

**2022**  
SITC

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# The Society for Immunotherapy of Cancer 37<sup>th</sup> Annual Meeting and Pre-Conference Programs

THE LEADING CANCER IMMUNOTHERAPY AND TUMOR IMMUNOLOGY CONFERENCE



Society for Immunotherapy of Cancer

#SITC22

# First efficacy and multi-omic analysis data from phase 1 clinical trial of oncolytic viral immunotherapy with CAN-2409 + valacyclovir in combination with nivolumab and standard of care in newly diagnosed high-grade glioma

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# Disclosures



## Research Support

- Agios, Astra Zeneca/Medimmune, Bayer, Celgene, Eli Lilly, Genetech/Rocher, Kazia, MediciNova, Merck, Novartis, Nuvation Bio, Oncoceutics, Vascular Biogenics, VBI Vaccines

## Advisory Board

- Agios, Astra Zeneca, Bayer, Black Diamond, Boston Pharmaceuticals, Elevate Bio, Imvax, Karyopharm, Merck, Mundipharma, Novartis, Novocure, Nuvation Bio, Prelude Therapeutics, Sapience, Vascular Biogenics, VBI Vaccines, Voyager, QED

## Sponsor of the study being presented

- Candel Therapeutics, Inc.

# Suppressed tumor microenvironment and negative prognostic factors determine poor prognosis in high-grade glioma patients

High-grade glioma tumor microenvironment is characterized by poor T cell infiltrate, enrichment in M2 suppressive macrophages and suppressive microglia

Negative prognostic factors influencing survival:

***Age, sex, MGMT\* methylation status, IDH, extent of tumor resection***

Radiation and temozolomide induce lymphopenia

Corticosteroids may impact immune response



Weller M et al. Nat Rev Neurol 2017; 13:363-374  
Grossman SA et al. Clin CA Res 2011; 17:5473-5480  
Chongsathidkiet P et al Nat Med 2019; 24:1459-1468

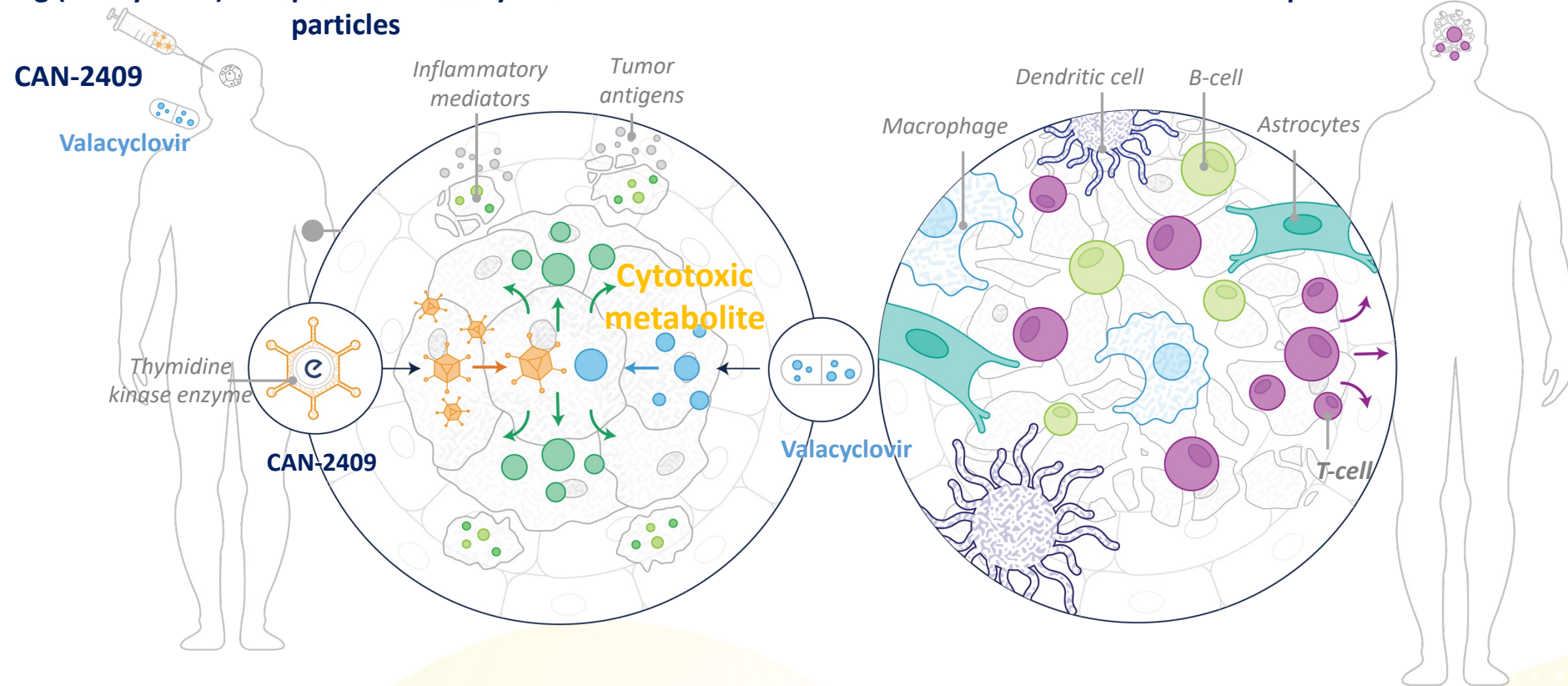
# CAN-2409: a systemic immunotherapy delivered intratumorally

