



Adult Brain Tumor Consortium

Preliminary report of an ongoing 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

Patrick Y. Wen and E. Antonio Chiocca – Dana-Farber Cancer Institute/Brigham and Women's Hospital

Patrick Y. Wen, Laura K. Aguilar, Xiaobu Ye, David Reardon, Wenya Linda Bi, Pierpaolo Peruzzi, Nirav J. Patel, Roy Strowd, Stephen B. Tatter, Ian Y. Lee, Tobias Walbert, James M. Snyder, Steven Brem, Arati Desai, Stephen J. Bagley, Nduka Amankolor, Frank S. Lieberman, Megan M. Mantica, Lenika Lopez, Susan Bell, Andrea G. Manzanera, Francesca Barone, Brian Guzik, Sean Lawler, Lixian Jin, William C. Timmer, Neeraja Danda, Serena Desideri, L. Burt Nabors, Stuart A. Grossman, Estuardo Aguilar-Cordova, Paul P. Tak, E. Antonio Chiocca

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Disclosures

Research Support

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

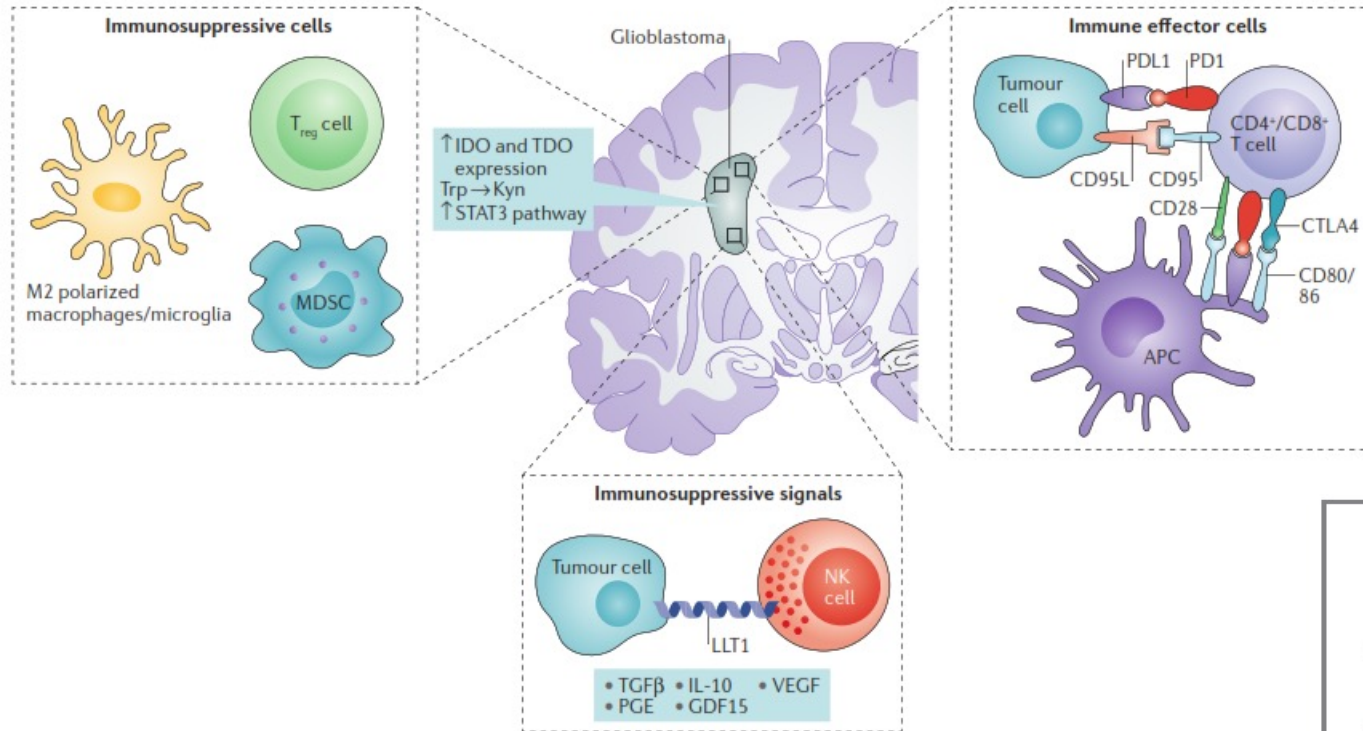
Advisory Board

- Agios, Astra Zeneca, Bayer, Black Diamond, Boston Pharmaceuticals, Elevate Bio, Invax, 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.

Immune system is suppressed in glioblastoma



Glioblastomas make immunosuppressive substances and Tregs are increased

T cells sequestered in bone marrow

- Radiation and temozolomide produce lymphopenia
- Corticosteroids may impact immune response

