DCVax®-L: Mechanism of Action, Immunological Effects, and Clinical Trial External Controls Methodology

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Overview

1. Introduction to DCVax®-L
2. Mechanism of Action
3. Immune Monitoring
4. DCVax®-L Phase III Trial -- External Controls
5. Compassionate Use -- Observations
6. Conclusions

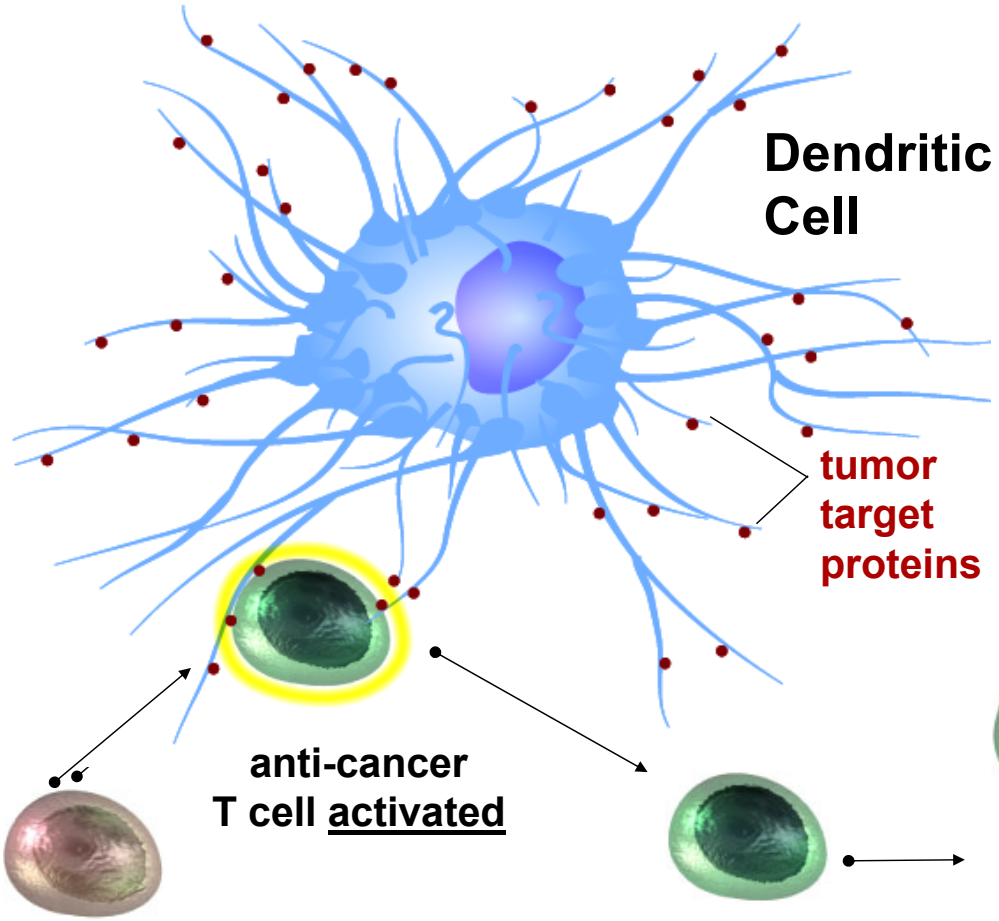
DCVax®-L Introduction

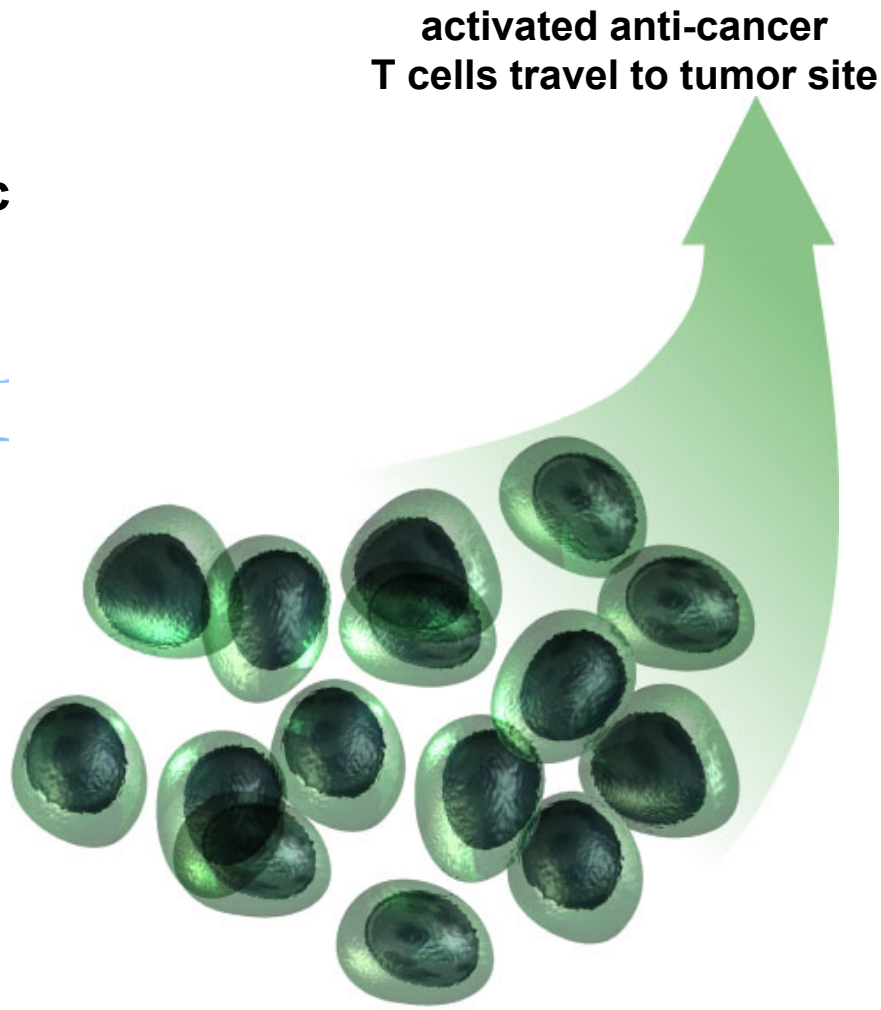
- DCVax®-L is comprised of autologous dendritic cells (DCs) loaded with autologous tumor cell lysate
  - Uses dendritic cells, which are the master cells of the immune system
    - DCs instill both **targeting** and **direction** of the response
  - Uses tumor cell lysate to ensure a **broad-spectrum** immune response against multiple antigens
  - Uses lysate from patient's own tumor to ensure **correct antigens targeted**
- DCVax®-L treatment is intended as adjuvant treatment following surgery
