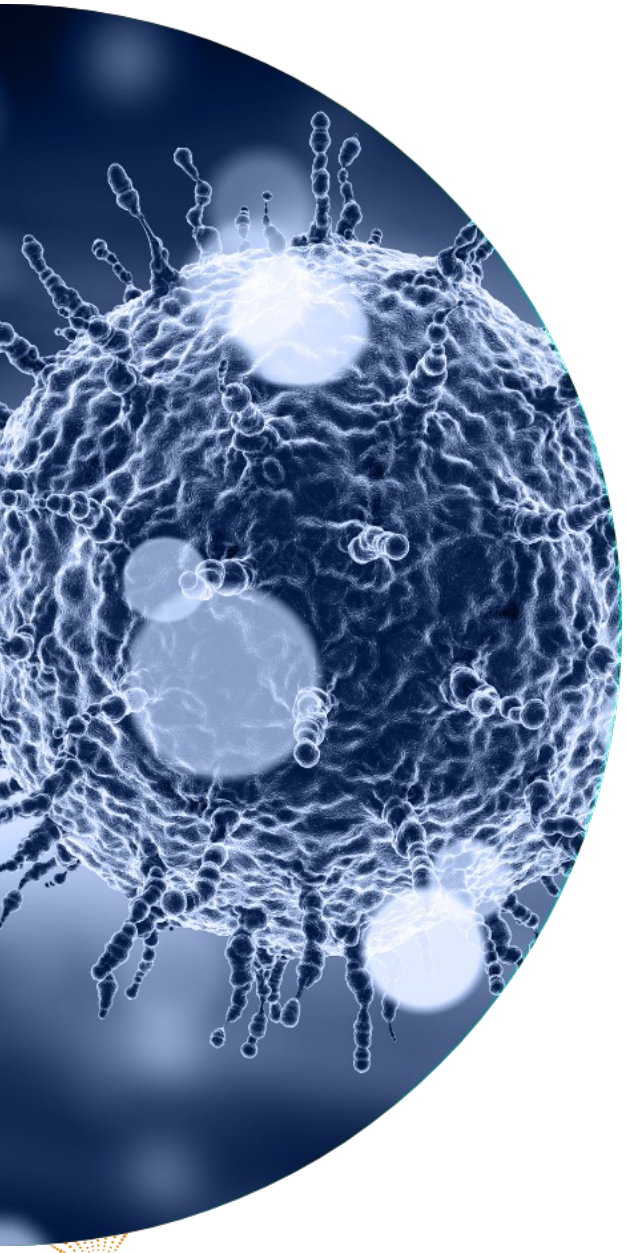


CANDEL THERAPEUTICS

Safety and survival outcomes in recurrent high-grade glioma patients treated with CAN-3110, a first-in-class ICP34.5 expressing oncolytic HSV1

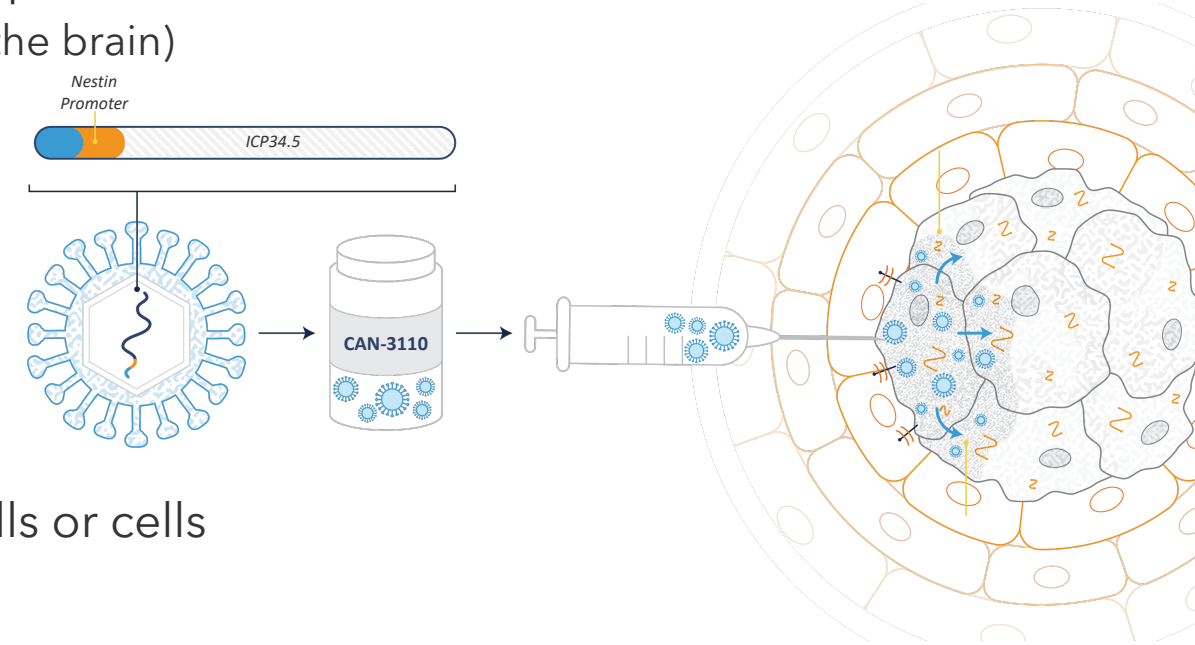
Francesca Barone, MD, PhD
Chief Scientific Officer, Candel Therapeutics, Inc.

CANDEL THERAPEUTICS

CAN-3110 a novel oncolytic virus engineered for enhanced activity and safety

HSV-1 engineered for immunogenic potency and specificity

- ICP34.5-null viruses have shown safety, but replicate poorly
- CAN-3110: ICP34.5 expression under control of Nestin promoter
  - Nestin overexpressed in gliomas (and tumors outside of the brain)
  - Improves replication
  - Provides tumor-specific oncolytic activity

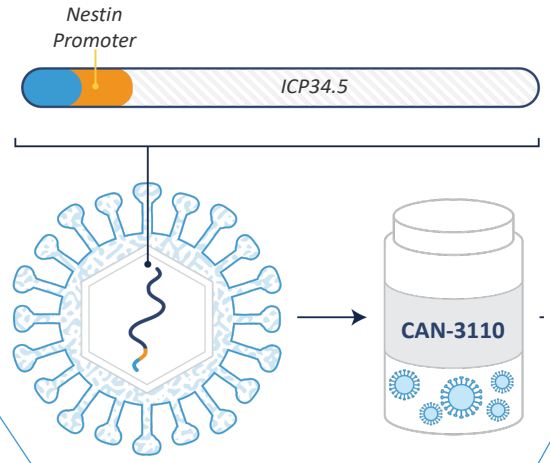


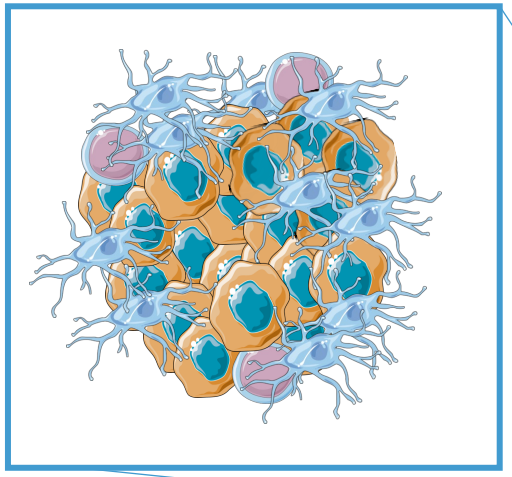
Designed for safety

- Disruption of ICP6 limits virus replication to dividing cells or cells with p16 tumor suppressor pathway defects
- Remains sensitive to anti-herpetic drugs
- Nestin provides tumor specificity

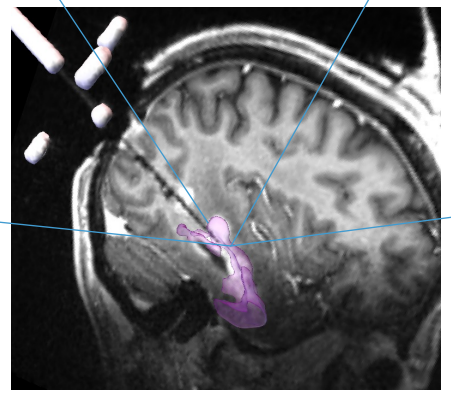
CAN-3110 induces tumor cell death and reprograms the highly immunosuppressive microenvironment of HGG