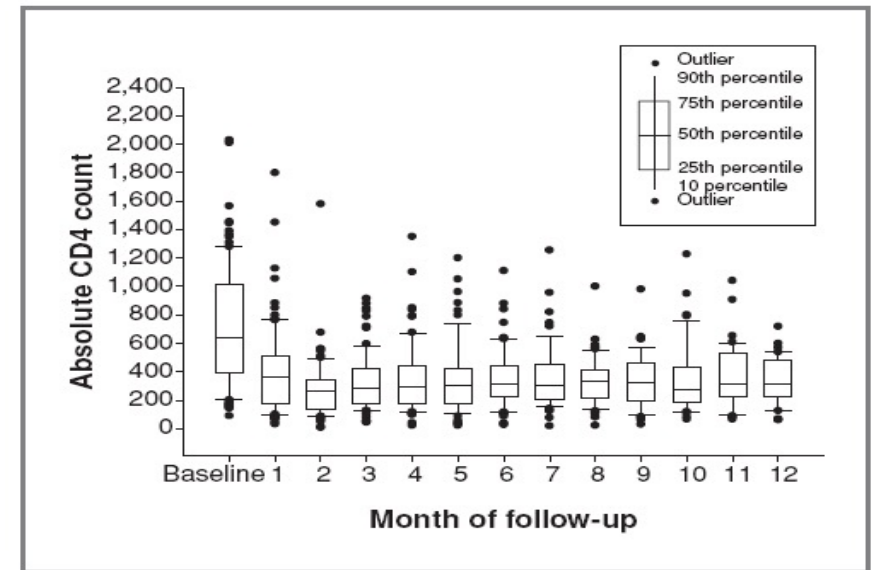


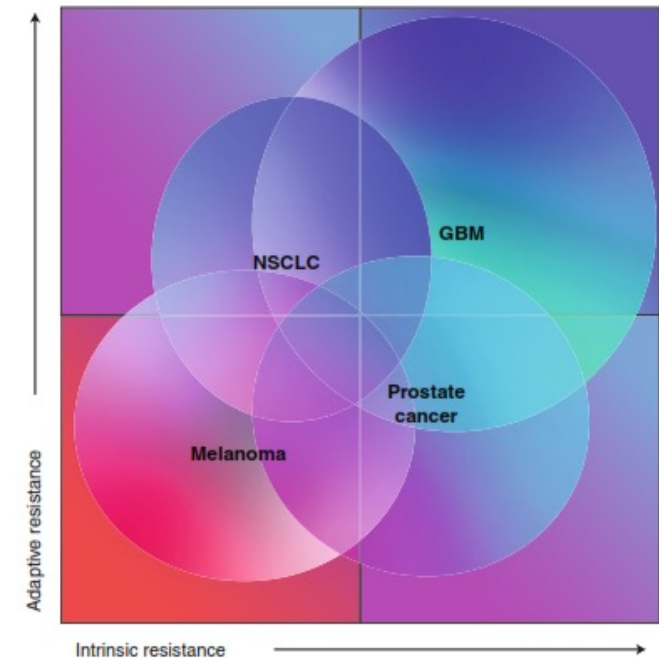
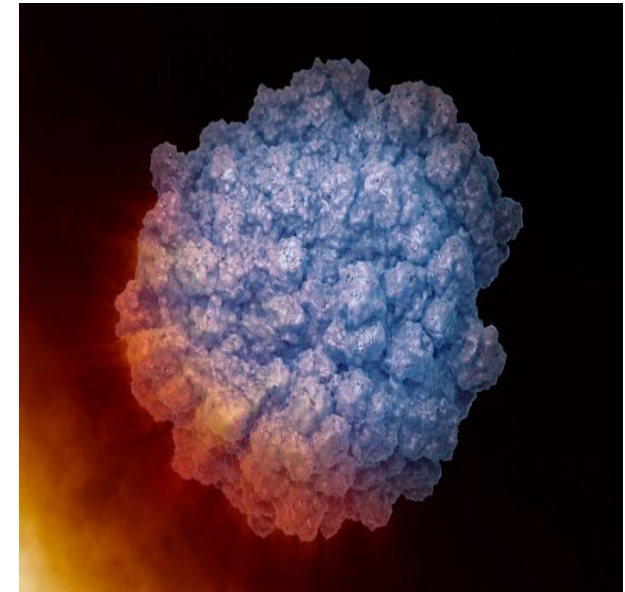
Figure 1. CD4 count trend over time.

Glioblastoma has comparatively fewer T cells; considered a “cold tumor”

Predictors of response to checkpoint blockade

Determinants of Response	Glioblastoma
PDL1-expression	↑ / ↓
High CD8+ T cell infiltration (“hot tumor”)	↓
TCR clonality	↓
High mutational load	↓
High neoantigen load	↓
Copy number loss	↑
Aneuploidy	↑
Immune gene signature (IFN- γ , activated T cells)	↓
hypoxia / lactate signature	↑

Jackson Nat Immunol 2019; 20:1100-1109
 images adapted from Wellcome Images by Mark Mazaitis;