1. CAN-2409 locally administered followed by oral prodrug (valacyclovir)

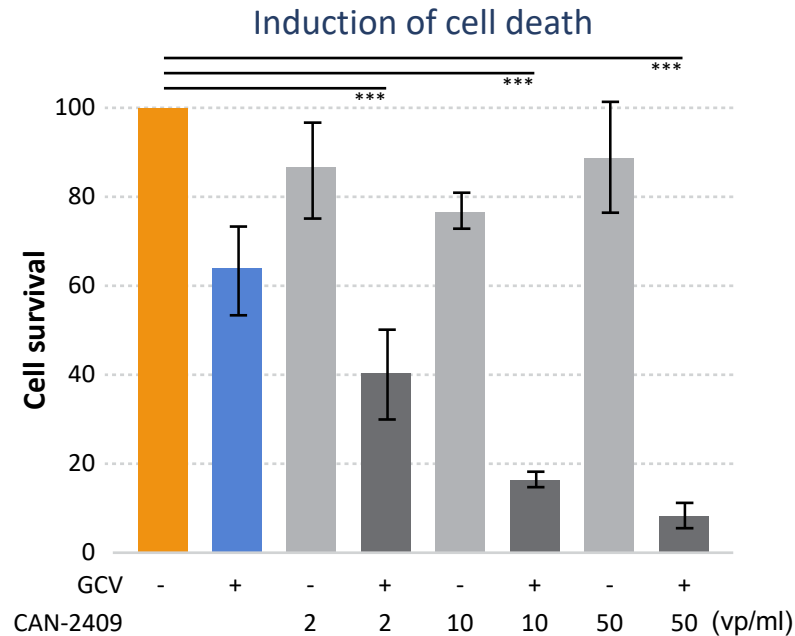
2. Localized cytolytic mechanism combined with proinflammatory viral particles

3. CAN-2409 induces tumor infiltrating lymphocytes

4. Local immunization yields systemic anti-tumor response



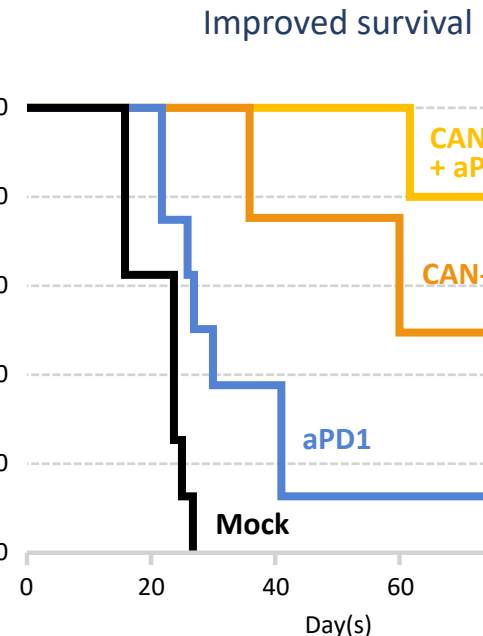
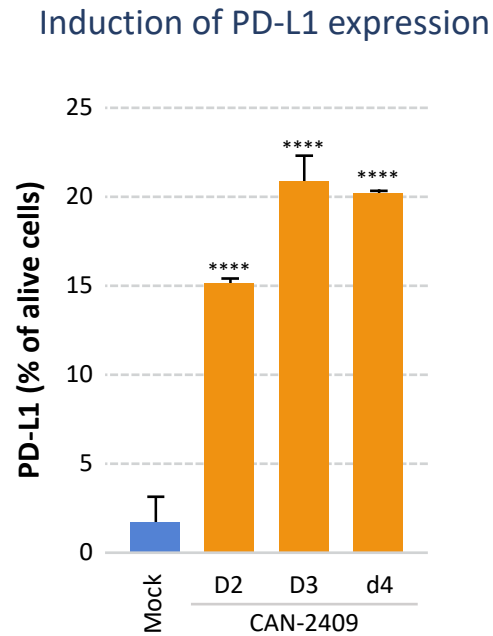
# Opportunity for combination therapy with immune checkpoint inhibitor: improved effect in mouse model of high-grade glioma



**Model: In vitro experiments with murine CT-2A-Luc HGG cells**

\*\*\*p ≤ 0.001, \*\*\*\*p ≤ 0.0001

Speranza MC et al. Neuro Oncol 2018; 20:225-235



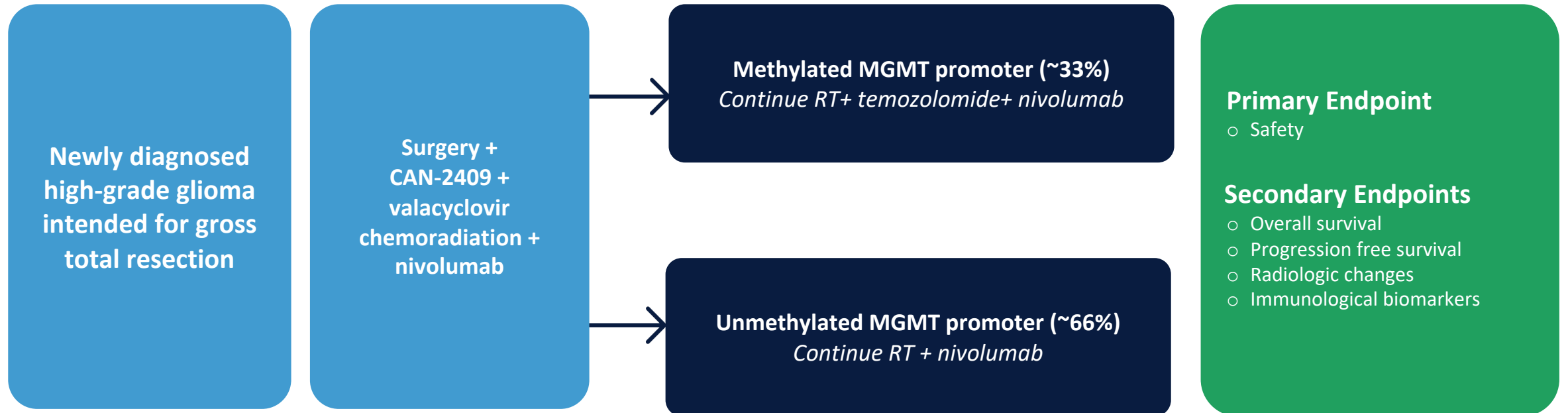
**Model: Intracranial injection of murine CT-2A-Luc HGG cells in mice**

N=26; \*\*\*p ≤ 0.001, \*\*p ≤ 0.01, \*p ≤ 0.05

# Phase 1 clinical trial of CAN-2409 plus valacyclovir combined with nivolumab in high-grade glioma



A protocol of the Adult Brain Tumor Consortium (ABTC) in collaboration with Bristol-Myers Squibb (BMS) and Candel Therapeutics, Inc.