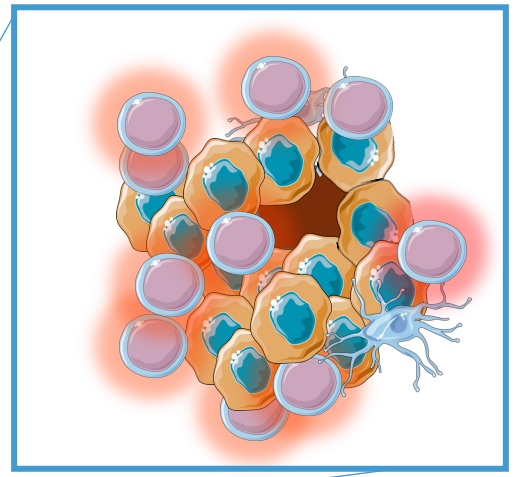
- Tumor cell death
- Release of tumor antigens
- Expansion of T cell repertoire
- Activation of local microenvironment





Cold tumor
Highly immunosuppressive TME
Cancer cell proliferation





Hot tumor
Inflamed TME
Cancer cell necrosis

Trial Design: Phase 1b Clinical Trial of CAN-3110 in Recurrent High-Grade Glioma

PI: Dr. E. Antonio Chiocca (Brigham & Women's)

Patients with recurrent high-grade glioma

Lesions ≥ 1.0 cm

NCT03152318

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

Arm B

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

BREAK THROUGH CANCER

Arm C

Repeat Dosing (up to 6)
+1 x 10^8 PFU x 6 doses
+1 x 10^9 PFU x 6 doses
12 patients targeted

Primary Endpoints

- Safety
- Determine maximum tolerated dose

Secondary Endpoints

- Immunological biomarkers
- MRI assessment of disease and progression free survival
- MRI alteration of permeability and flow at injection site

CANDEL THERAPEUTICS

Patient demographics and baseline characteristics

		Arm A (n=41*)	Arm B (n=9)	Total (n=50*)
Age, Median (range)		54 years (27 - 74)	54 years (41 - 70)	55 years (27 - 74)
Sex, n (%)				
	Female	21 (51%)	3 (33%)	24 (48%)
	Male	20 (49%)	6 (67%)	26 (52%)
Race, n (%)				
	White	38 (93%)	8 (89%)	46 (92%)
	Black or African American	1 (2%)	0 (0%)	1 (2%)
	Asian	2 (5%)	1 (11%)	3 (6%)
Ethnicity, n (%)				
	Non-Hispanic	40 (98%)	8 (89%)	48 (96%)
	Hispanic or Latino	0 (0%)	1 (11%)	1 (2%)
	Unknown	1 (2%)	0 (0%)	1 (2%)
IDH Status, n (%)				
	Wild-Type	32 (78%)	7 (78%)	39 (78%)
	Mutant	9 (18%)	2 (22%)	11 (25%)
MGMT Status, n (%)				
	Methylated	16 (39%)	2 (22%)	18 (36%)
	Unmethylated	23 (56%)	7 (78%)	30 (60%)
	Unknown	2 (5%)	0 (0%)	2 (4%)
Grade, n (%)				
	III	7 (17%)	0 (0%)	7 (14%)
	IV	34 (83%)	9 (100%)	43 (86%)
KPS Score, Median (range)		90 (70 - 100)	90 (80 - 100)	90 (70 - 100)

* See below

- 41 unique patients were dosed; one patient was treated twice, in cohort IX and X
- A total of 50 unique patients

CANDEL THERAPEUTICS

CAN-3110 related SAEs in rHGG (arms A and B)

Cohort (arm)	Number of treated patients	Dose Level (PFU)	Number of patients with DLT	Number of patients with related SAE	Case #	Time (days)
1 (A)	3	$1x10^6$	0	0	NA	NA
2 (A)	3	$3x10^6$	0	0	NA	NA
3 (A)	3	$1x10^7$	0	0	NA	NA
4 (A)	3	$3x10^7$	0	0	NA	NA
5 (A), 1 (B)	6	$1x10^8$	0	0	NA	NA
6 (A)	3	$3x10^8$	0	0	NA	NA
7 (A), 10 (A), 2 (B)	21	$1x10^9$	0	1	046(IDHmut)	2
8 (A)	3	$3x10^9$	0	1	033(IDHmut)	16
9 (A)	6	$1x10^{10}$	0	0	NA	NA
TOTAL	50*		0	2	Time range (days)→	2 to 16

As of cutoff date 25 Apr 2023

DLT: dose limiting toxicity, SAE: serious adverse event

* Total includes one patient who received two injections, one in cohort 9 (A) and one in cohort 10 (A)

CANDEL THERAPEUTICS

Safety summary: related adverse events* (AEs) in rHGG

Arm A (n=41)	n (%)
General disorders and administration site conditions	
Fever	3 (7%)
Musculoskeletal and connective tissue disorders	
Muscle weakness	3 (7%)
Nervous system disorders	
Seizure	3 (7%)

Arm B (n=9)	n (%)
Nervous system disorders	
Edema Cerebral	1 (11%)
Hemianopia	1 (11%)
Hypoesthesia	1 (11%)

* events manifesting in ≥5% of patients

Safety summary: adverse events in rHGG

Arm A (n=41*)

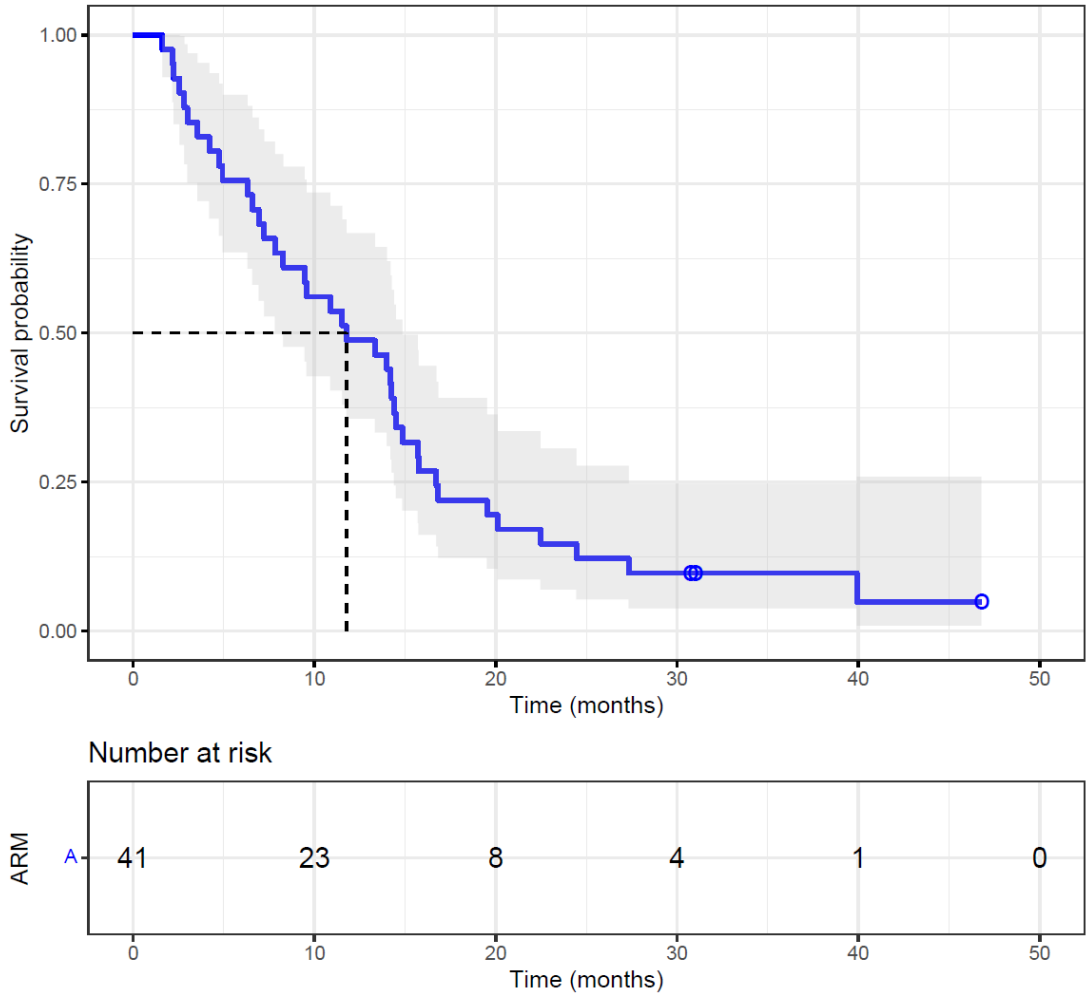
- No patients experienced a DLT in Cohorts I-X
- All patients (n=41) experienced at least 1 AE
- 27% of patients (n=11) experienced at least 1 related AE
- 59% of patients (n=24) experienced at least 1 serious AE
  - Most Serious AEs: Edema Cerebral (n=8 [20%]) and Seizure (n=5 [12%])
- 5% of patients (n=2) experienced at least 1 serious related AE
  - 001-033: Grade 3 – Seizure, Cerebral hematoma
  - 001-046: Grade 2 - Seizure, muscle weakness , facial paresis
- Most *TEAEs were Grade 1-3
  - Most common Grade 3 AEs include Edema Cerebral (n=8 [20%]), Seizure (n=5 [12%]) and Muscle weakness (n=5 [12%]).
  - One patient experienced a grade 5 cardiac arrest, non-related
  - No grade 4 AEs