CAN-2409 creates a “hot” tumor microenvironment

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

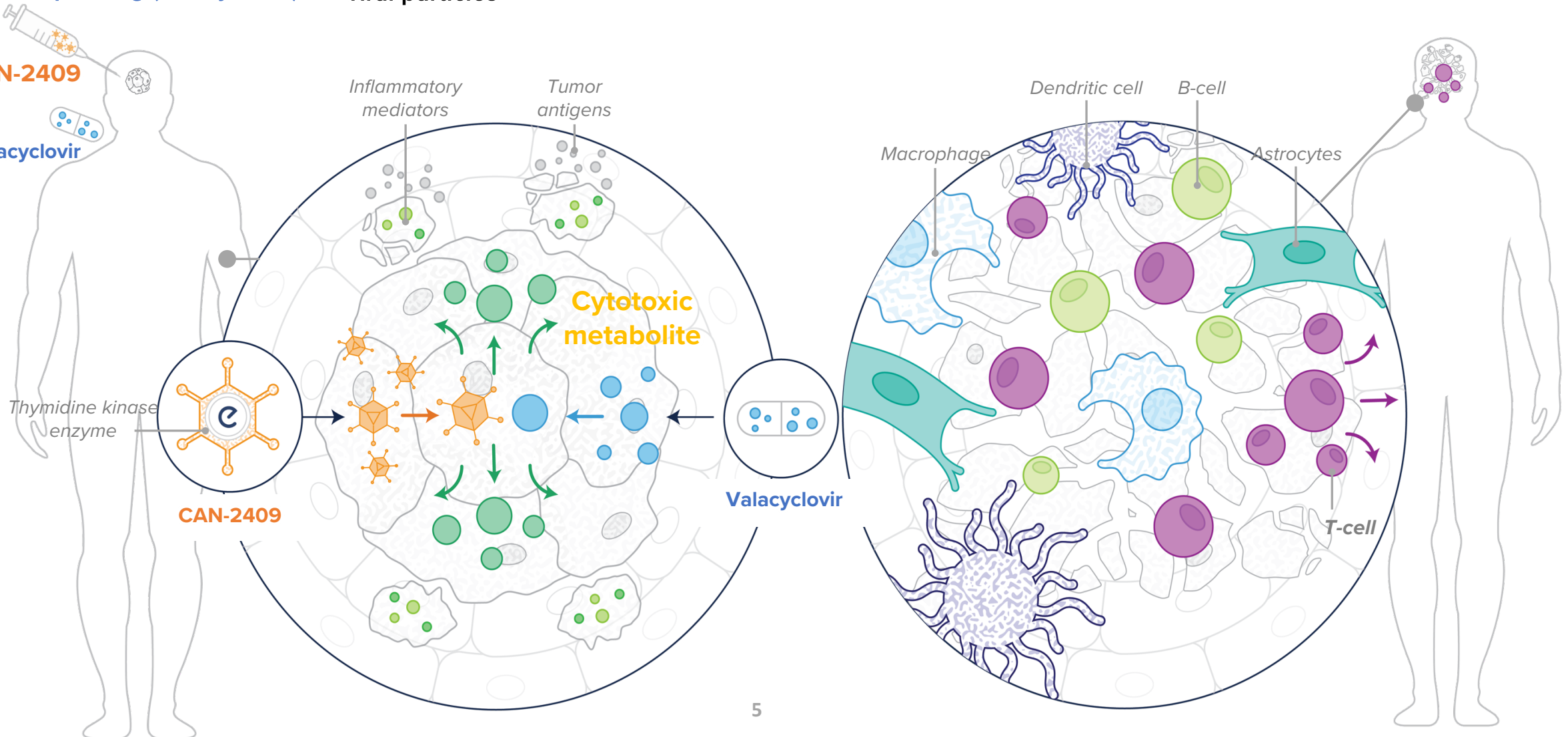
2. Localized cytolytic mechanism combined with proinflammatory viral particles

3. CAN-2409 induces tumor infiltrating lymphocytes

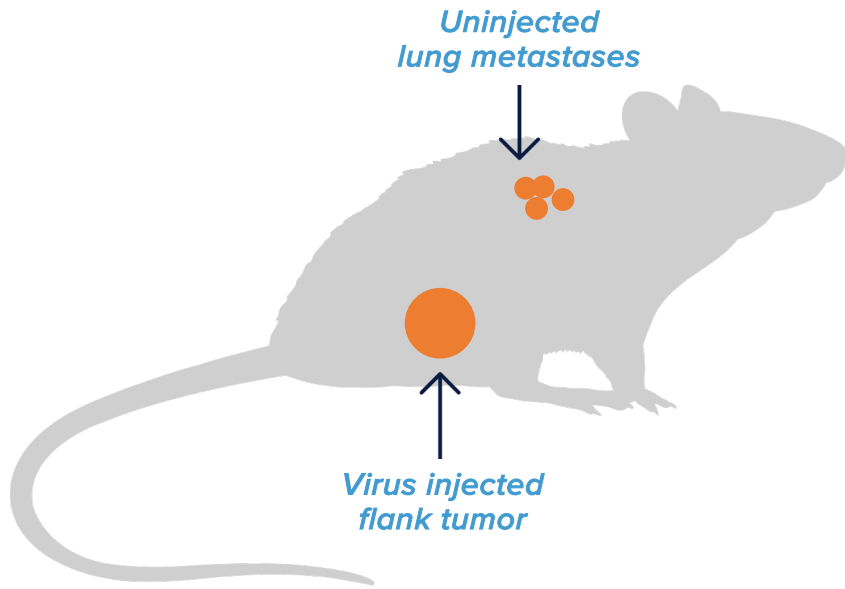
4. Local immunization yields systemic anti-tumor response

CAN-2409

Valacyclovir



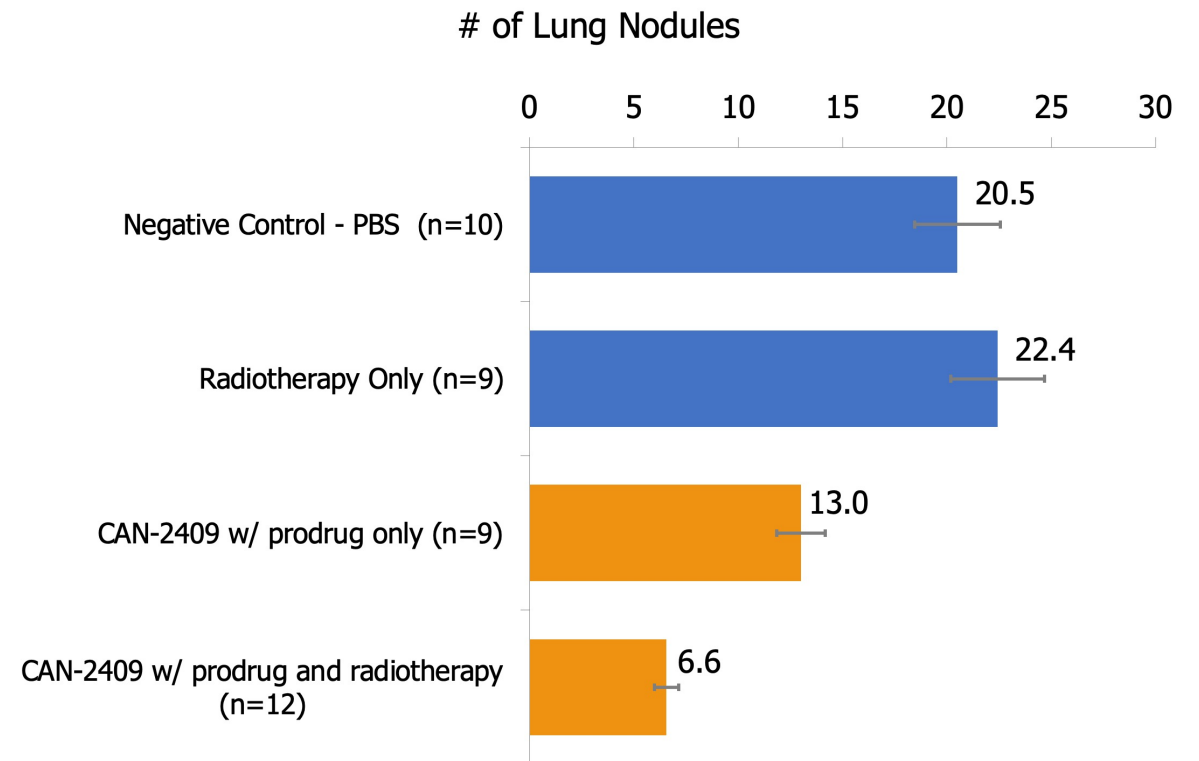
CAN-2409 treatment induces immune response to cancer in injected tumor and uninjected metastases and synergizes with radiation



