs) including headache and Grade 4/5 muscular weakness (2.2%). Most TEAEs were mild/moderate in intensity and Grade 1-3 in toxicity. Notably absent was Grade 4 diarrhea, a hallmark of other approved camptothecin chemotherapies. **CONCLUSIONS:** AR-67 was well tolerated and exhibited a safety profile consistent with or better than currently approved camptothecins. 6/30 treated patients in Cohort 1 and 2/13 patients in Cohort 2 achieved the primary endpoints of 6- and 2-month PFS, respectively. PR was the best overall response in 3/45 treated patients and SD was the best overall response in 7/45 patients.

INTRODUCTION

AR-67 (formerly DB-67) is a novel 3rd generation camptothecin designed to improve safety and potency relative to other members of this widely used drug class [1].

Previous studies suggest that AR-67 may have therapeutic potential in recurrent GBM (reGBM) based on its potency against relatively resistant GBM cell lines in vitro [2]; its activity in a murine intracranial glioma xenograft model (2); its presence in brain tissue following dosing in a murine NSCLC xenograft model [3,4]; its extended residence in murine and human tumor tissues (relative to its circulating half life) [3,4]; the superior blood stability of the active over the inactive form in vitro [5] and in vivo [6]; and its notable lack of dose-limiting Grade 4 diarrhoea in clinical Phase 1 studies [6], an otherwise problematic characteristic of this drug class.

Here, we report for the first time the results of a Phase 2 clinical study designed to assess the efficacy and tolerability of AR-67 in reGBM patients, for whom there are few options and no uniform standard of care.

Compound	Structure	MW
AR-67		478.6

METHODS

Objectives:

The primary objective of this open-label, multicenter study was to determine the 6-month progression free survival (PFS) when intravenous (IV) AR-67 was administered in adults with confirmed reGBM who had not recently (>90 days) recurred after treatment with bevacizumab (including patients who had received temozolomide, but not bevacizumab). The primary objective in the rapid bevacizumab failure group (<90 days) was to determine the 2-month PFS.

Protocol Design:

Forty-six patients with recurrent GBM were enrolled into our Phase 2 trial to evaluate the safety, tolerability and efficacy of AR-67. One patient originally assigned to Cohort 1 succumbed to disease prior to dosing, leaving a total of 45 patients who received at least one dose of drug. The 45 patients were divided into two initial Cohorts, which were to be analysed separately with respect to activity:

- **Cohort 1** consisted of patients (N = 30) who either had never received bevacizumab (Avastin®), or had not failed bevacizumab within 90 days or more after their last dose.
- **Cohort 2** consisted of patients (N = 13) who had recently received bevacizumab (Avastin®), but had failed/progressed within 90 days of their last dose despite treatment.
- **Cohort 3** was designated retrospectively, and consisted of 2 patients whose bevacizumab status was unknown or not captured.

Dose/ Route/Schedule:

AR-67 was administered once daily by IV infusion for 5 consecutive days on a 21-day cycle. Drug (7.5 mg/m2) was to be given until the onset of toxicity requiring discontinuation or tumor progression. Tumor response was assessed ≥ 14d after every second cycle and before every third cycle using MRI.

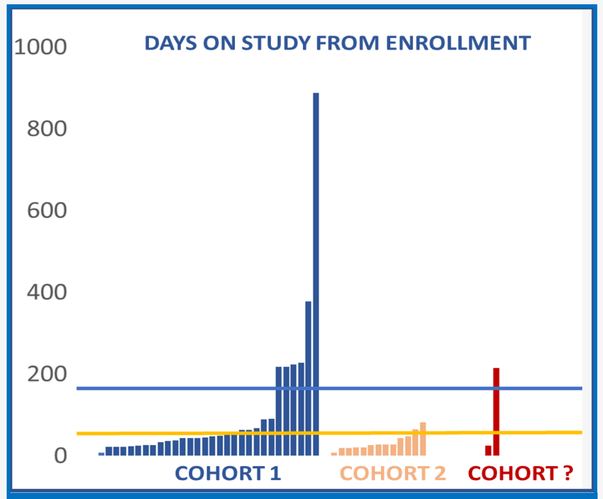
Figure 1: Disposition of Enrolled Patients

ENROLLMENT SUMMARY

Activity Population(s): Cohort 1 = 30 patients
Cohort 2 = 13 patients
Safety Population: 45 patients

RESULTS

Figure 2: Days on Study from Enrollment by Cohort and Patient



ACTIVITY SIGNAL

1 patient—888 days on study
1 patient –378 days on study
4 patients—217-227 days on study

→ 20% Cohort 1 patients exceeded 6 months PFS

Table 1: Evidence for Reduced Toxicity Profile vs Marketed Camptothecin

	AR-67	Irinotecan®			
	reGBM Single agent, infusion N = 45	Colorectal Single agent, bolus N = 223	Colorectal w/5FU, LV; bolus N = 225	Metastatic Colorectal Previously Treated N = 304	Recurrent Colorectal N = 316 across 2 studies
Neutropenia (Grade 4)	0%	12%	24%	12%	18%*
Diarrhoea (Grade 4)	0%	7%	5%	14%**	22%* (grades 3,4)
Nausea (Grades 3,4)	2%	16%	16%	17%	12%*
Vomiting (Grades 3, 4)	0%	12%	10%	12%	14%*

* = average across 2 studies
** = late diarrhoea

TOXICITY SUMMARY

AR-67 does not display the severe dose limiting toxicities typical of the marketed camptothecin-based chemotherapy standard, Irinotecan®

DISCUSSION/CONCLUSIONS

AR-67 was designed to circumvent the major limitations of camptothecin—based chemotherapies which, otherwise, constitute a widely used drug class for treating solid tumors. These limitations include dose limiting toxicities and modest progression free survival rates (PFS-6 << 20%) when used as a single agent in GBM [7-9]. Here, AR-67 was evaluated *as a single agent* for activity and safety in a Phase 2 trial with patients who were diagnosed with recurrent GBM, a highly aggressive cancer with poor survival rates.

Our findings show:

- **AR-67** demonstrated evidence of activity as a **single agent** in patients with reGBM;
- **20% of reGBM** patients who had never received bevacizumab, or had not failed bevacizumab treatment within 90 days of last dose, surpassed the PFS-6 endpoint, similar to, or better than, results reported from other clinical studies with camptothecins in reGBM;
- **Cohort 2** patients (those who had recently failed bevacizumab treatment) did not fare as well as Cohort 1 patients, with only 2 of 13 (15%) reaching PFS-2 (the primary endpoint for this Cohort);
- **AR-67's safety profile** suggests a significant improvement in the major dose-limiting toxicities of this otherwise widely-used chemotherapeutic drug class;
- **AR-67** is a promising candidate for further clinical study in patients with reGBM.

REFERENCES

1. Curran et al. 2000. Ann NY Acad Sci 922: 112-121.
2. Pollack et al. 1999. Cancer Research 59: 4898-4905.
3. Tsakalozou 2013. University of Kentucky Dissertation, College of Pharmacy. 216 pp.
4. Tsakalozou et al. 2014. Cancer Chemother Pharmacol 74: 45-54.
5. Bom et al. 2000. J Med Chem 43: 3970-3980.
6. Arnold et al. 2010. Clin Cancer Res 16(2): 673-680.
7. Prados et al. 2006. Neuro-Oncology 8: 189-193.
8. Vredenburgh et al. 2007. J Clin Onc 25 (30): 4722-4729.
9. Hu et al. 2013. J Neurooncol 111:347-353.