Arm B (n=9)

- All patients (n=9) experienced at least 1 AE
- 11% of patients (n=1) experienced at least 1 related AE
  - 001-060: Grade 2 – Edema cerebral, left leg numbness, left visual field defect
- 22% of patients (n=2) experienced at least 1 serious AE
  - 001-061: Grade 3 – Edema cerebral, muscle weakness
  - 001-065: Grade 3 – Cerebrospinal fluid leakage, left hemiparesis, pseudo-meningocele and muscle weakness
- No patient (n=0) experienced a serious related AE
- All *TEAEs were grade 1-3
  - Most common Grade 3 AEs include Muscle Weakness (n=2 [22%])
  - No grade 4 or 5 AEs

* 41 unique patients were dosed; 00030 was treated twice, Cohort IX and X
* Treatment Emergent Adverse Events (TEAEs)

Encouraging overall survival in rHGG after single injection (arm A)

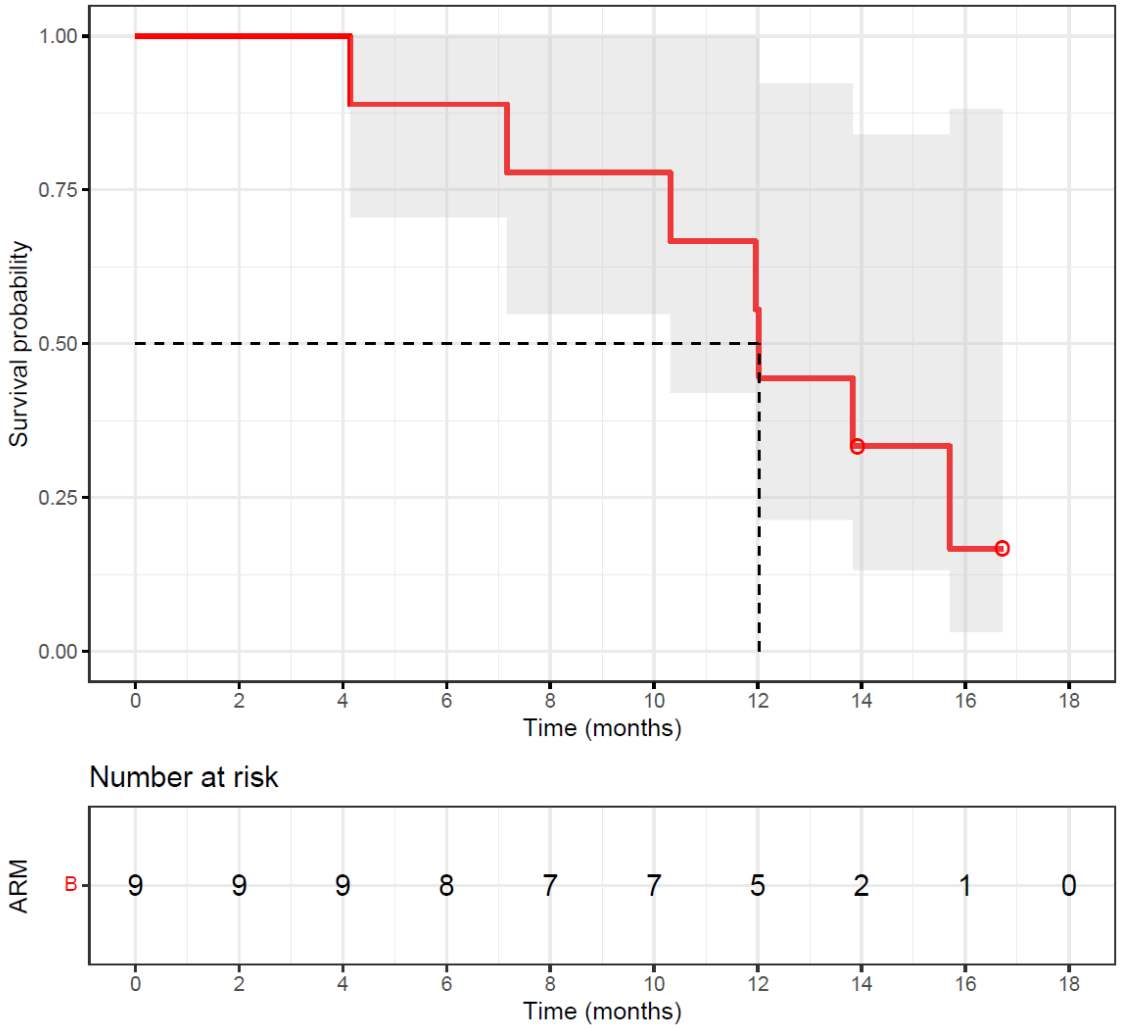


N = 41
Median overall survival: 11.8 months
Cutoff date: 20 Apr 2023

Expected median overall survival: <6-9 months

- 41 unique patients were dosed; one patient was treated twice, in cohort IX and X
- A total of 50 unique patients

Overall survival data rHGG arm B confirms data in arm A

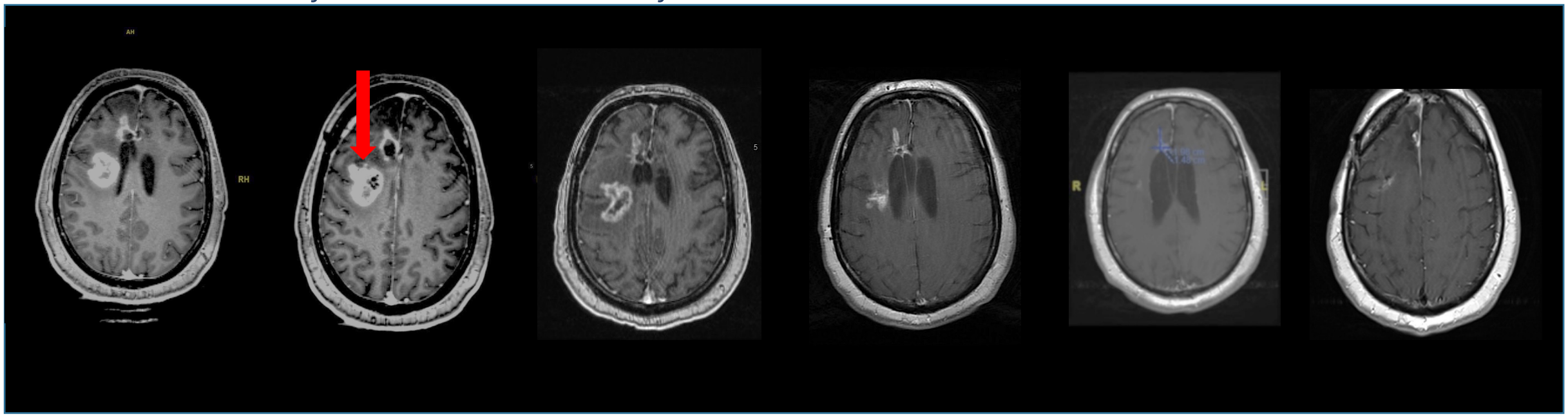


N = 9 patients pretreated with cyclophosphamide
Median overall survival: 12 months
Cutoff date 20 Apr 2023

Expected median overall survival: <6-9 months

Monotherapy activity of CAN-3110 in rHGG (arm A)

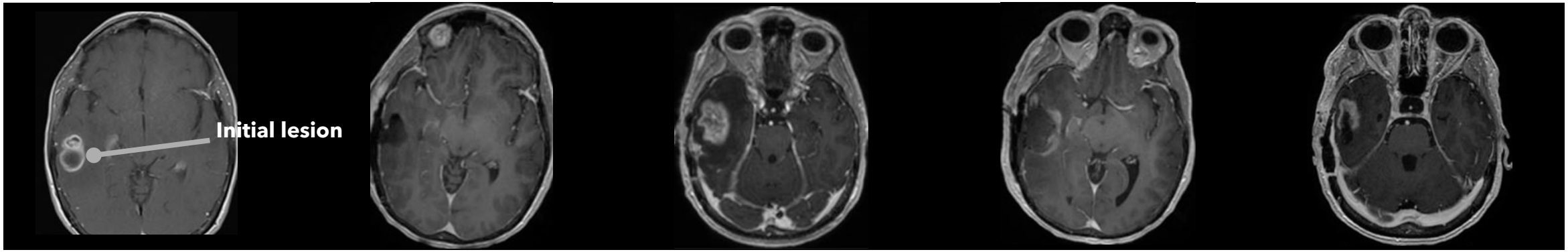
Clinical effect on injected tumor and uninjected tumor



Baseline	Day 0	Day 56	Day 111	Day 168	Day 280
	Black hole within tumor image is injection site 10^6 PFU dose	Reduction in contrast area with no additional treatment	Patient back to work		

56 YOM, IDH wild-type, MGMT partially methylated, right frontal mesial lesion initially treated with GTR, chemoradiation. Recurrences at two sites.