Mice receive one of four treatment regimens

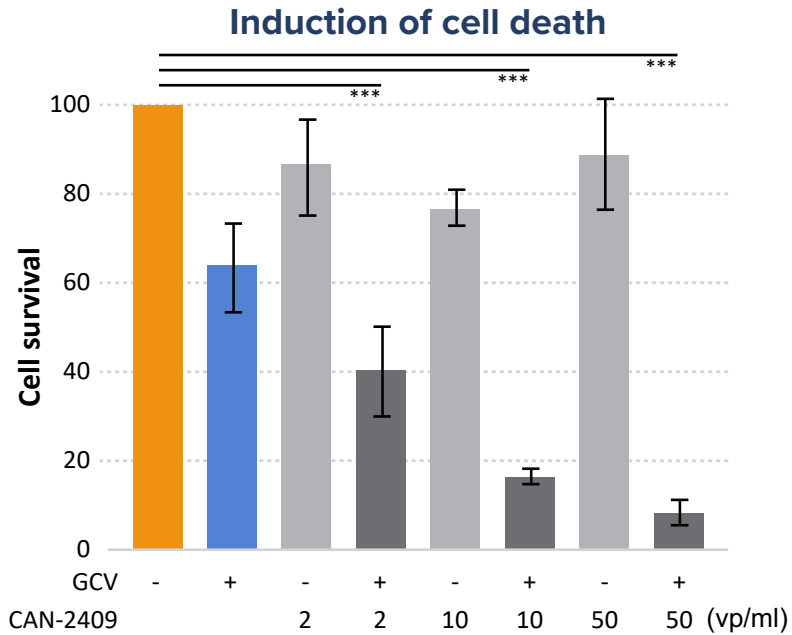
1. PBS
2. Radiotherapy
3. CAN-2409 with prodrug
4. CAN-2409 with prodrug plus radiotherapy

Decrease in uninjected lung metastases



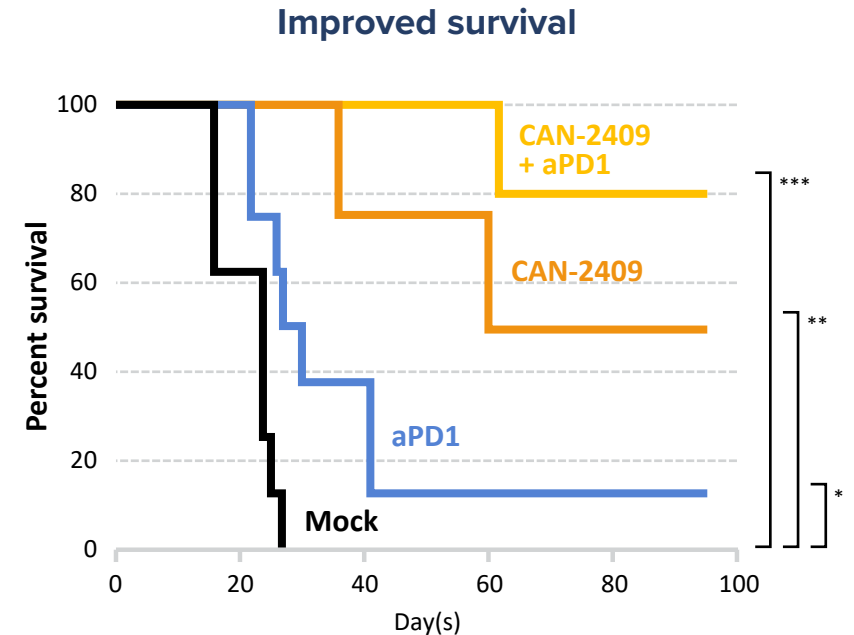
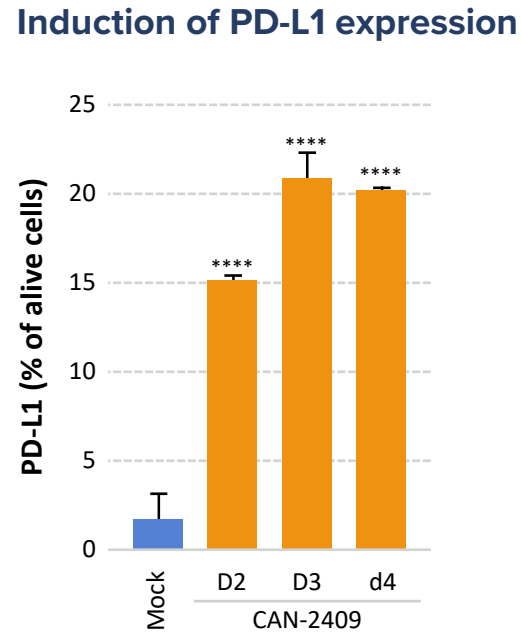
Model of prostate cancer: RM-1 cells in C57BL/6 mice

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



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 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.