NCT03576612

#### Methodology for primary endpoint:

Evaluate safety of the combination of CAN-2409 +VCV + nivolumab +/- temozolomide

Enrolment in sets of 9 patients (~3 methylated and 6 unmethylated)

If DLT rate  $\leq 33\%$ , proceed with next set of 9 patients

Target ~12 methylated and ~24 unmethylated evaluable patients

# Patient demographics safety population (41 patients)

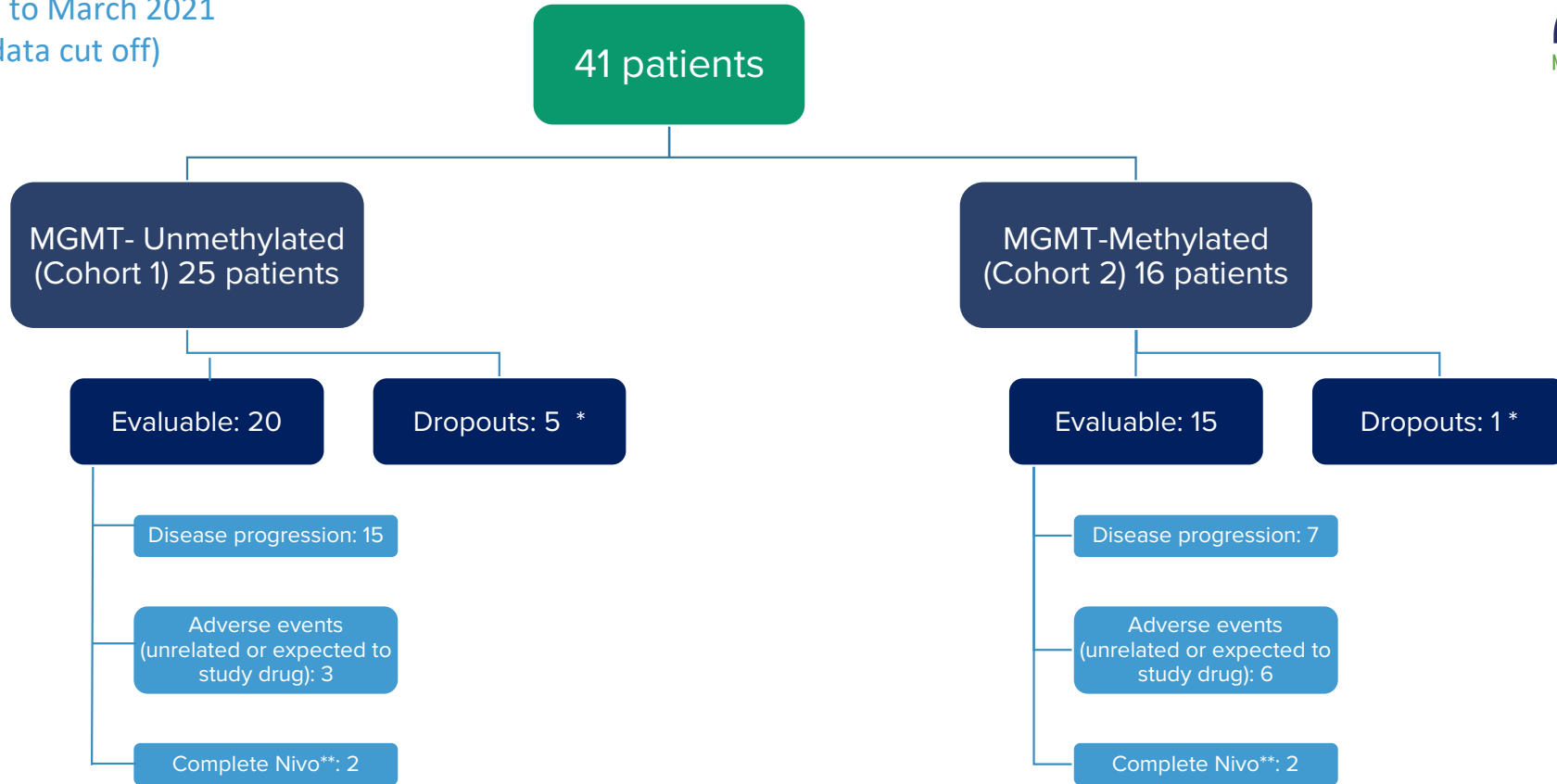


Number of patients: 41	
Characteristic	N (%)
<b>Age</b>	
Median age (years)	62
Range	28-81
<b>Sex</b>	
Female	14(34)
Male	27(66)
<b>Race</b>	
White/Caucasian	34(83)
Black/African American	3(7)
American Indian or Alaska Native	1(2)
Asian	1(2)
Not reported	2(5)
<b>Ethnicity</b>	
Not Hispanic or Latino	38(93)
Hispanic or Latino	1(2)
Unknown	1(2)
Not reported	1(2)

Number of patients: 41	
Characteristic	N (%)
<b>KPS (Baseline)</b>	
Median KPS	90
Range	80-100
<b>KPS (Day 15)</b>	
Median KPS	80
Range	20-100
<b>MGMT</b>	
Methylated	16(39)
Unmethylated	25(61)
<b>IDH</b>	
Wild type	39(95)
Mutant	2(5)
<b>Histopathologic diagnosis</b>	
Glioblastoma	40(98)
Diffuse astrocytoma	1(2)
<b>Type of resection</b>	
Gross total resection	30(73)
Subtotal resection	11(27)

# CONSORT diagram

Enrollment February 2019 to March 2021  
9 patients alive (9/30/22 data cut off)