Durable response for 2Yrs after CAN-3110 in rHGG (arm A)



Day -262
Initial presentation

Day -259
Initial resection

Day -47
Tumor recurrence

Day -30
2nd subtotal resection

Day -14
Rapid progression

Day 0
CAN-3110 Injection

Day 91
Tumor recurrence with TIL

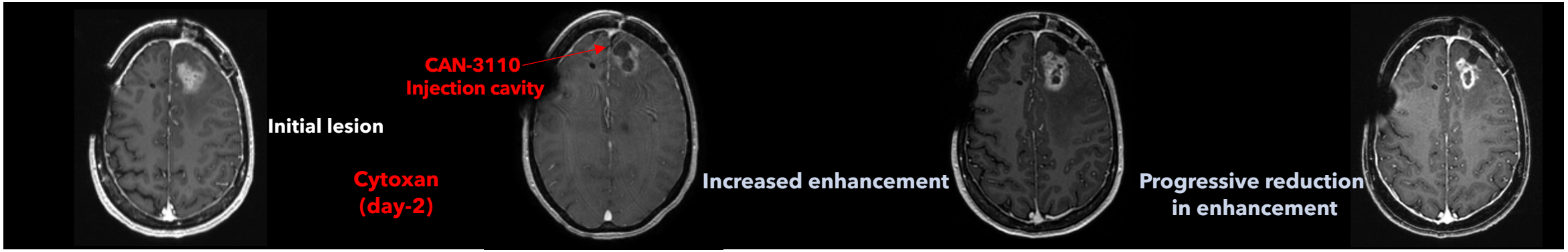
Day 96
After resection, histology shows TILs

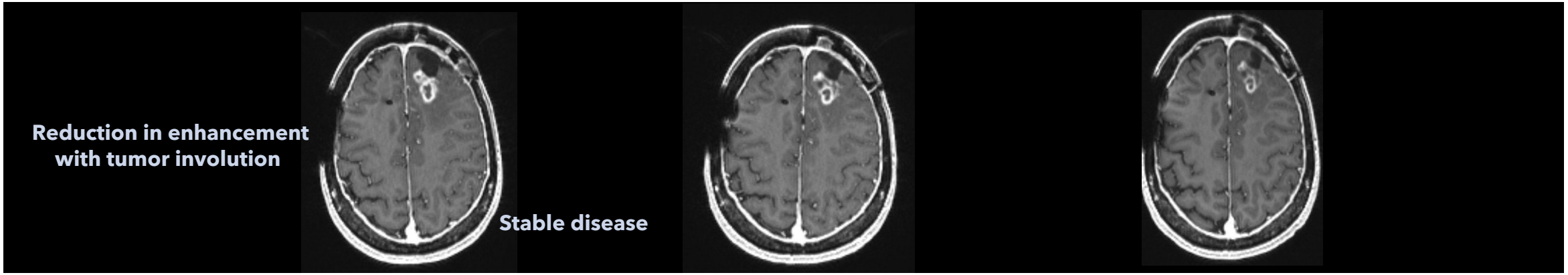
Day 630
No visible tumor

61 YOF, IDH wild-type, MGMT methylated glioblastoma, right temporal lesion initially treated with surgery, chemoradiation and temozolomide
CAN-3110 dose: 10^8 PFUs. Patient passed away as passenger in a motor vehicle accident on day 717.

CANDEL THERAPEUTICS

Continued improvement for >12Mos after CAN-3110 monotherapy (arm B)

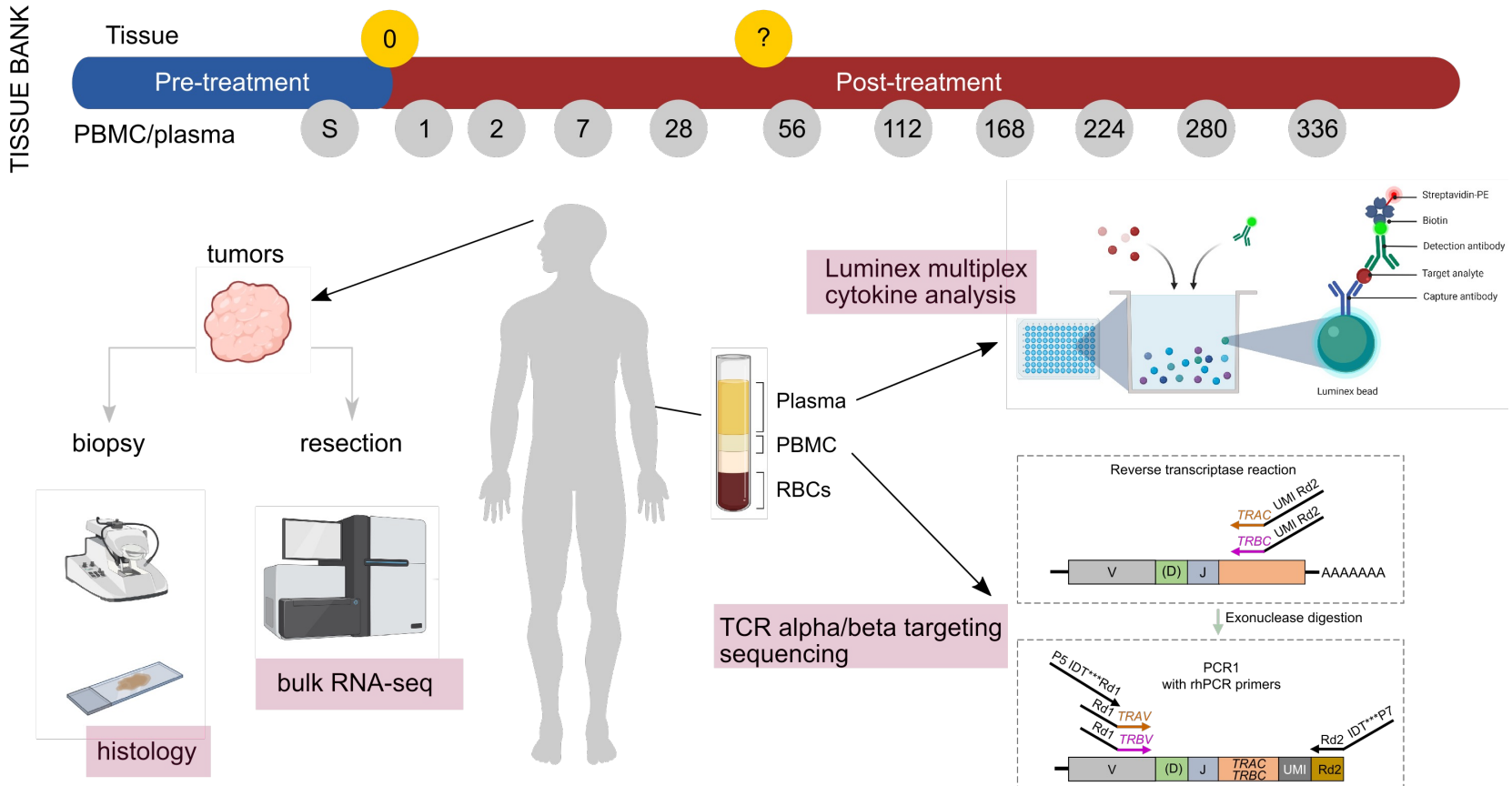




52 YO RH WF, IDH mutant, MGMT methylated grade IV astrocytoma (left frontal, invading corpus callosum in a butterfly fashion and lobulating into lateral and third ventricle). Recurrent disease, 1Yr after original resection. Enrolled in arm B: Cytoxan (24 mg/kg; day -2) & CAN-3110. Since injection KPS remains between 90 and 100, pt. independent at home with family, without other therapies.