- DCVax®-L has been used to treat ~600 patients with GBM, and tens of patients with other cancers
- Phase III trial showed association between DCVax-L treatment and extended survival *(L. Liau et al., JAMA Oncology, January 2023)*
- Manufacturing takes 8 days, and produces several years of doses, which are cryopreserved. The personalized doses are then "off the shelf" throughout the treatment regimen.

Mechanism of Action

DCVax-: Mechanism of Action

Multiplier effect





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Antigen Uptake and Presentation

Proteomics analyses were conducted on the following materials to determine protein content and diversity:

- Tumor lysate
- Unpulsed DCs
- DCs pulsed with tumor lysate
- Peptides eluted from pulsed DCs

Example findings from a **single sample**:

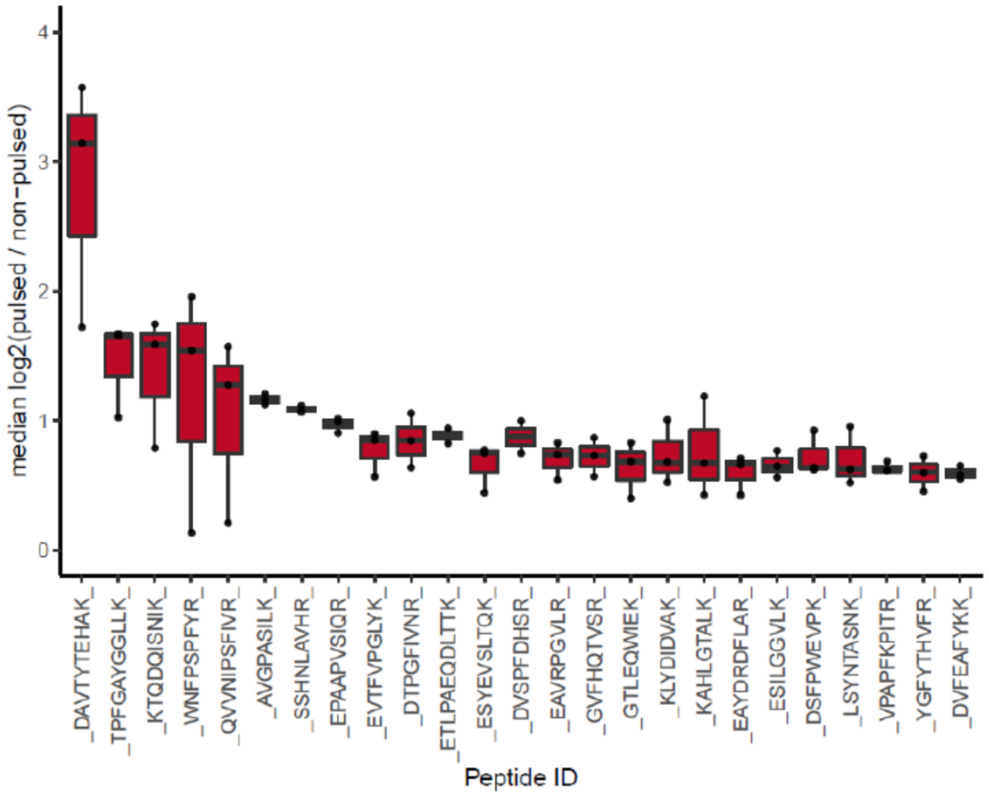
- 25,109 MHC class I-associated peptides
- Of these, 4,386 at least 1.5-fold more abundant on DCs after pulsing