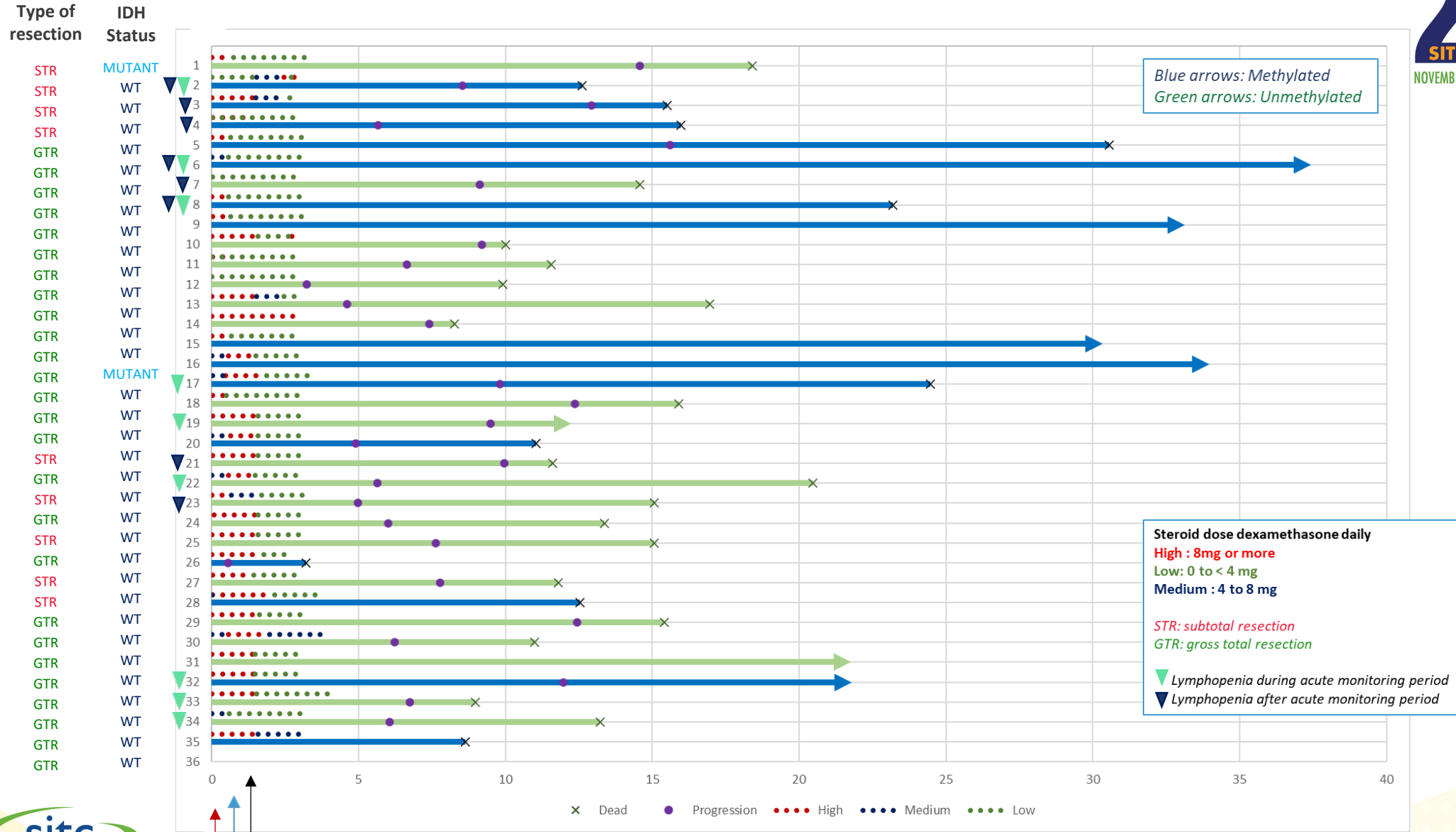
\*\*Received 26 nivolumab infusions

\*Received less than 80% of any planned dose of treatment regimen for reasons unrelated to study treatment

Evaluable : Patients who completed >80% of treatment during the acute monitoring period (2 weeks after the 4th dose of nivolumab).

Safety population: Any patient who received investigational agent.

# Evaluable subject progress (35 patients)



# Safety of the combination of CAN-2409 plus valacyclovir and nivolumab



- Patients did not experience unexpected serious adverse events
- Adverse events considered at least possibly related to CAN-2409, valacyclovir or nivolumab during acute monitoring period (0-71 days) are shown below

## Most common adverse events occurring in >10% of patients

Adverse Event	CTC grade				Total=41 N (%)
	1	2	3	4	
Fatigue	11 (27)	4 (10)	1 (2)	0	16 (39)
Nausea	9 (22)	1 (2)	2 (5)	0	12 (29)
ALT increased	9 (22)	0	1 (2)	0	10 (24)
Headache	6 (15)	0	2 (5)	0	8 (20)
Anemia	3 (7)	3 (7)	1 (2)	0	7 (17)
Fever	5 (12)	2 (5)	0	0	7 (17)
AST increased	7 (17)	0	0	0	7 (17)
Hyponatremia	4 (10)	2 (5)	1 (2)	0	7 (17)
Vomiting	4 (10)	1 (2)	1 (2)	0	7 (17)
Platelet count decreased	4 (10)	0	0	2 (5)	6 (15)
Blood bilirubin increased	4 (10)	1 (2)	0	0	5 (12)