CANDEL THERAPEUTICS

Biomarker Analysis



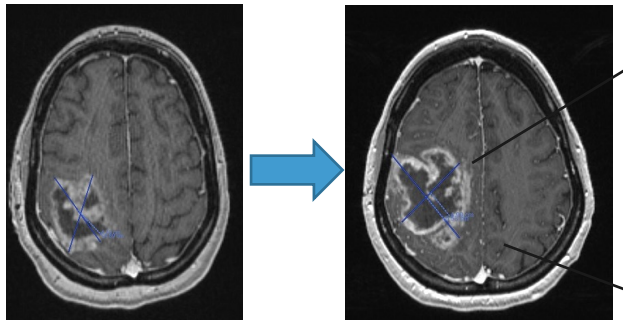
Bioinformatic Analysis

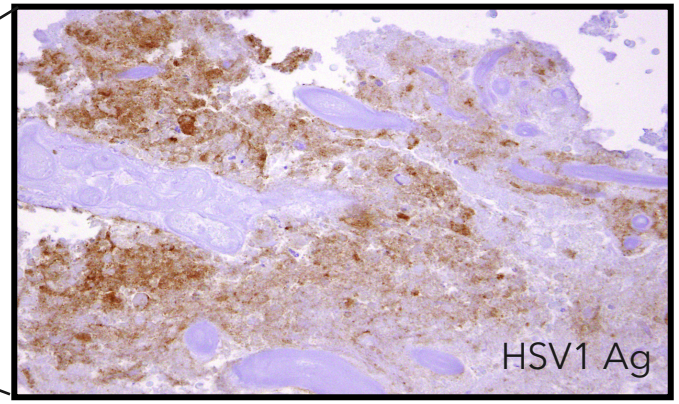
Data process (pipelines)	Bioinformatic workflow analysis	Longitudinal analysis
genomic alignment	transcriptomic anlaysis	Tracking clonotypes
annotation	pathway analysis	cytokine changes and biomakers
VDJ alignment & assemble	TCR clonotype analysis	

CANDEL THERAPEUTICS

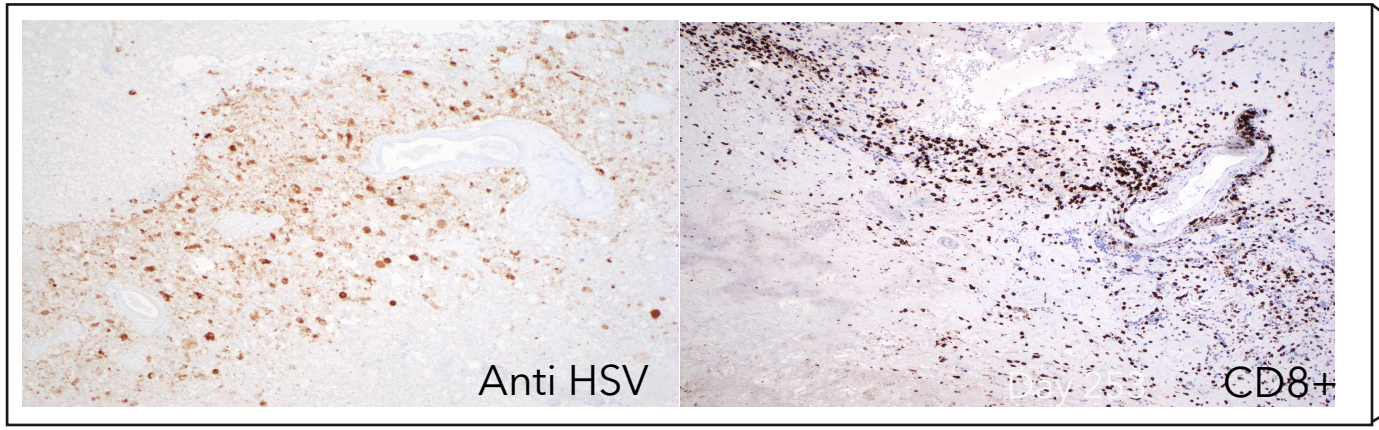
Persistent HSV antigen expression associated with CD8+ T cell infiltration after CAN-3110 treatment

Patient A
(6 weeks post-HSV 10e6 PFUs)

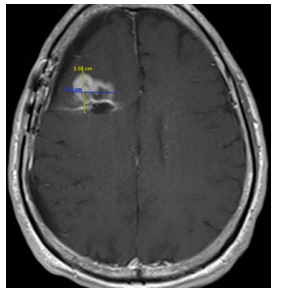




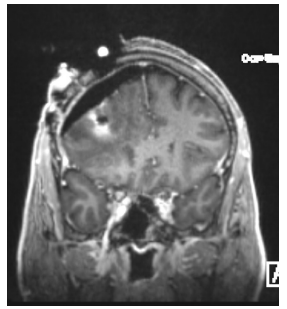
Patient B
(9 mos post-HSV 10e9 PFUs)