- 12,940 MHC class II-associated peptides
- Of these, 7,224 were at least 1.5-fold more abundant on DCs after pulsing

DCVax-L Immunopeptidomics: MHC Class I

399 tumor-associated peptides (~9 mers) presented by MHC Class I

Examples of peptides highly enriched post lysate pulsing:



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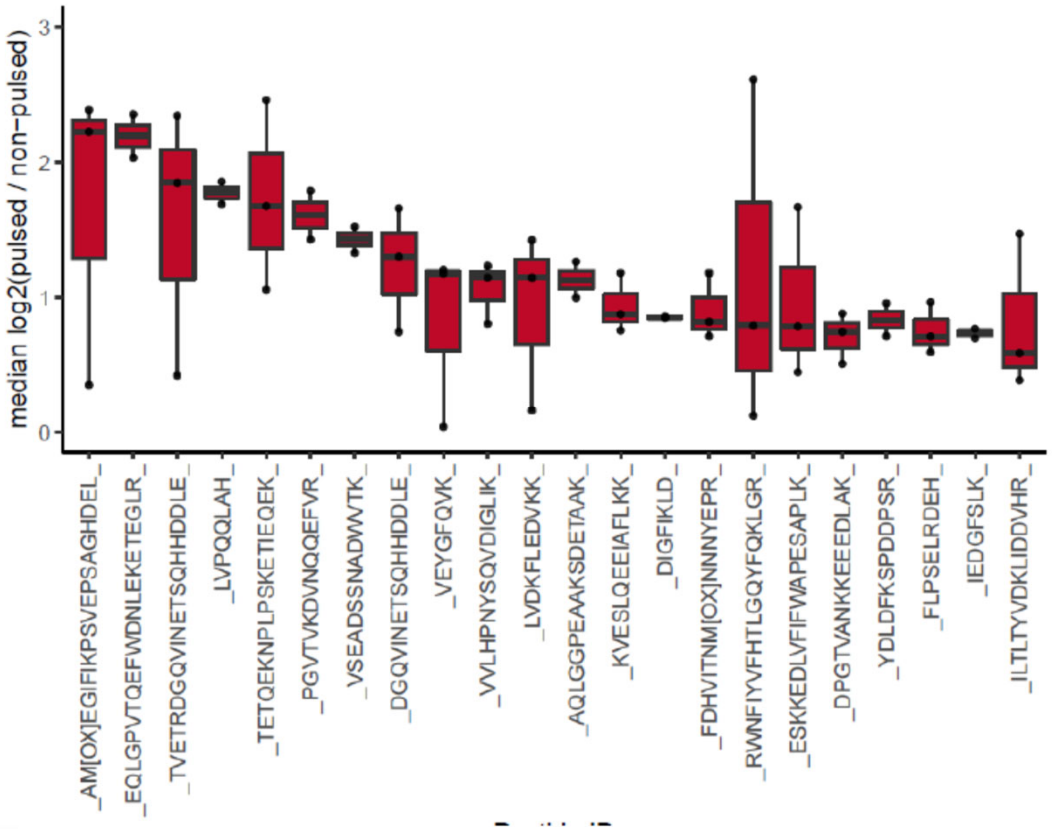
DCVax-L Immunopeptidomics: MHC Class II

220 tumor-associated peptides (~16 mers) presented by MHC Class II

Examples of peptides highly enriched post lysate pulsing:



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DCVax-L Immunopeptidomics

Examples of peptides in pulsed DCs that were previously identified in GBM:

Tubulin beta-4A chain	Absent from normal tissues - known to be present in GBM. Marker of progression in multiple cancers. Known hyper expression in CaPro
Dematin	Inhibitory protein in GBM
Dihydropyrimidinase-related protein 4	Common p53 target in cancer cells. Known survival gene in GBM
PREX2	Mutations promote proliferation and invasion of melanoma, HCC and CaPanc. Regulates GBM proliferation in vitro
Zinc finger X-chromosomal protein	Upregulates cMyc to maintain glioma CSC Promotes cell growth and mets in glioma , laryngeal scc, gallbladder cancer and CaBr. Confers self renewal properties through activation of NANOG and SOX2.
Protein enabled homolog	Actin regulator over-expressed in GBM, CaBr, CRC, CaOva
G protein-regulated inducer of neurite outgrowth 1	Detected in CPTAC GBM discovery study. Negative prognostic marker for NSCLC.
Disheveled-associated activator of morphogenesis 2	Promotes gliomagenesis

DCVax-L Immunopeptidomics

Examples of peptides in pulsed DCs that were previously known to be associated with other tumors (TAA) but not previously identified in GBM:

E3 ubiquitin-protein ligase TRIM68	Expressed in multiple cancers.
Spermatogenesis-associated protein 2	Associated with poor prognosis in CaOva
Mammalian ependymin-related protein 1	Stage and metastasis related in CaBladder
Metallophosphoesterase 1	HCC malignancy associated
Agrin	Proteoglycan involved in many human cancers. Mediates angiogenesis in TME. Promotes progression in NSCLC
Integrin beta-4	Known cancer antigen in multiple cancers
Cyclin-Q	AKA CDK10. Known TAA but function controversial
Protein ABHD16B	TAA in multiple tumors
Tyrosine-protein kinase Fes/Fps	Proto-oncogene
Beta-actin-like protein 2	Mediator of tumor progression.

Proteomic Analyses - Observations

- The DCVax-L lysate preparation process releases multiple cancer-related proteins from which immunogenic cancer-specific peptides can be processed.

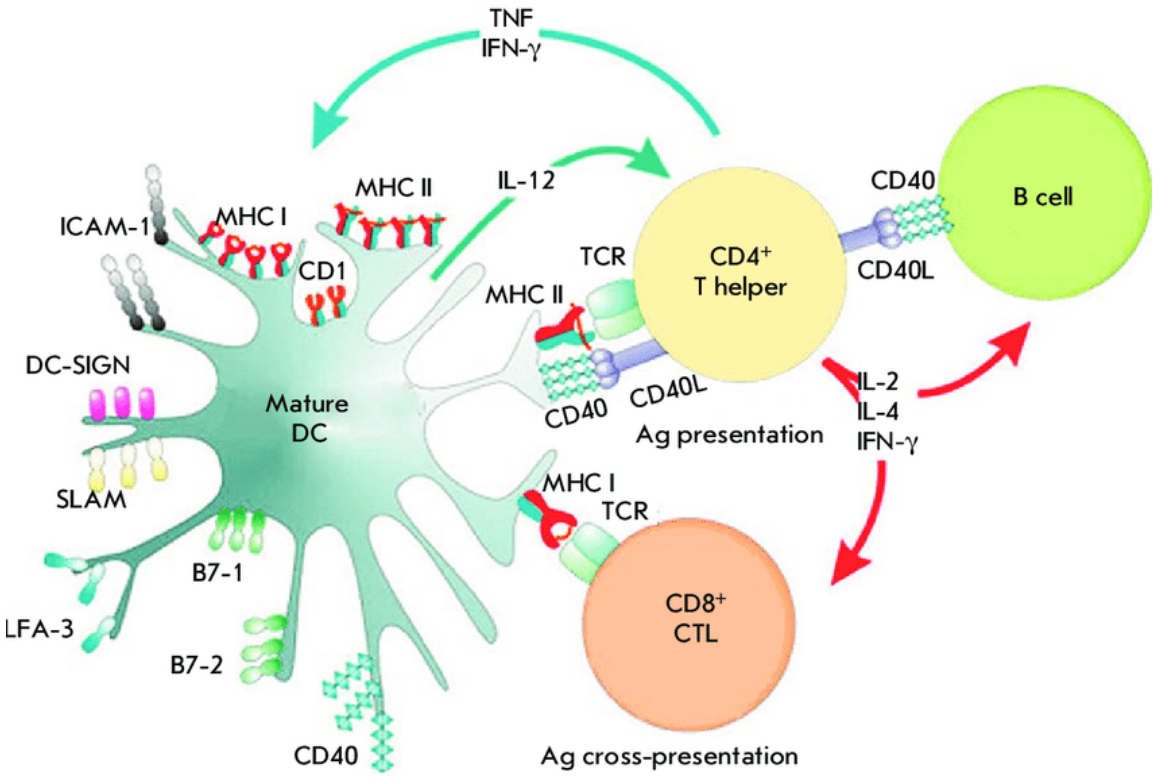
- DC Vax-L preparations pick-up, process and **present <u>hundreds</u> of tumor-specific peptides to T cells** through MHC class I and class II for a **broad spectrum** of immune responses.