## Additional grade 3-4 adverse events occurring in >1 patient

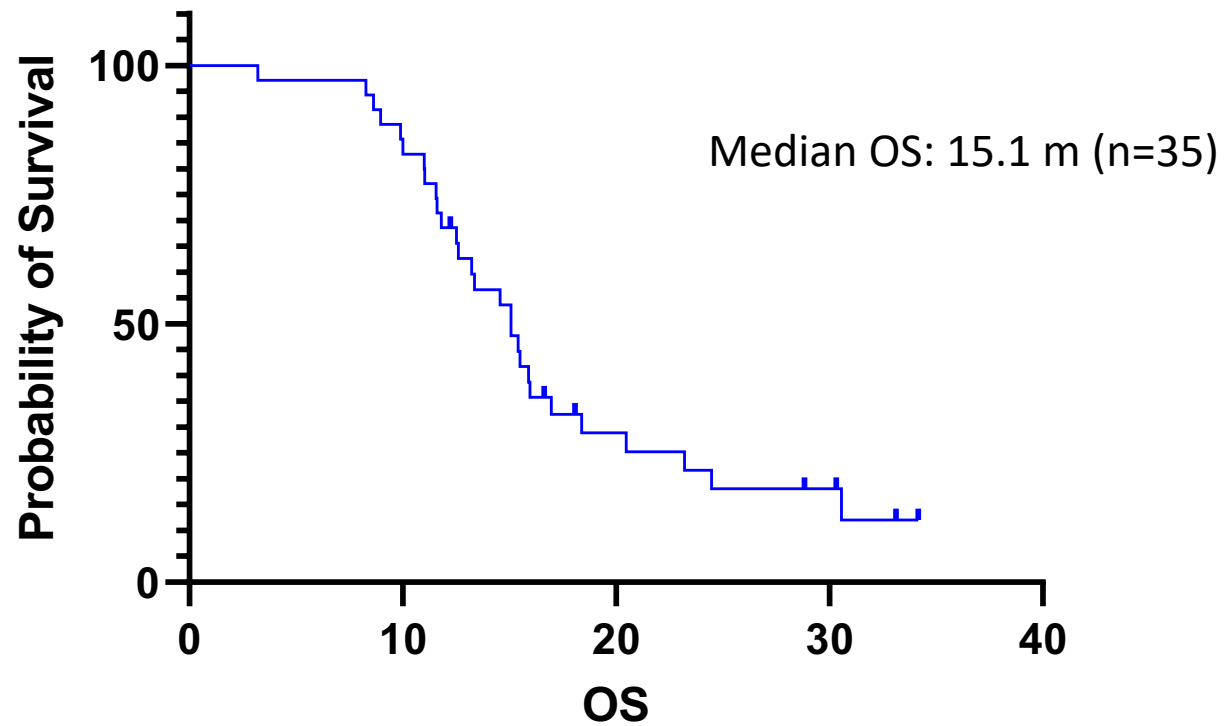
Event	CTC grade		Total=41 N (%)
	3	4	
Neutrophil count decreased	1 (2)	1 (2)	2 (5)
Acute kidney injury	2 (5)	0	2 (5)
Hypertension	2 (5)	0	2 (5)

9 discontinuations due to adverse events:

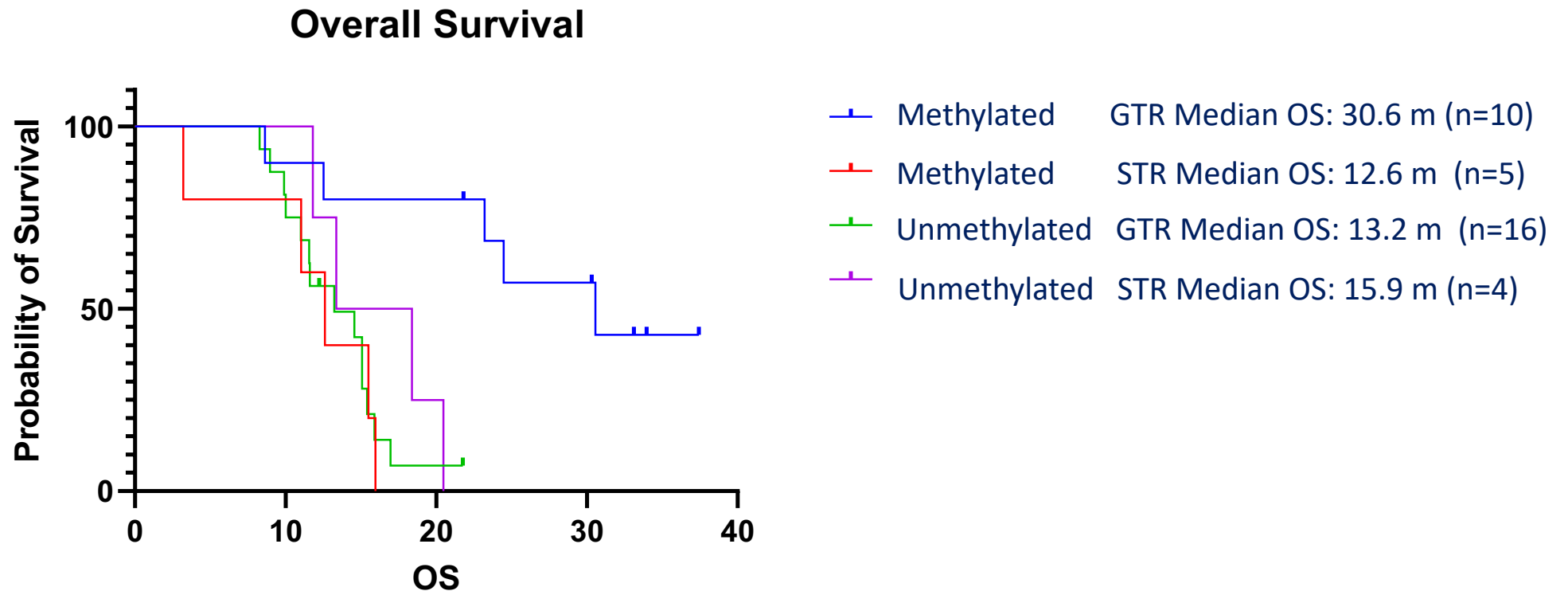
- 3 expected temozolomide toxicity (myelosuppression)
- 3 expected nivolumab toxicity (1 aseptic meningitis, 2 AST/ALT increase)
- 2 due to underlying disease symptoms
- 1 unrelated medical event (prostate cancer)