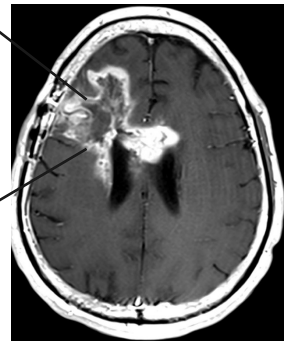
Preoperative



Intraoperative injection

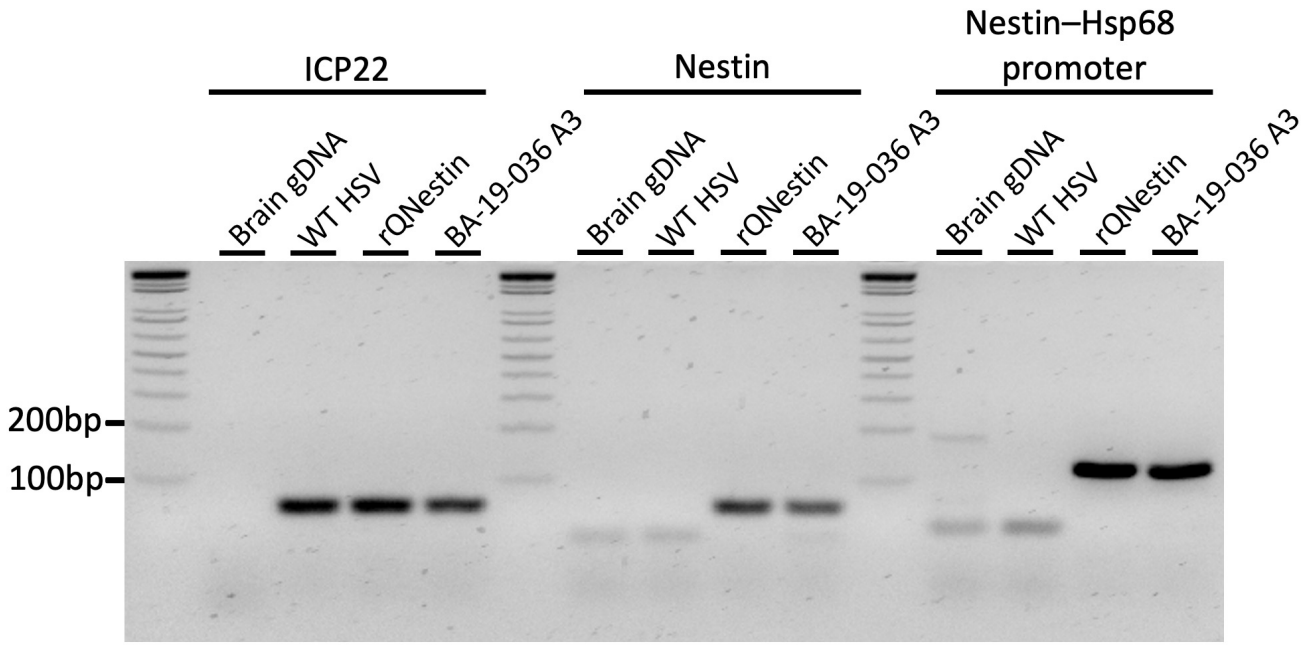


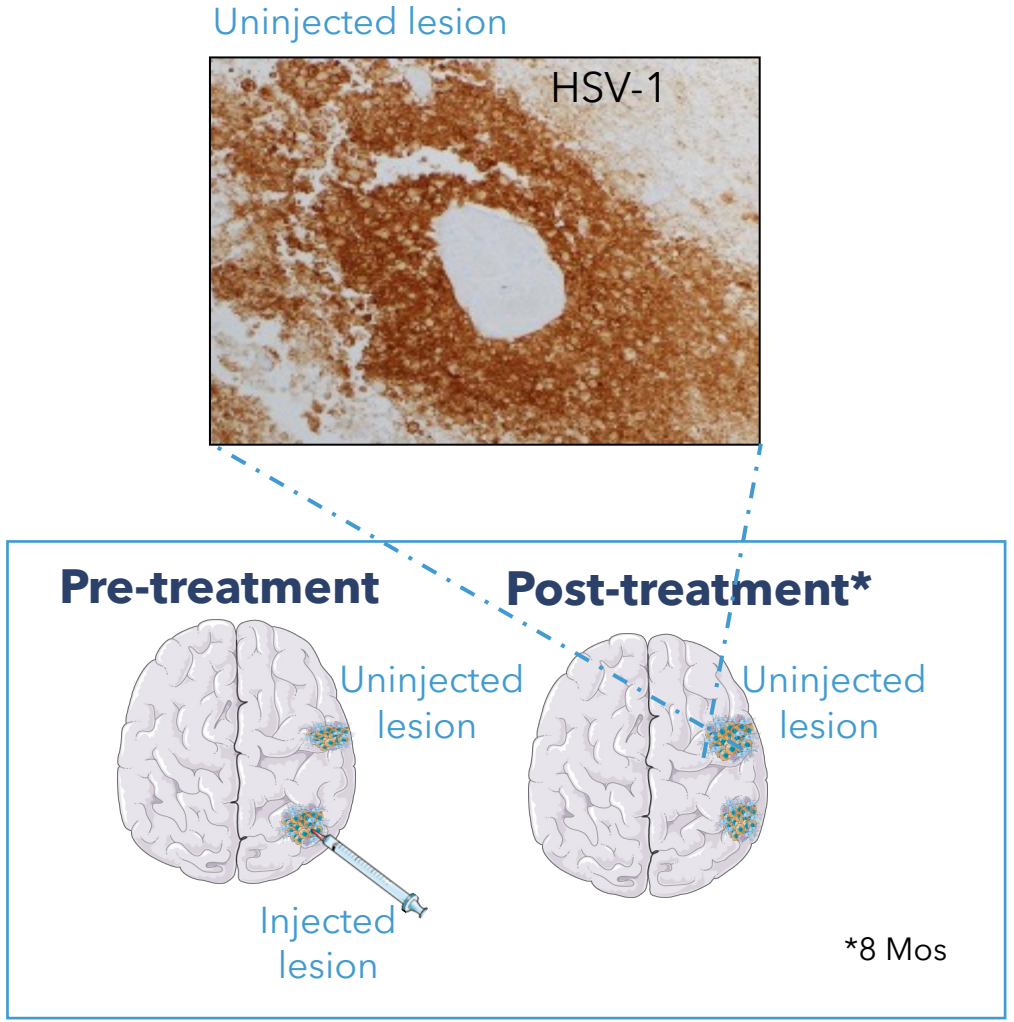
Recurrence



13/27 patients presented positive oHSV antigen in post-injection samples collected in a range of 24 to 801 days post treatment

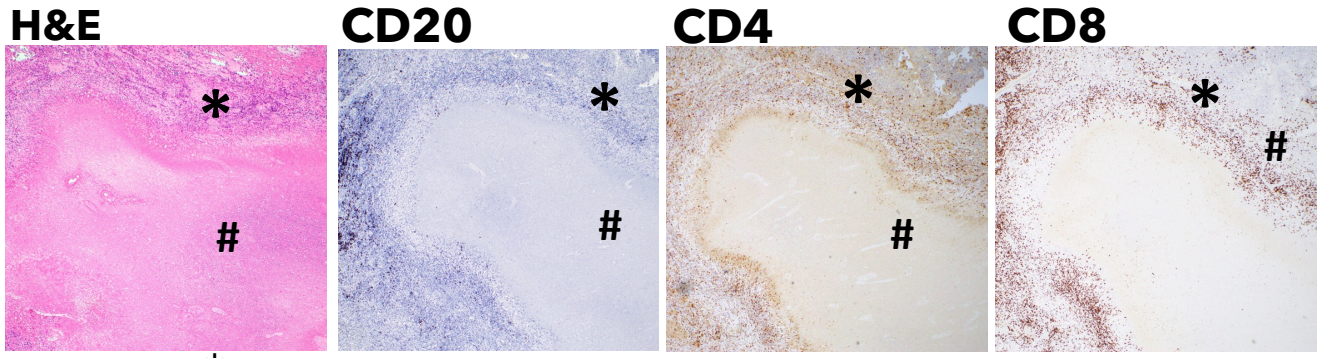
Persistent HSV antigen expression in uninjected lesion 8 Mos after CAN-3110 injection in multifocal rHGG



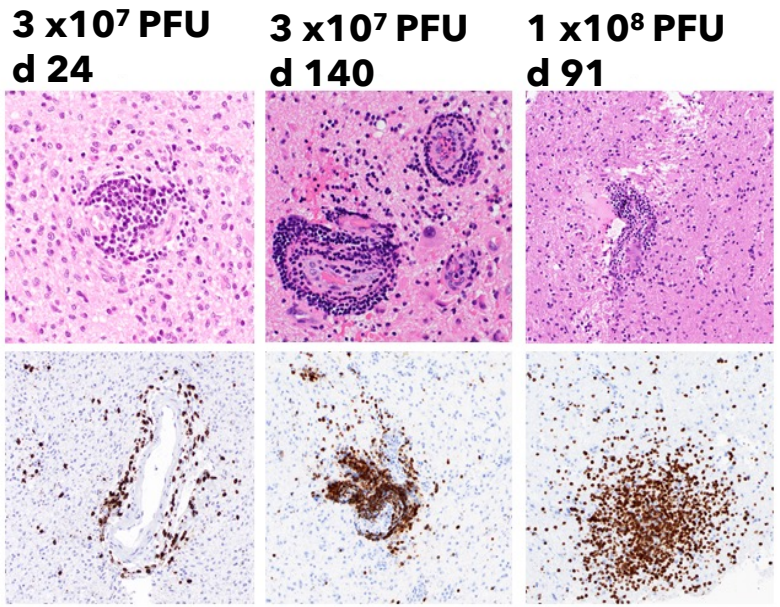


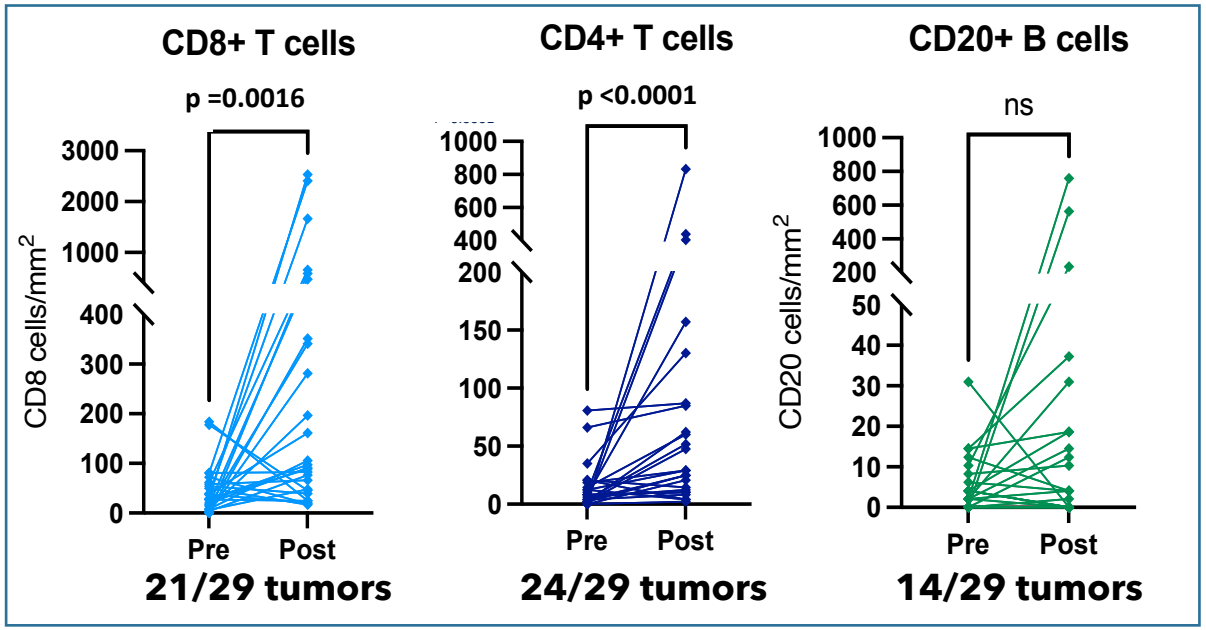
Increased infiltration by immune cells at the site of the tumor after CAN-3110 treatment in rHGG