- DC Vax-L presents peptides from both
  - (i) known GBM associated tumor antigens and
  - (ii) TAA antigens which have <u>not</u> been reported in GBM before

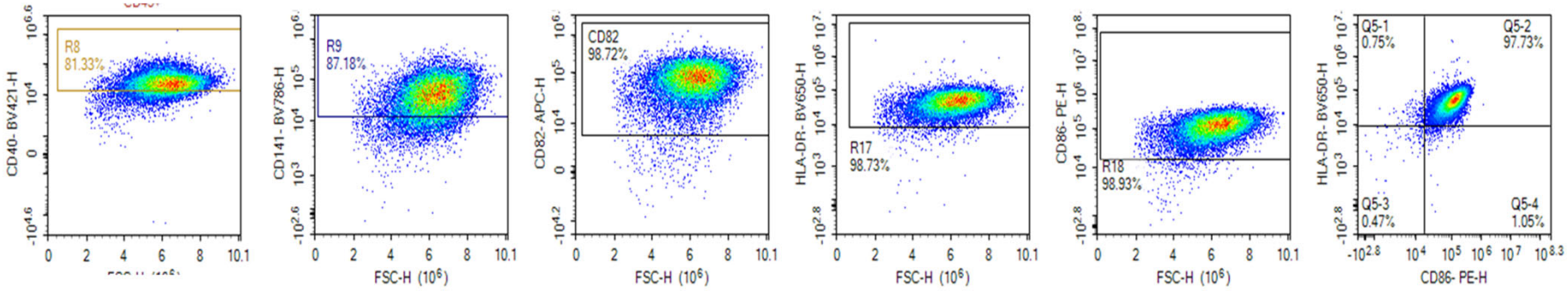
- The presentation of MHC class II peptides to CD4 T cells suggests that DC Vax-L is likely to generate T cell memory responses *in vivo.*

T cell Stimulation by DCs

- Lysate-loaded DCs induce a primary T cell response through a combination of different signals:
  - Interaction of the T cell receptor (TCR) with multiple peptide antigens associated with MHC molecules
  - Costimulatory signals such as CD40, CD80, CD86
  - Cytokine production