# Evaluable population survival curves

## OS All

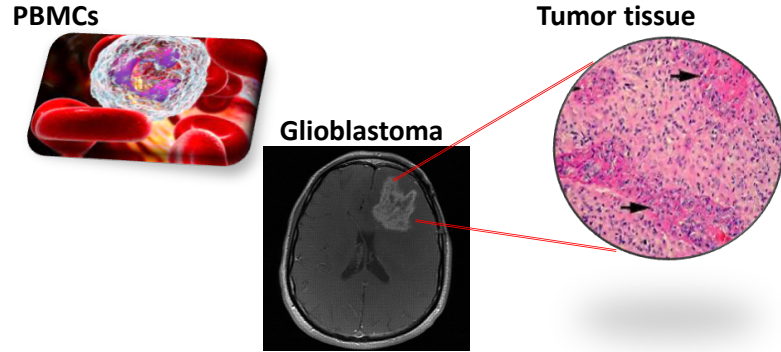


# Evaluable population survival curves: MGMT methylation status and extent of resection

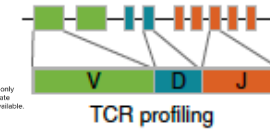
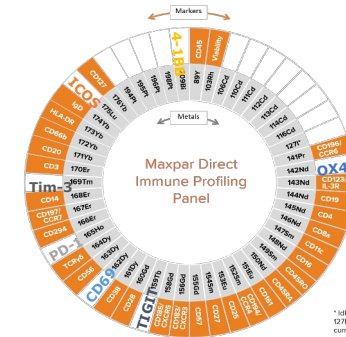


# Immune profiling in collaboration with CIMAC-CIDC

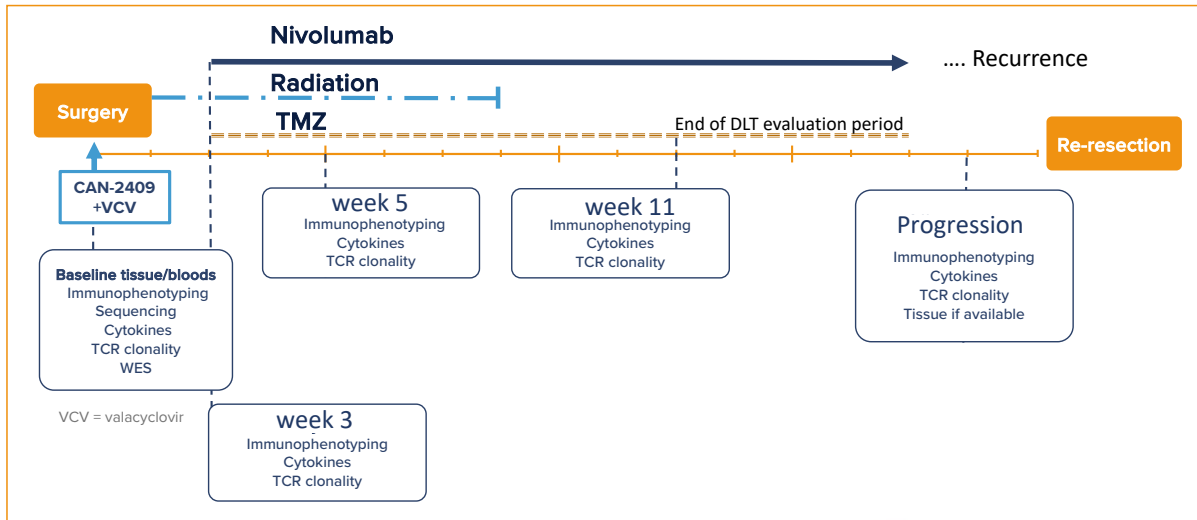
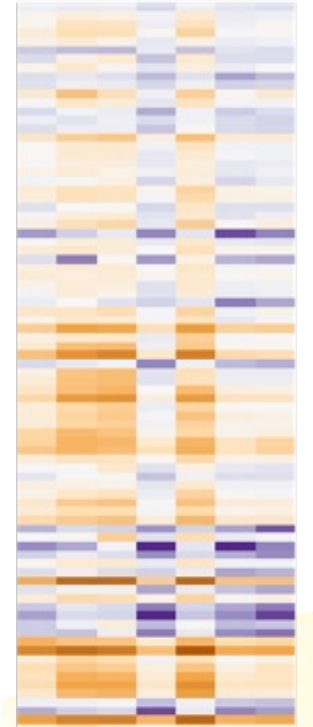
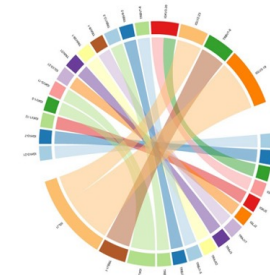
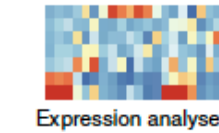
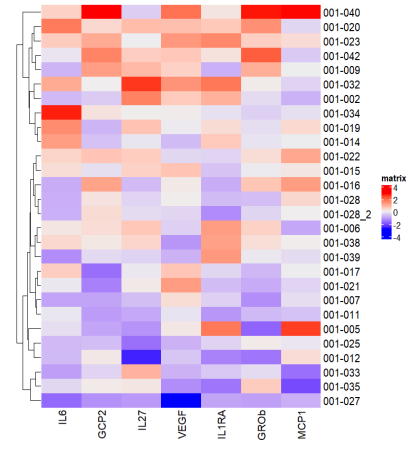
Longitudinal analysis in both tumor and peripheral blood:



- WES
- RNAseq
- TCR sequencing
- mRNA Seq
- OLINK proteomics
- MIBI on brain samples

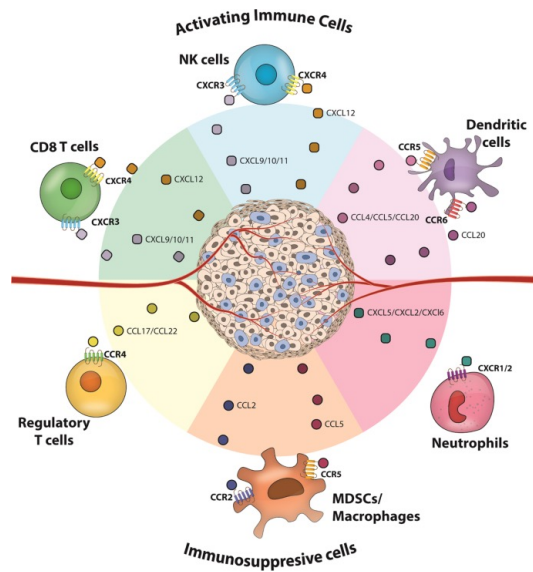


\* full list only 12/21 available currently available.