Post-injection necrotic tumor areas surrounded by T cells

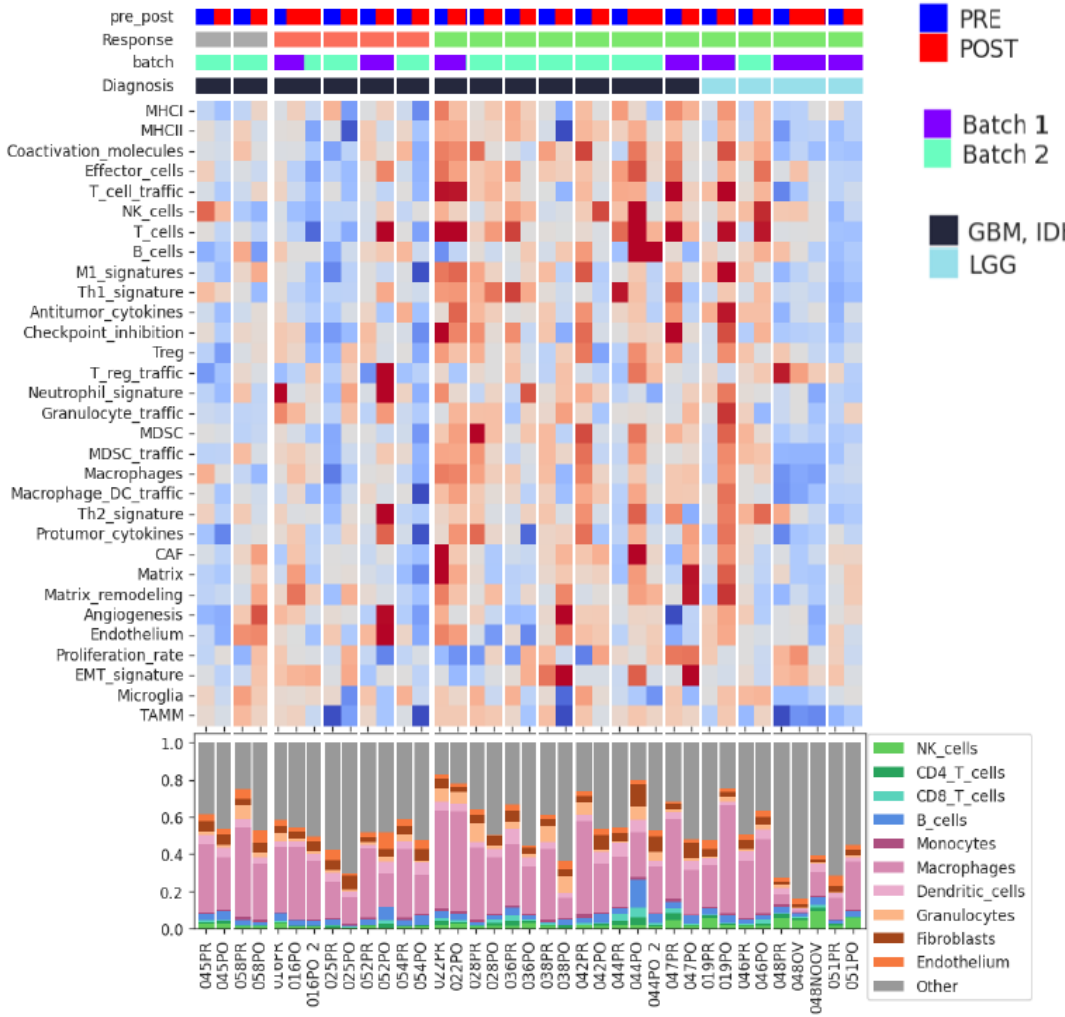


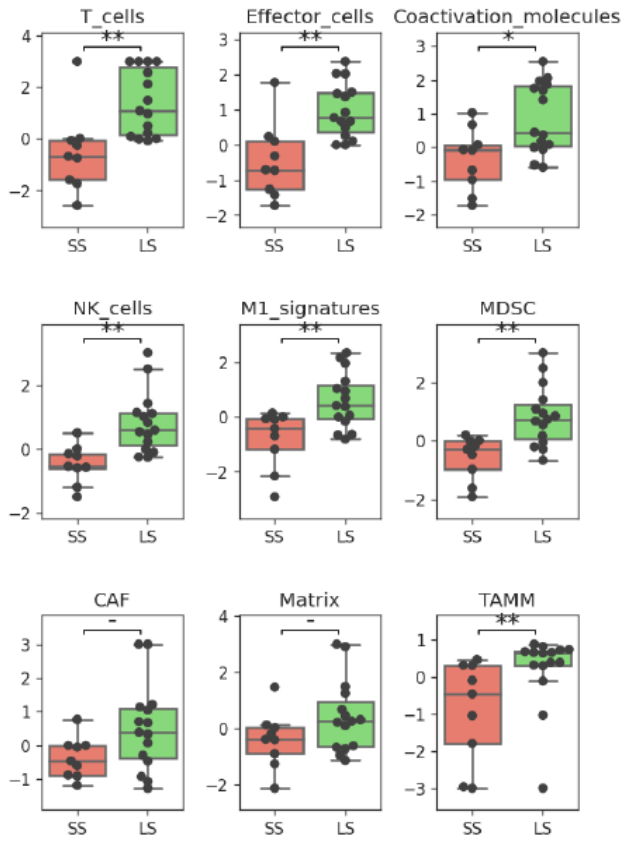
necrosis; * immune cell infiltrate





Changes in tumor microenvironment after CAN-3110 are associated with improved survival in rHGG



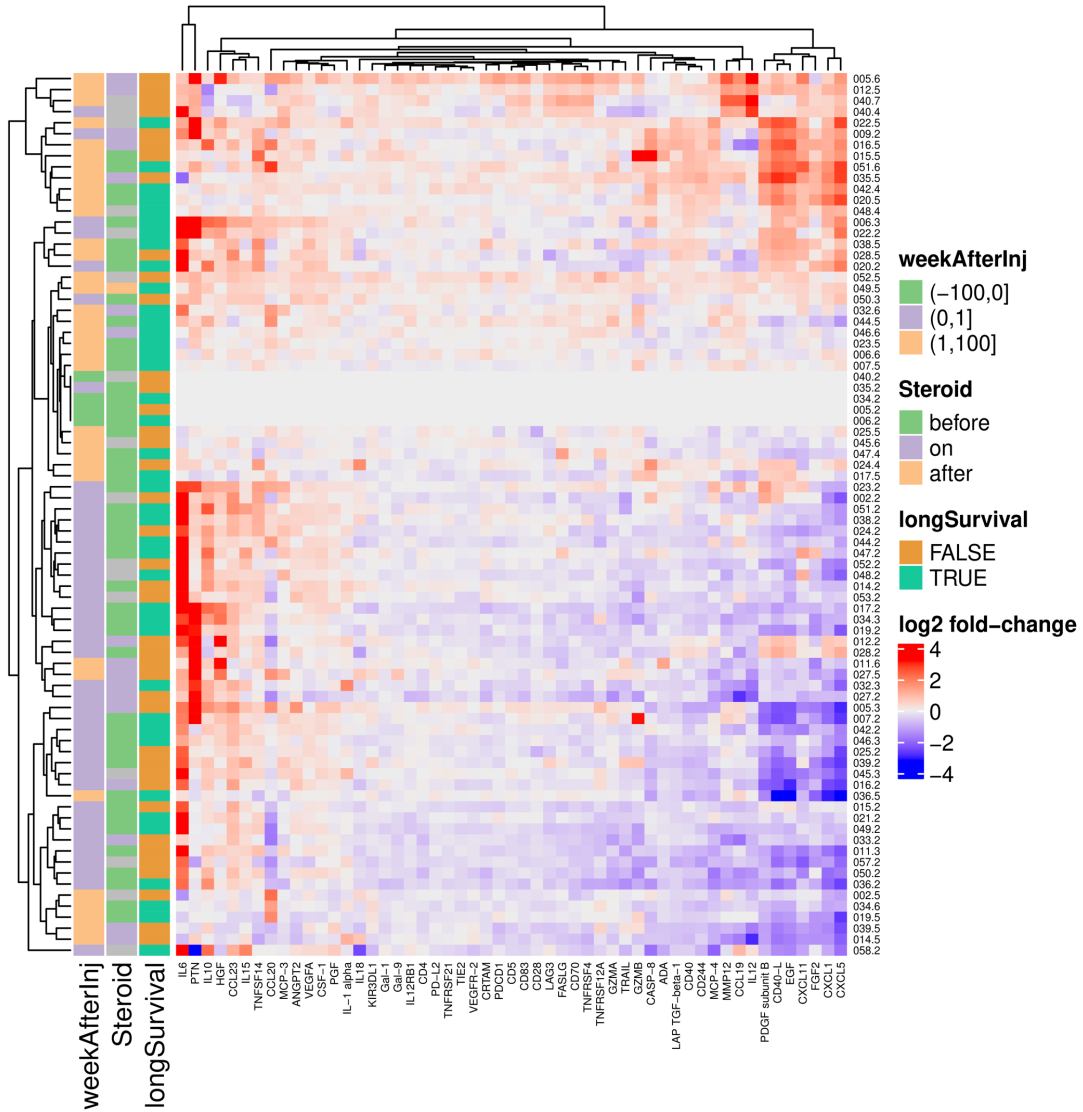


*only GBM IDH WT samples are shown on the boxplots

LS - long survivors, post-injection survival > 12 months
SS - short survivors, post-injection survival < 12 months
ND - insufficient data