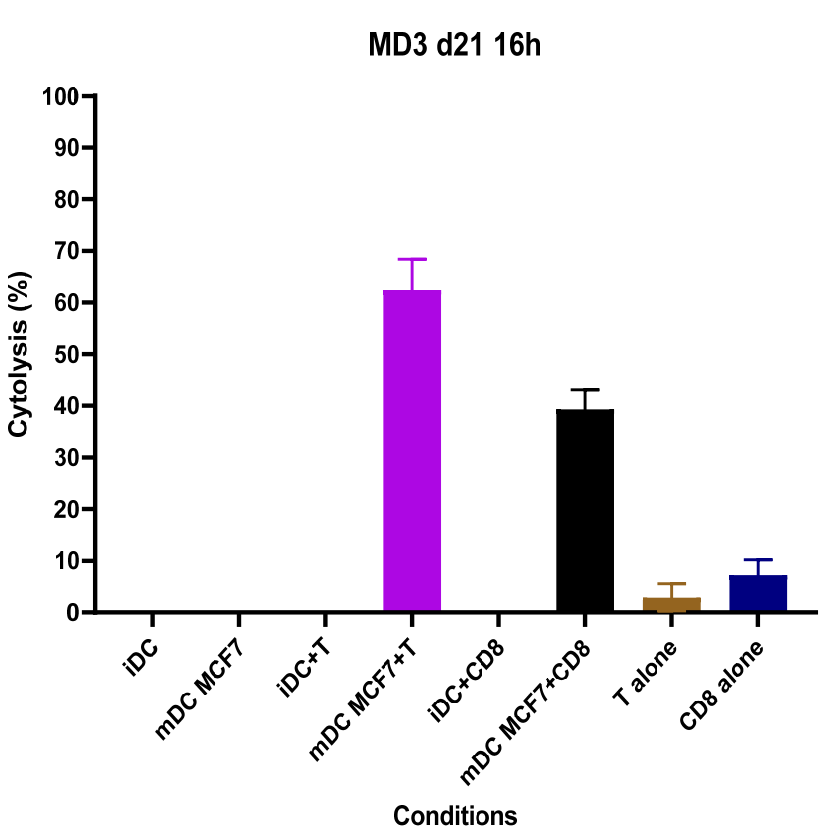
Costimulatory Molecules

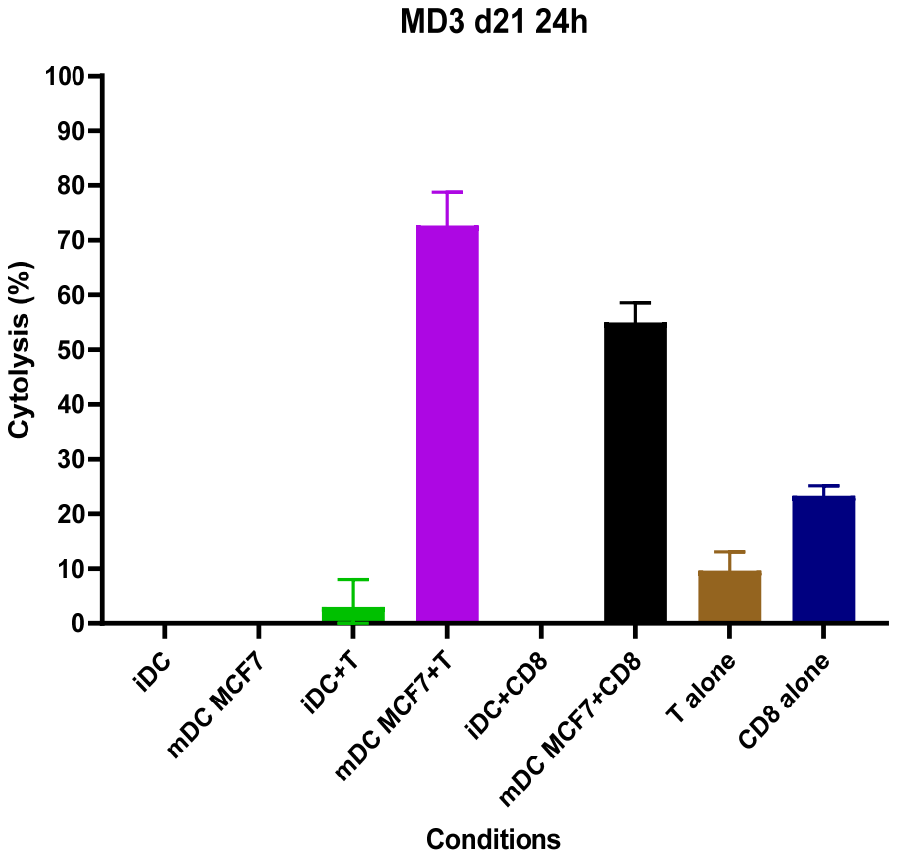


The dendritic cells in DCVax-L express the following (co-)stimulatory molecules (among others):

- **CD40** – interacts with CD40-L on the T cells
- **CD141** – involved in antigen presentation
- **CD82** – stabilizes DC-T cell interactions
- **CD86** – interacts with CD28 in the stimulation of helper T cells
- **CD80** – interacts with CD28 and CTLA-4 in the stimulation of helper T cells
- **HLA-DR** – involved in antigen presentation to helper T cells
- **CD83** – marker for CD maturation

Induction of CTL Activity





Killing of target cells is observed if T cells were stimulated by DCs loaded with tumor cell lysate

