Longitudinal stereotactic injections of oncolytic immunoactivating rQNestin34.5v.2 (CAN-3110) with concomitant biopsies for "-omic" analyses in recurrent glioblastoma (GBM)

Poster 392a
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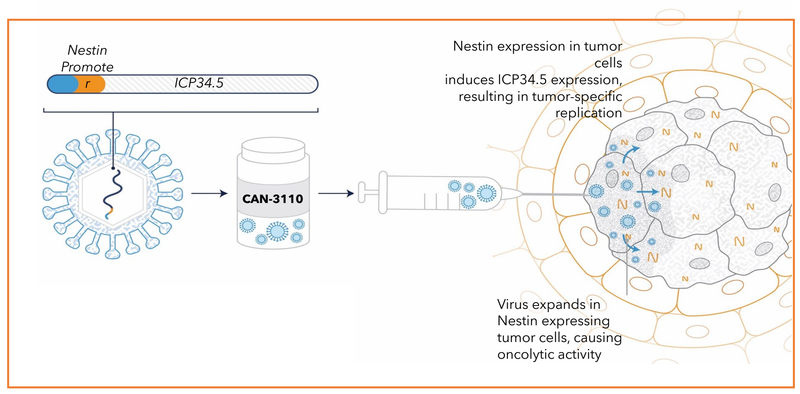
Introduction

- Glioblastoma (GBM), the most common primary malignant brain tumor, remains incurable. Numerous clinical trials of highly promising treatment modalities have not met efficacy objectives to support regulatory approval.
- A key limitation in trial evaluation has been the lack of tumor sampled at various timepoints during therapy to allow analyses of the treatment's effect.
- Sequential biopsies have not been pursued due to possible morbidity, relative surgical inaccessibility of GBM within the brain, and quality and quantity of stereotactic biopsies to permit detailed analyses.
- We hypothesized that the convergence of modern neurosurgical techniques and imaging with sophisticated "omics" analyses would overcome these limitations.



- rQNestin34.5v.2 or CAN-3110 is a replication-competent herpes simplex virus (HSV) engineered to enhance selective killing of cancer cells while sparing healthy neighboring cells. CAN-3110 is engineered for selective replication by placing ICP34.5, the gene controlling HSV replication, under the control of the Nestin promoter.
- A single dose escalation Phase I clinical trial of CAN-3110 in recurrent high-grade glioma arm A of a trial of CAN-3110 was initiated at Brigham and Women's Hospital in Boston and demonstrated that a single administration of CAN-3110 is safe and well tolerated, with no dose-limiting toxicity reported (Ling et al. Nature, October 2023).
- Positive HSV-1 serology was a predictor of response and was associated with improved survival. Increased infiltrating immune cells in the tumor microenvironment and expansion of the T cell repertoire after treatment were also associated with improved survival.
- In the clinical trial, the investigators observed a nearly doubling of the expected median overall survival after a single CAN-3110 injection compared to historical reports of 6 to 9 months or less in this therapy-resistant condition.

Trial design

NCT03152318

Patients with recurrent high-grade glioma

Arm A
Dose escalation (Cohort I-IX)
Single stereotactic injection of CAN-3110

3+3 dose escalation
1×10^6 to 1×10^{10} PFU in half-log increments
30 patients dosed

Dose expansion (Cohort X)
1×10^9 PFU
11 patients dosed

Ling et al. Nature, Oct 2023

Arm B
Pre-Administration of Cytoxan
3×10^8 PFU
6×10^9 PFU
9 patients dosed

ASGCT oral presentation May 2023

BREAK THROUGH CANCER
Collaborating for Cures

Arm C
Repeat Dosing (up to 6)
+1 x 10^8 PFU x 6 doses
+1 x 10^7 PFU x 6 doses
12 patients targeted

Key inclusion criteria

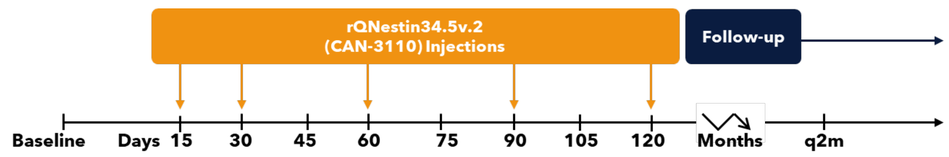
- Prior diagnosis of IDH wild-type glial tumor including GBM, grade 3 anaplastic astrocytoma or oligodendroglioma or or grade 2 astrocytoma with genetic features consistent with GBM.
- Prior history of external beam radiotherapy > 5,000 cGy delivered to the tumor at least 4 weeks prior to registration.
- Prior history of temozolomide chemotherapy provided concurrent with external beam radiotherapy and after as per current standard of care.
- For use of other investigational drug or other anti-tumor treatment, a treatment specific washout period must have elapsed before CAN-3110 administration (see full protocol).
- The initial recurrent or residual gadolinium-enhancing lesion to be treated must be > 1.0 cm in diameter and less than or equal to 2 cm in greatest maximal diameter, as determined by MRI.
- Karnofsky Performance Score > 70
- No dexamethasone therapy for at least 14 days prior to the first rQNestin34.5v.2 inoculation.
- Have residual tumor or be at first or second relapse.