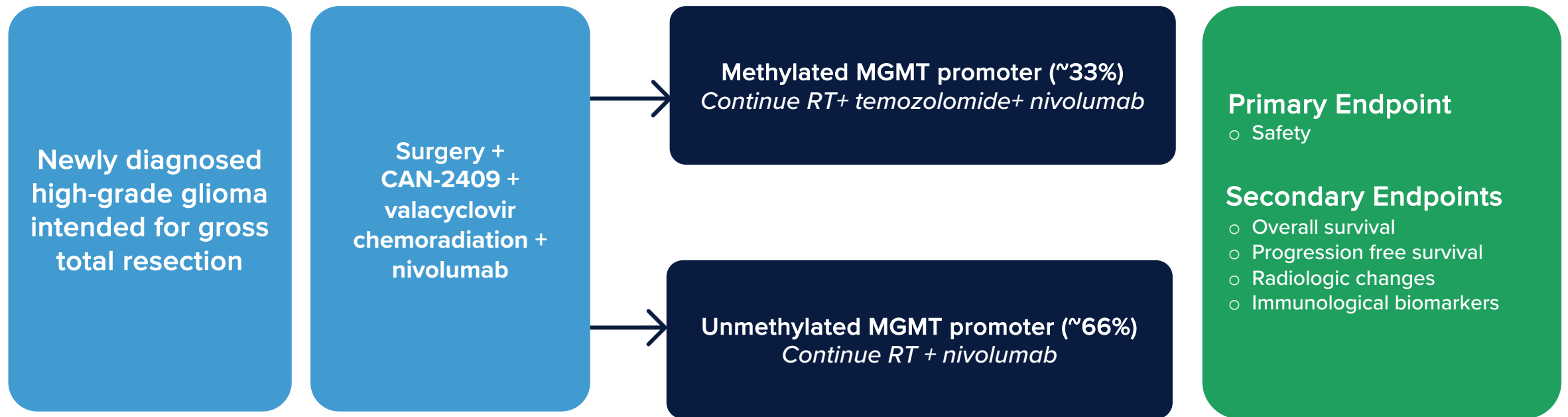


Bristol Myers Squibb™



Study Chair: Patrick Y. Wen and E. Antonio Chiocca

Participating sites: Dana-Farber Cancer Institute/Brigham, Henry Ford Cancer Center, John Hopkins University, University of Pennsylvania, University of Pittsburgh Medical Center, Wake Forest University



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)

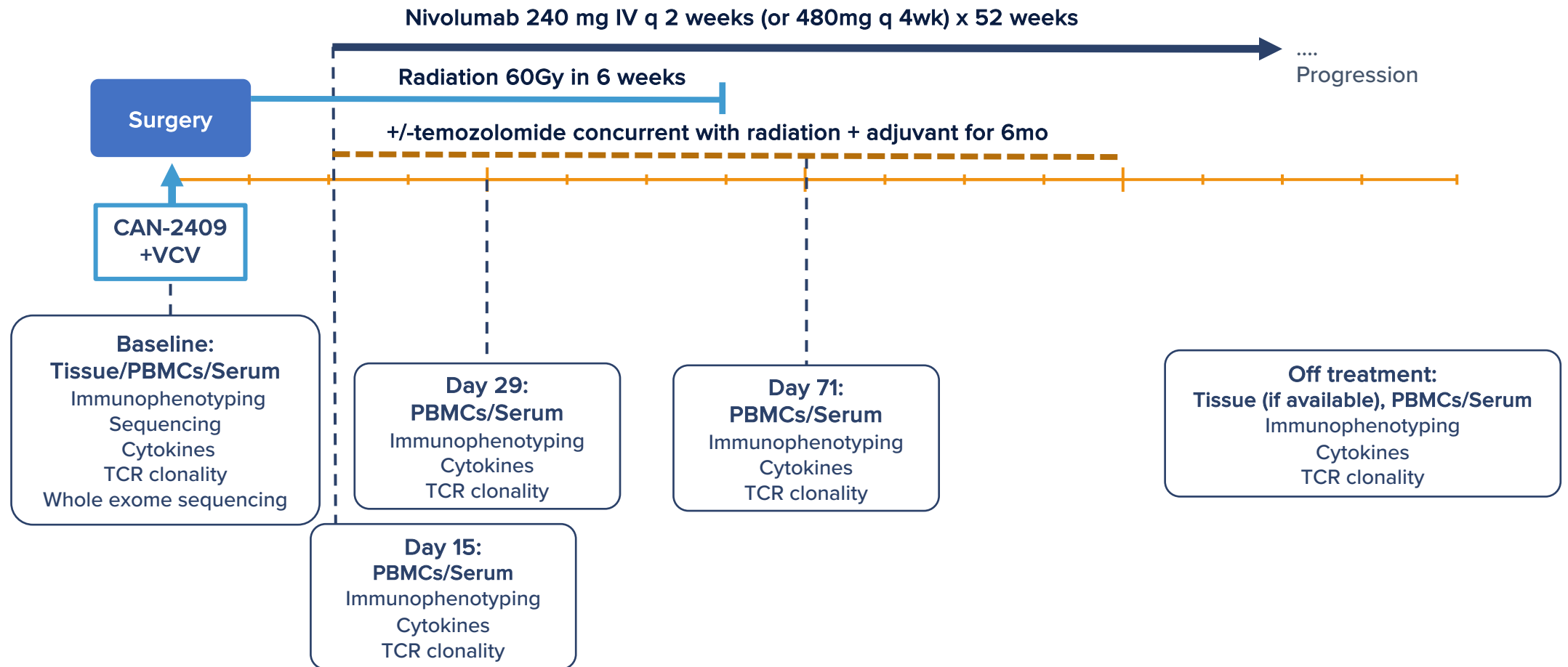
If DLT rate $\leq 33\%$, proceed with next set of 9 patients

Target ~12 methylated and ~24 unmethylated evaluable patients

NCT03576612

Phase 1 clinical trial treatment and evaluation schema

- Patients enrolled prior to surgery with diagnosis of HGG confirmed in operating room prior to injection
- CAN-2409 (1ml total) injected by neurosurgeon into 10 sites in the tumor bed



CAN-2409 2.5×10^{11} vp in 1ml
 VCV=valacyclovir 2 grams TID x 14 days
 Treatment as in Wheeler L et al, Neuro-onc 2016 18:1137-1145.