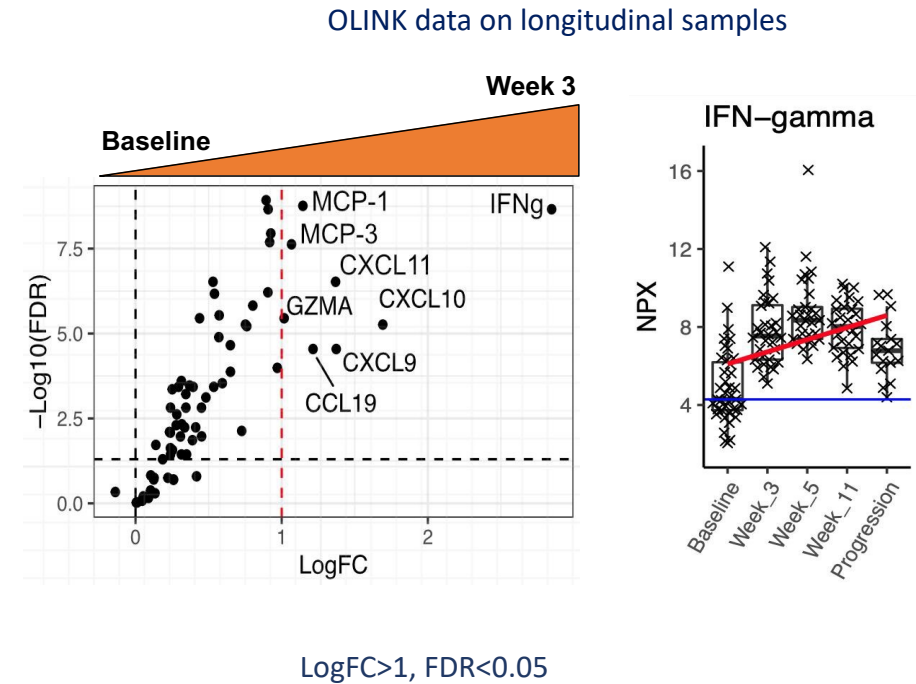
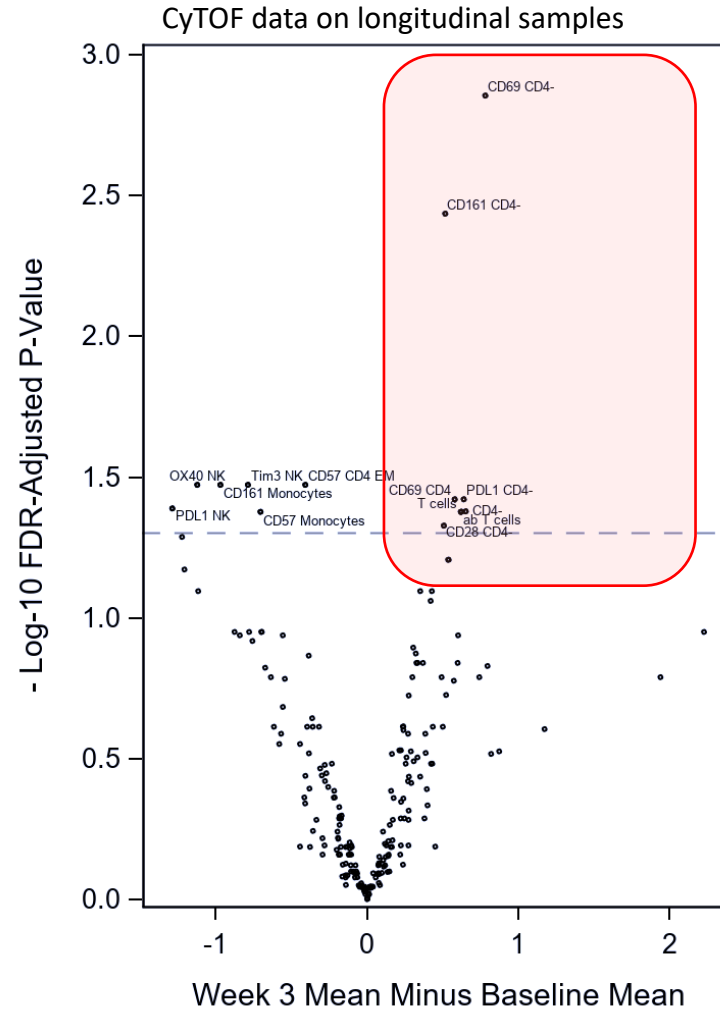