Franz and Lowdell, 2022

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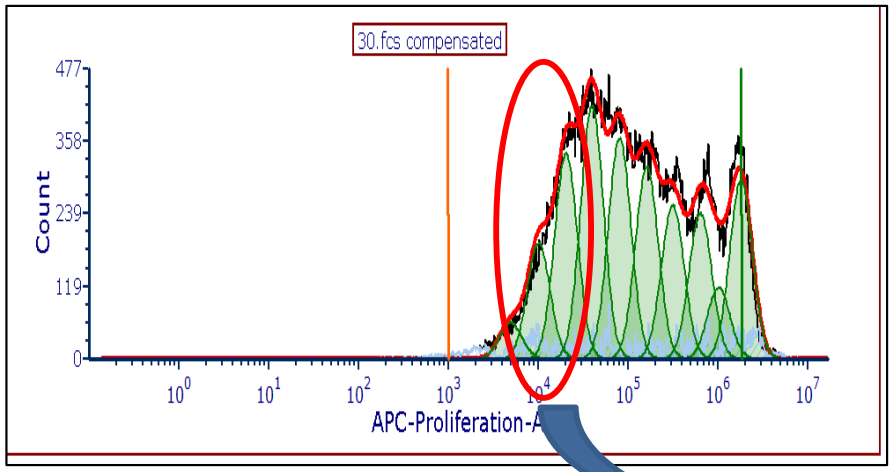
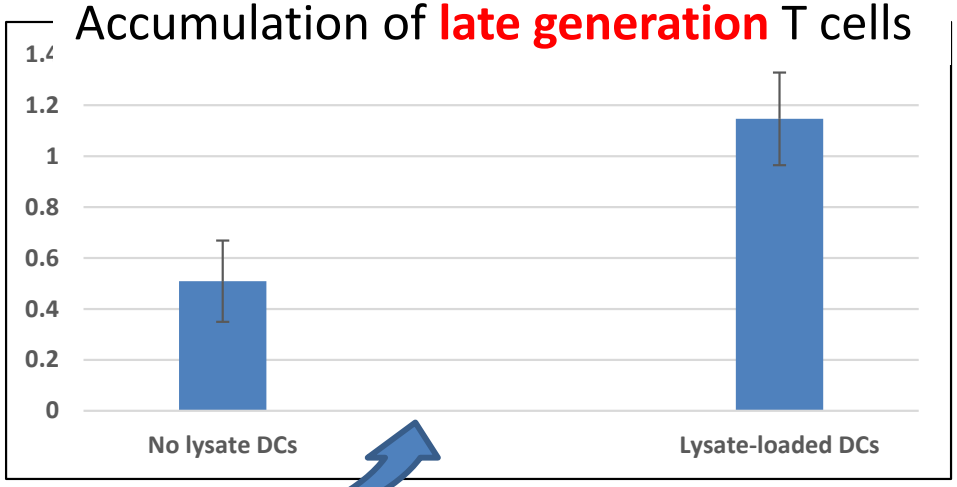
Enhanced T Cell Stimulation

Multiplier Effect





Number of divisions

DCs stimulate T cell proliferation leading to multiple 'generations' of T cells

Addition of tumor cell lysate to the DCs results in more T cell divisions

Tumor lysate-loaded DCs (DCVax-L) have acquired additional T cell stimulatory capacity, resulting in more 'late generation' T cells to fight the tumor

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Lekhana Bhandary and Andrew Kozbial, 2022

DCVax-L Mechanism of Action: Summary

- The DCs in DCVax-L express the requisite co-stimulatory molecules for productive interaction with T cells
- The DCs also express CD141, a molecule involved in effective antigen presentation to T cells
- Incubation of the DCs with tumor cell lysate adds additional T cell stimulatory capacity to the DCs
- Incubation with lysate also leads to the presentation of antigens on the cell surface, which can induce T cells to become CTL 'killer' T cells
- The additional stimulatory capacity, combined with the induction of CTLs, enhances the 'multiplier effect'

Conclusions

- Mechanism of action studies demonstrate uptake and presentation of a broad range of antigens, which is important to prevent tumor escape
- Immune monitoring data demonstrate activation of a wide repertoire of T cells, which can travel to the brain to attack tumor cells locally