PBMCs = Peripheral blood mononuclear cells

Patient demographics

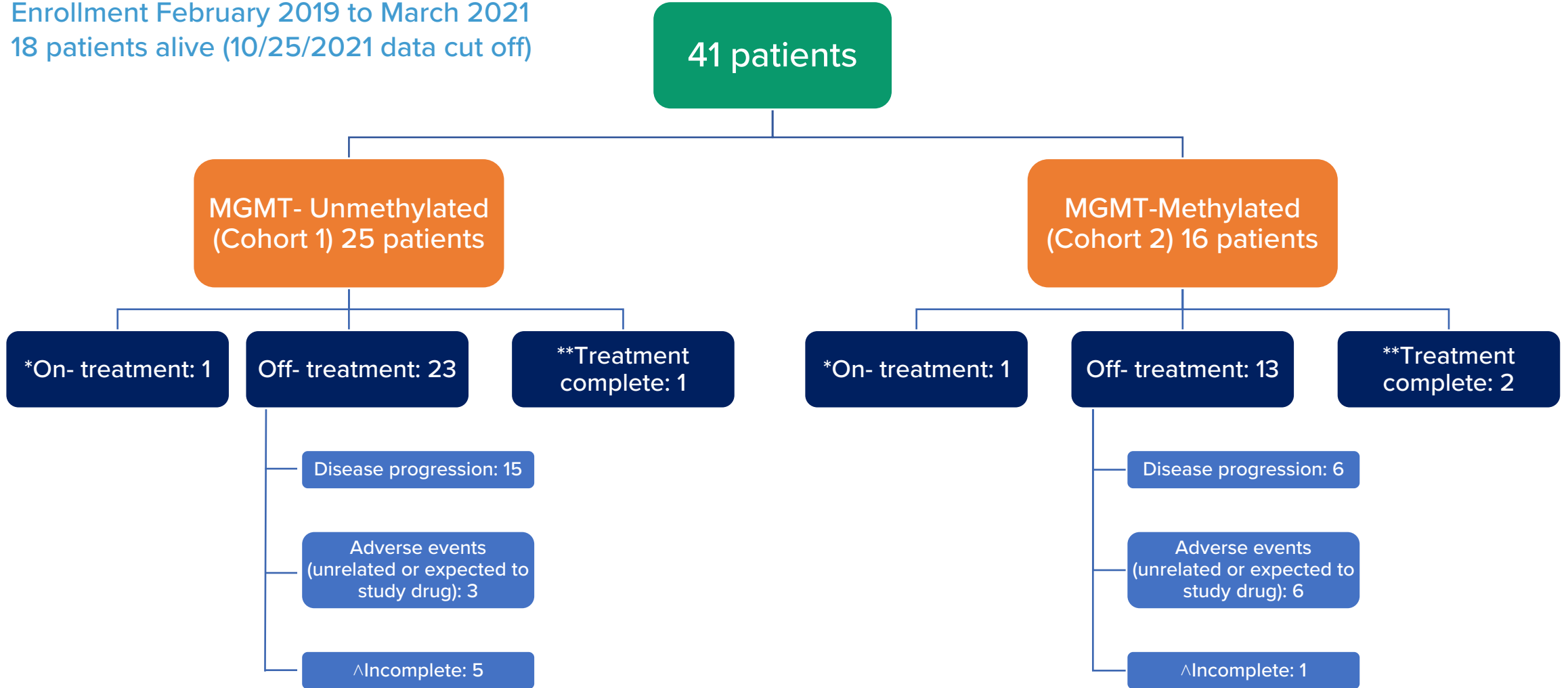
Number of patients: 41	
Characteristic	N (%)
Age	
Median age (years)	62
Range	28-81
Sex	
Female	14(34)
Male	27(66)
Race	
White/Caucasian	34(83)
Black/African American	3(7)
American Indian or Alaska Native	1(2)
Asian	1(2)
Not reported	2(5)
Ethnicity	
Not Hispanic or Latino	38(93)
Hispanic or Latino	1(2)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

Number of patients: 41	
Characteristic	N (%)
KPS (Baseline)	
Median KPS	90
Range	80-100
MGMT	
Methylated	16(39)
Unmethylated	25(61)
IDH	
Wild type	37(90)
Mutant	2(5)
Unknown	2(5)
Histopathologic diagnosis	
Glioblastoma	40(98)
Diffuse astrocytoma	1(2)
Type of resection	
Gross total resection	30(73)
Subtotal resection	11(27)

High dose (8 mg) corticosteroids used in ~50% of patients

CONSORT diagram

Enrollment February 2019 to March 2021
18 patients alive (10/25/2021 data cut off)



**Still on nivolumab*

***Received 26 nivolumab infusions*

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

Safety of the combination of CAN-2409, valacyclovir and nivolumab

- There were no 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 below

Most common adverse events occurring in >10% of patients

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	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	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	6 (15)
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