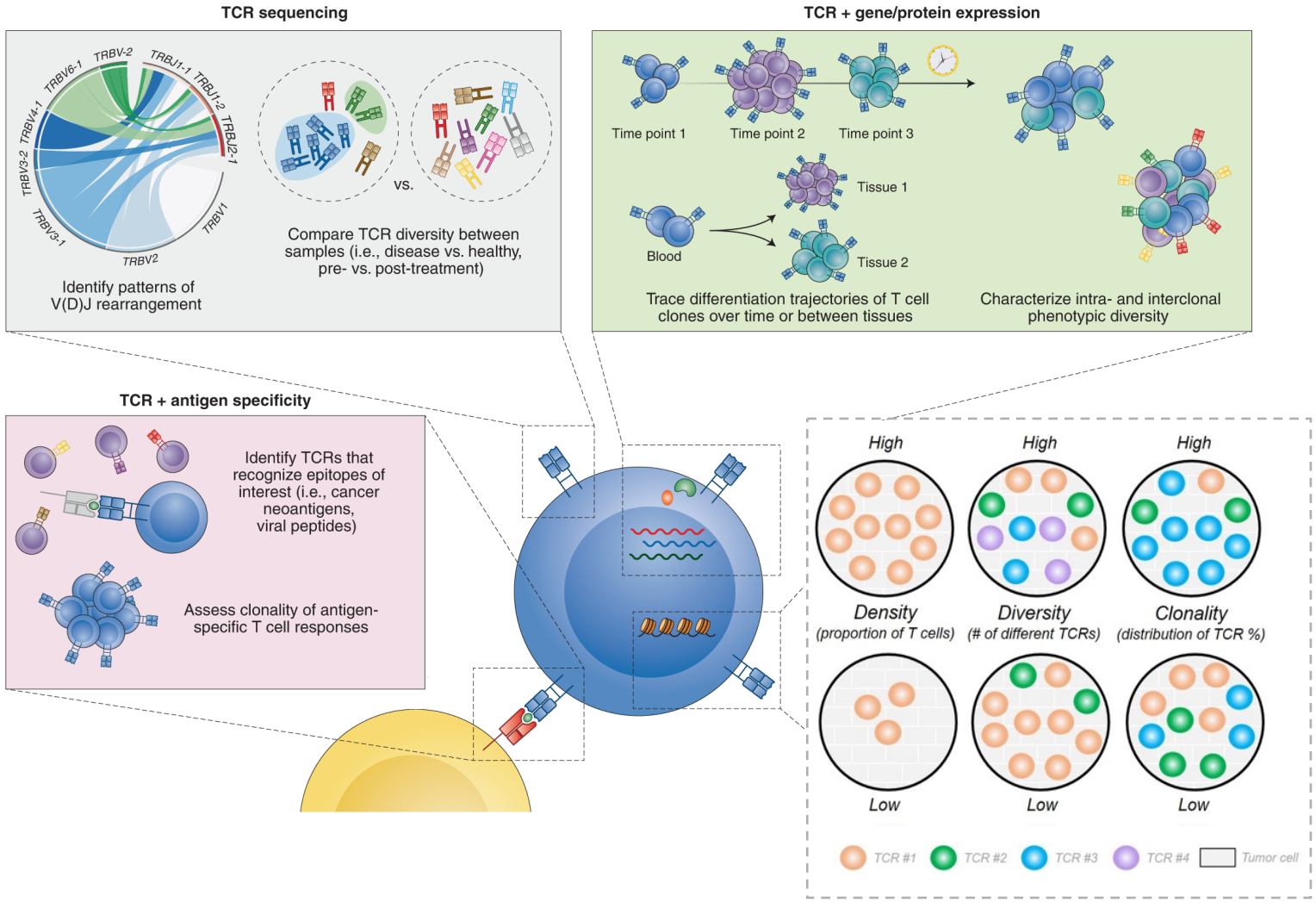
17 paired samples bioinformatic analyses by BostonGene, Inc.

Changes in protein biomarkers in peripheral blood after CAN-3110 injection in rHGG

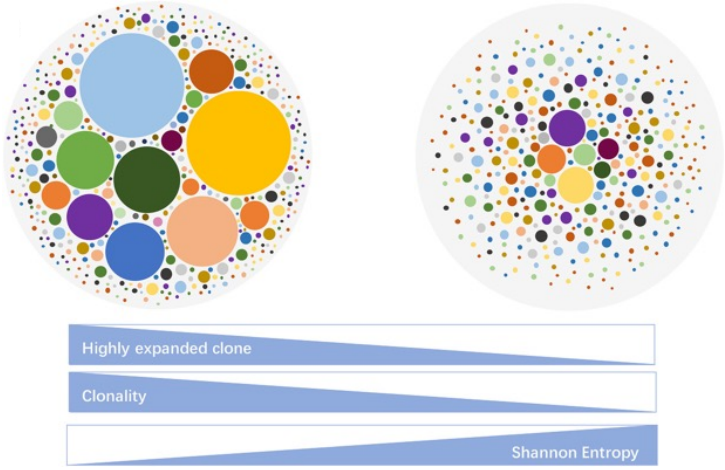


From 96 protein panel biomarkers, 53 showed statistically significant changes compared to baseline at the 1st or 2nd time points after treatment; those include IL-6, PTN, MMP12, CCL19, CD40L

T cell receptor (TCR) analysis interpretation tool



Relationship between clonality and diversity/entropy

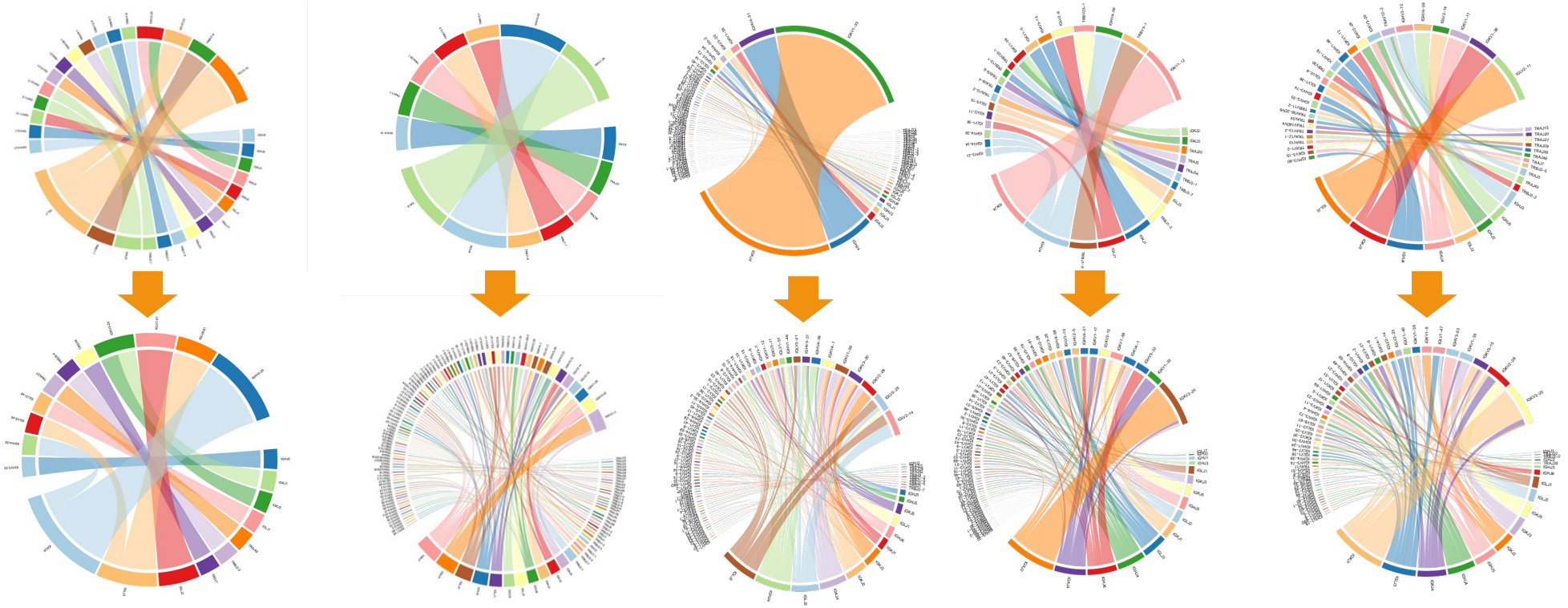


Increases in T cell density, entropy, and clonality are observed in long survivors after CAN-3110 injection

Long survivors

Short survivor

CAN-3110 injection



Conclusions

- Treatment with CAN-3110 in rHGG is well tolerated with no dose-limiting toxicity observed
- Persistence of HSV antigen expression associated with tumor necrosis and increased immune cell infiltration after CAN-3110 injection in both injected and uninjected lesions
- Evidence of abscopal effect
- Increase in pro-inflammatory mediators after CAN-3110 injection in rHGG
- Immunological changes in the tumor microenvironment after CAN-3110 injection in rHGG are associated with improved survival
- Increases in T cell density, entropy, and clonality are observed in long survivors after CAN-3110 injection
- Next, we will evaluate the effects of repeat injections with CAN-3110, supported by the Break Through Cancer foundation

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