Key exclusion criteria

- Prior systemic malignancy requiring or expected to require more than surgical therapy within the past 24 months
- Active, known, or suspected immunosuppressive disorders, such as acquired or congenital immune deficiency syndromes and autoimmune diseases
- Participants who are receiving other investigational agents or immunotherapeutic agents during the period of rQNestin34.5v.2 longitudinal injections
- Certain tumor sizes and locations are exclusionary:
  - Participants with tumor ≤ 1 cm proximity to the ventricles will be allowed to enroll
  - Participants whose initial tumor size, location and rate of growth are deemed by the treating neurosurgeons and the CAC to not be able to tolerate the time period of expected longitudinal injections with biopsies, which could be as short as 15 days and as long as 120 days
  - Participants with multifocal or multicentric tumors or tumors arising in the brain stem or spinal cord or diffuse leptomeningeal disease.

Study details (Arm C)

- A multi-institutional phase 1 clinical trial was started in recurrent GBM (rGBM) patients treated with up to 6 stereotactic administrations of the oncolytic immunotherapy, rQNestin34.5v.2 (CAN-3110) over 4 months (day 0, 15, 30, 60, 90 and 120) with concomitant multisector biopsies.
- Two cohorts of 1 x10^8 pfu per injection and 1 x 10^7 pfus per injection of rQnestin34.5v.2 are planned for a total of 6 patients per cohort using a Bayesian optimal interval (BOIN) design for dose escalation.
- Before each injection, multiregional sector biopsies of rGBM are undertaken and the biopsies are processed for "-omic" analyses, including single cell RNA sequencing, proteomics / phosphoproteomic / immunopeptidomics, metabolomics, spatial transcriptomics and cell profiling.
- Concomitant CSF and blood analyses are performed to longitudinally correlate biofluid markers with the treated rGBM tissues.



Study objectives (Arm C)

- To determine safety and tolerability of up to 6 intratumoral repeated doses of rQNestin34.5v.2 (CAN-3110) with a starting dose of 10E^8 pfus per time point
- To assess the therapeutic benefit including overall survival (OS), progression-free survival (PFS), the tumor objective response rate (ORR) and rate of pseudoprogression (PSP).
- Exploratory objectives include assessment of :
  1) longitudinal persistence of rQNestin34.5v.2 antigen, HSV DNA and transcripts in injected rGBM;
  2) longitudinal changes in cellular, molecular, and immunologic variables in injected glioma;
  3) longitudinal changes in blood biomarkers from injected glioma;
  4) correlation of longitudinal changes in sampled glioma cellular, molecular and immunologic variables with changes in peripheral biomarkers and CSF biomarkers
  5) spatial correlation of longitudinal MR imaging changes with anatomic biopsy and injection sites of rQNestin34.5v.2 (CAN-3110).

Current status (Arm C)

- To date, 6 patients have been accrued in Arm C (funded by the Breakthrough Cancer Foundation), completing cohort 1 without reporting DLT or SAE from the injected oncolytic rQNestin34.5v.2 and/or the multiple longitudinal sampling procedures.

Patient	Age	KPS	Gender	Methylation status	IDH status	Recurrence	CAN-3110 Doses	Vital status
1	54	90	M	partial meth	wild type	1	4	Dead
2	66	70	F	unmethylated	wild type	1	6	Alive
3	75	90	F	unmethylated	wild type	1	6	Dead
4	64	100	M	methylated	wild type	1	5	Alive
5	61	100	F	unmethylated	wild type	1	4	Alive
6	68	70	F	unmethylated	wild type	2	4	Alive

- More than 300 longitudinal core biopsies were obtained from all 6 patients across the planned timepoints. The biopsies have been successfully processed for ongoing longitudinal scientific "-omic" data for the first 2 patients. Cohort 2 is scheduled to start enrollment in Q1-2 of 2024.
- Of the 6 patients treated on Arm C, there were 5 patients (83%) that reported at least one grade 2 or 3 adverse event.
- There were only three reported adverse events deemed possibly related to CAN-3110 including edema, joint pain and left hemiparesis, all grade 2 in severity.
- There were no grade 4 AEs or DLTs reported.

rQNestin34.5v.2 or CAN-3110 has been licensed to Candel Therapeutics