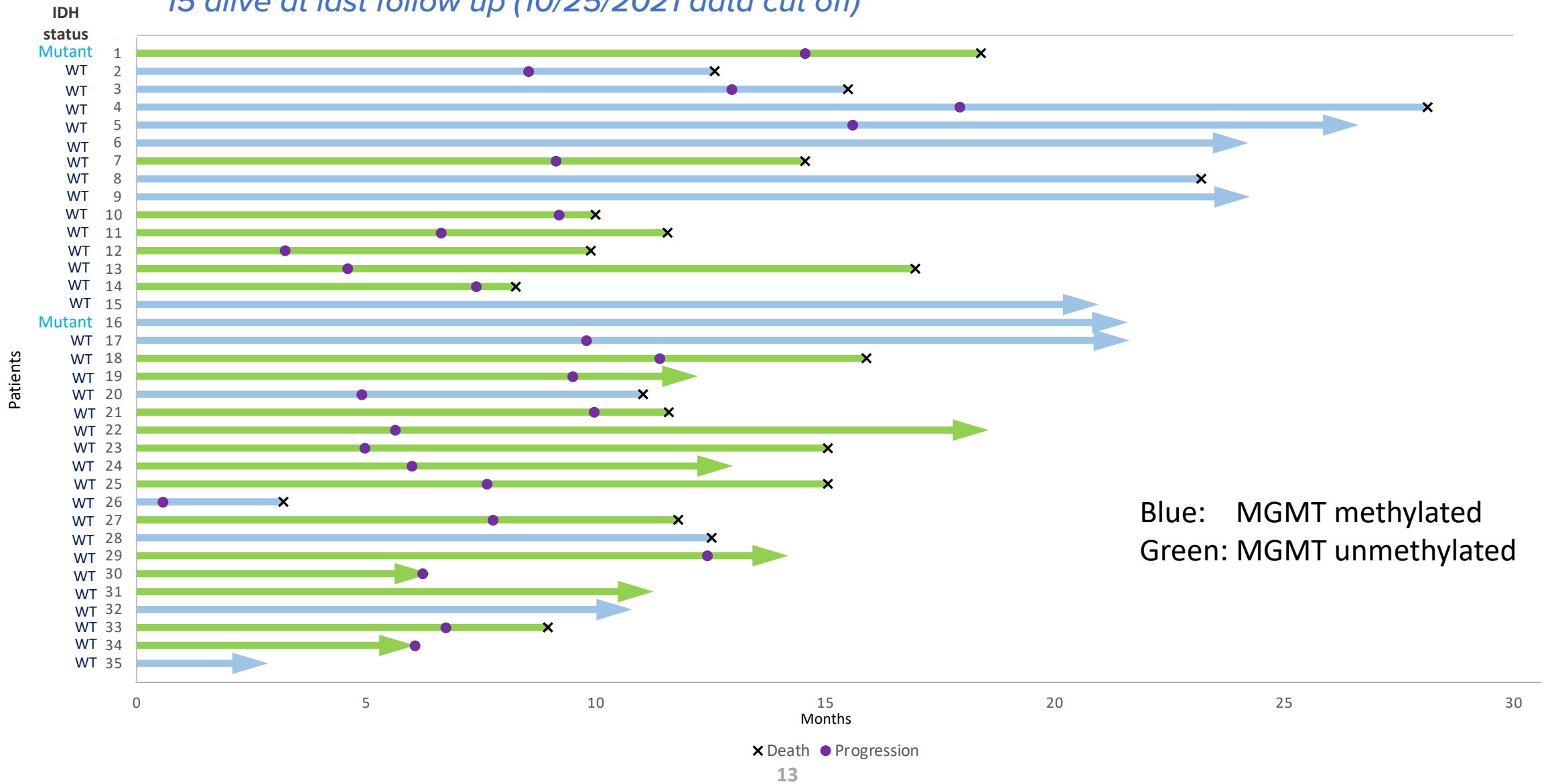
Event	CTC grade		Total=41 N (%)
	3	4	
Neutrophil count decreased	1 (2)	1 (2)	2 (5)
Acute kidney injury	2 (5)	0	2 (5)
Hypertension	2 (5)	0	2 (5)

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)

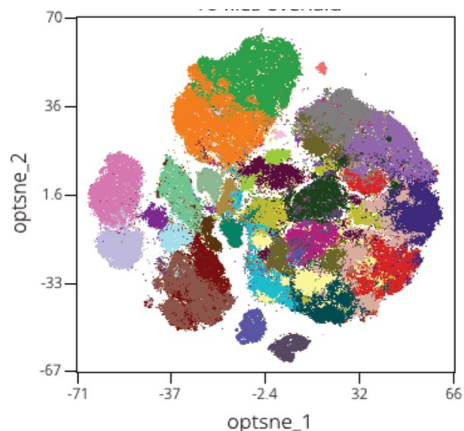
Swimmer plot of 35 evaluable patients

15 alive at last follow up (10/25/2021 data cut off)