# CAN-2409 injection in the brain elicits strong systemic activation of effector immune response

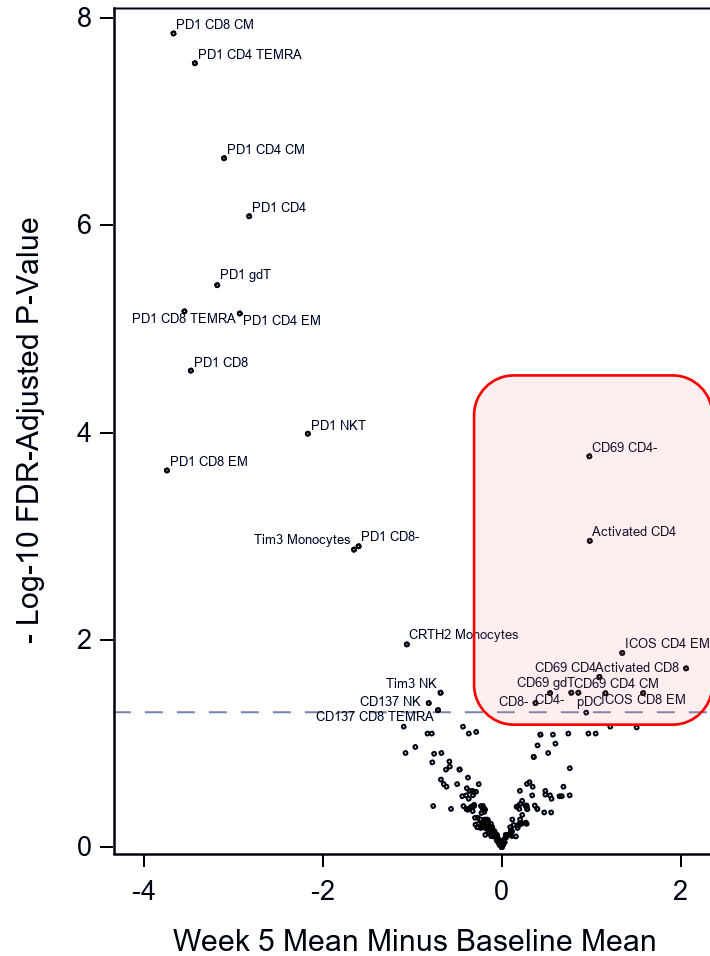
## Key effector cells in antitumoral response



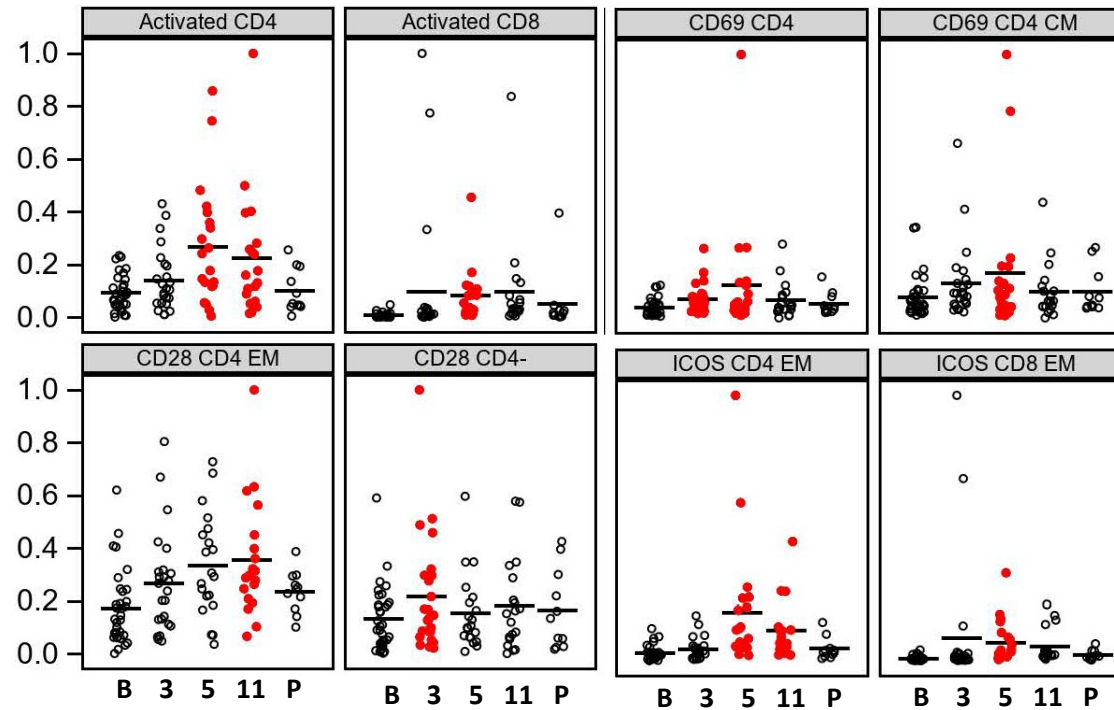
Kohli, K et al. Cancer Gene Ther 2020; 29, 10–21



# Combination of CAN-2409 and nivolumab results in expansion of activated CD4 & CD8 T cells and decreased exhaustion

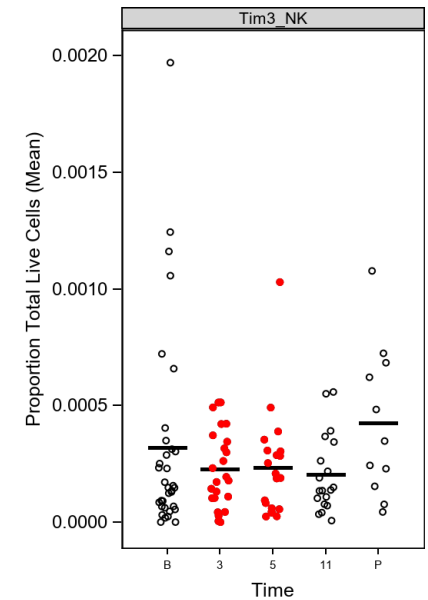


## Increased T cell activation



**Time post treatment (weeks)**

## Decreased exhaustion



FDR adjusted p. value range (0.04- .00095)

**B= baseline**  
**P= progression/off study**

# Conclusions



- Combination of nivolumab and intratumoral CAN-2409 is well tolerated with no DLT observed and no added toxicity to standard of care
- Median overall survival is comparable to historical standard of care outcomes
- Small patient number in different subgroups hampers conclusive outcome analysis
- Extensive longitudinal biomarker analysis supports CAN-2409 ability to activate systemic immune response
- Combination of CAN-2409 and nivolumab supports durable T cell activation and effector function