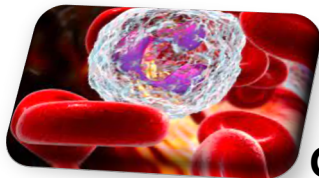


Immunological profiling in collaboration with Immuno-Oncology Biomarkers Network

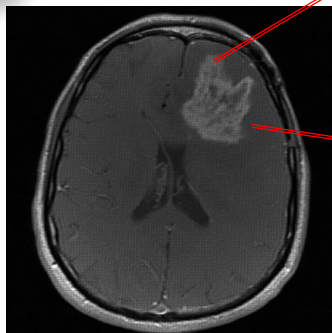
CytoF – Stanford University



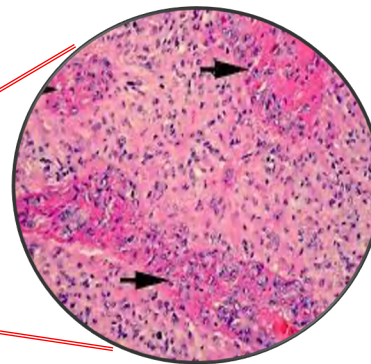
PBMCs



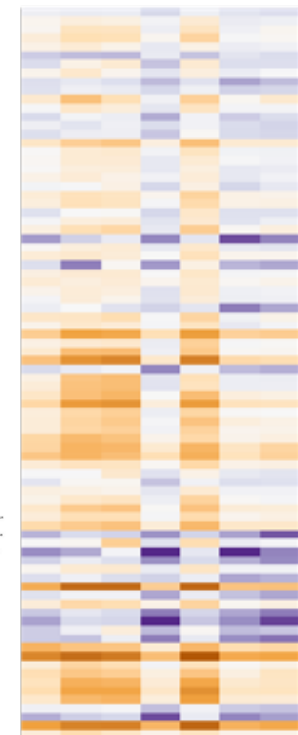
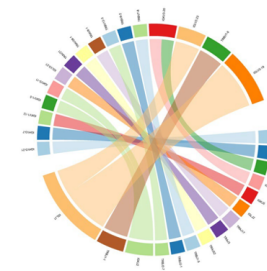
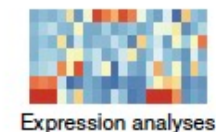
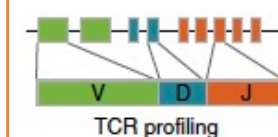
Glioblastoma



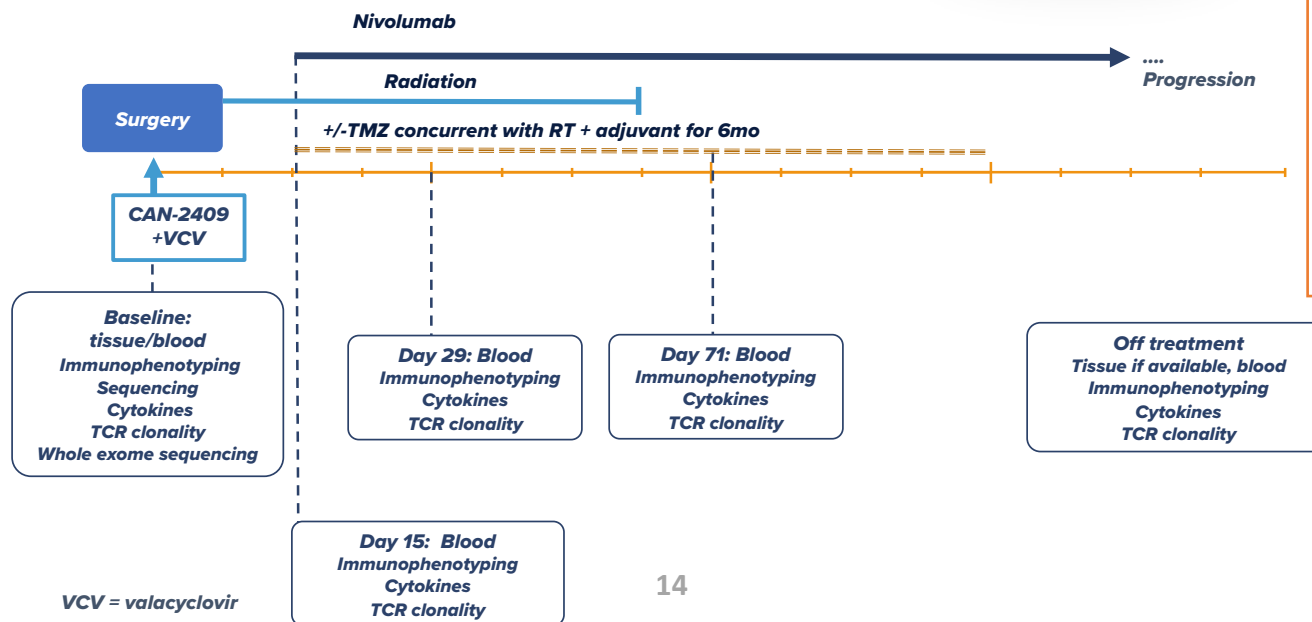
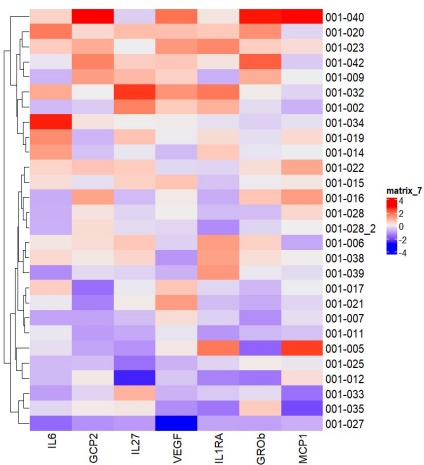
Tumor tissue



TCR sequencing WES, mRNA Seq - MD Anderson



Cytokine profiling Mount Sinai





Conclusions

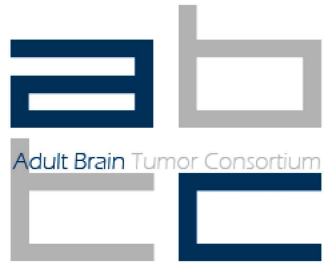
- The combination of CAN-2409 + nivolumab + SOC was well tolerated.
- Large number of patients censored preclude evaluation of survival at this preliminary data analysis. Clinical follow-up continues.
- Immunological profiling may provide more mechanistic insight and could help to identify biomarkers predictive of response to treatment.

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- Steven Brem, Arati Desai, Stephen J. Bagley and the study team at University of Pennsylvania
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- William C. Timmer, NCI
- Laura K. Aguilar, Lenika Lopez, Susan Bell, Andrea G. Manzanera, Francesca Barone, Brian Guzik, Estuardo Aguilar-Cordova, Paul P. Tak, Candel Therapeutics, Inc.
- NIH/NCI UM1 CA 137443 Grossman/Wen/Nabors (Co-PIs), Adult Brain Tumor Consortium

- Patients and their families

Thank You!



**Adult Brain
Tumor Consortium**

Questions?

**Contact Patrick Y. Wen at
patrick_wen@dfci.harvard.edu**

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