In Vivo Immune Monitoring

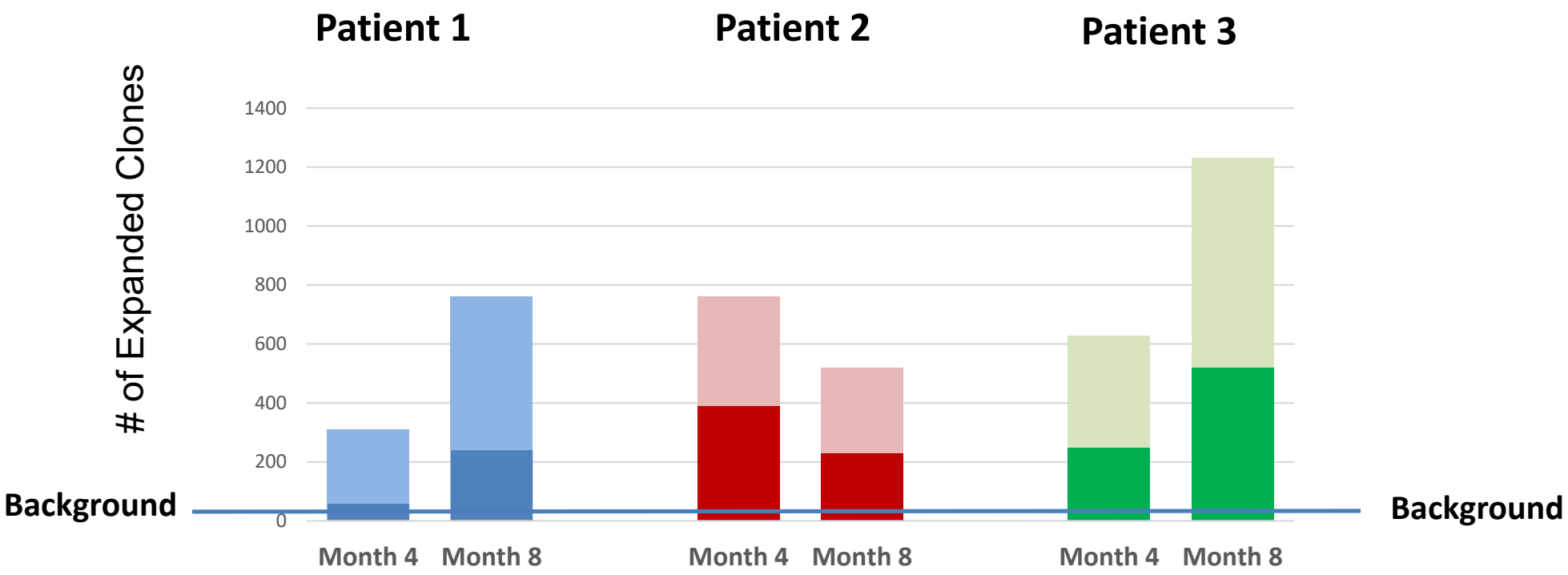
In Vivo Immune Monitoring

Consequential to our broad-spectrum approach, we use an analysis that allows monitoring of the entire T cell response (as opposed to monitoring the response to a single antigen), as follows:

- Each T cell that emerges from the thymus during development has a unique T Cell Receptor (TCR) DNA Sequence
- When a T cell divides in response to a stimulus, its specific TCR DNA sequence becomes more numerous
- Sequencing all TCRs allows one to:
  - Identify newly expanded T cell clones
  - Identify T cell clones that have further expanded (e.g. from baseline)

Expanded T Cell Clones

(compared to Baseline)



- These bars represent the total number of newly expanded T cell clones (dark color) or further expanded, pre-existing clones (light color)
  - ➢ Background in normal, unstimulated individuals would be 2 – 20 clones

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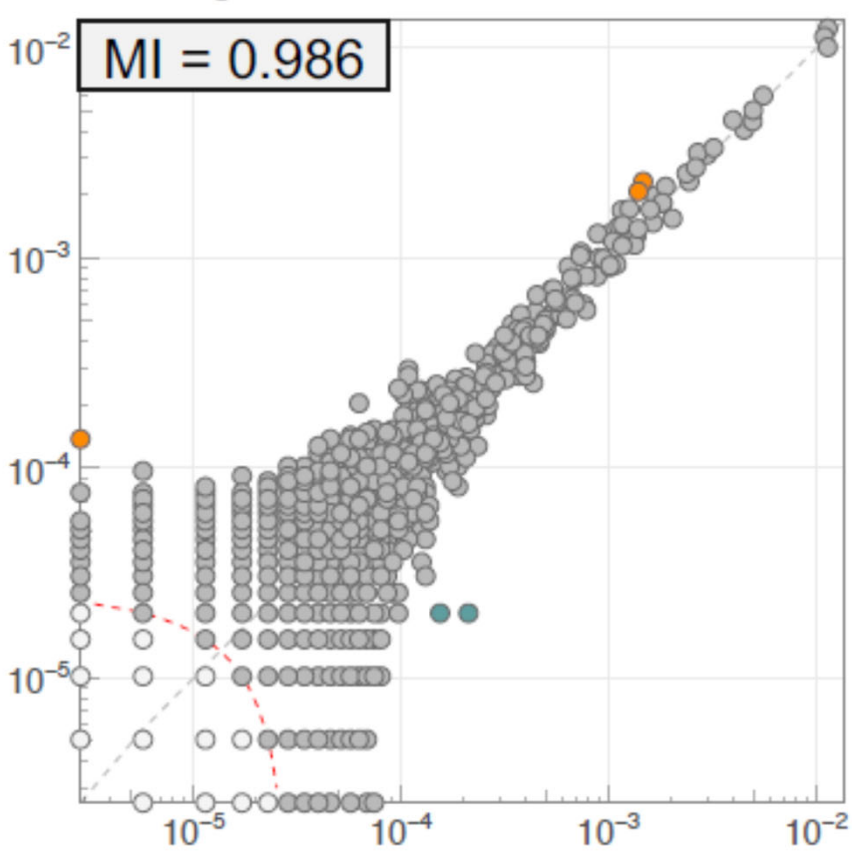
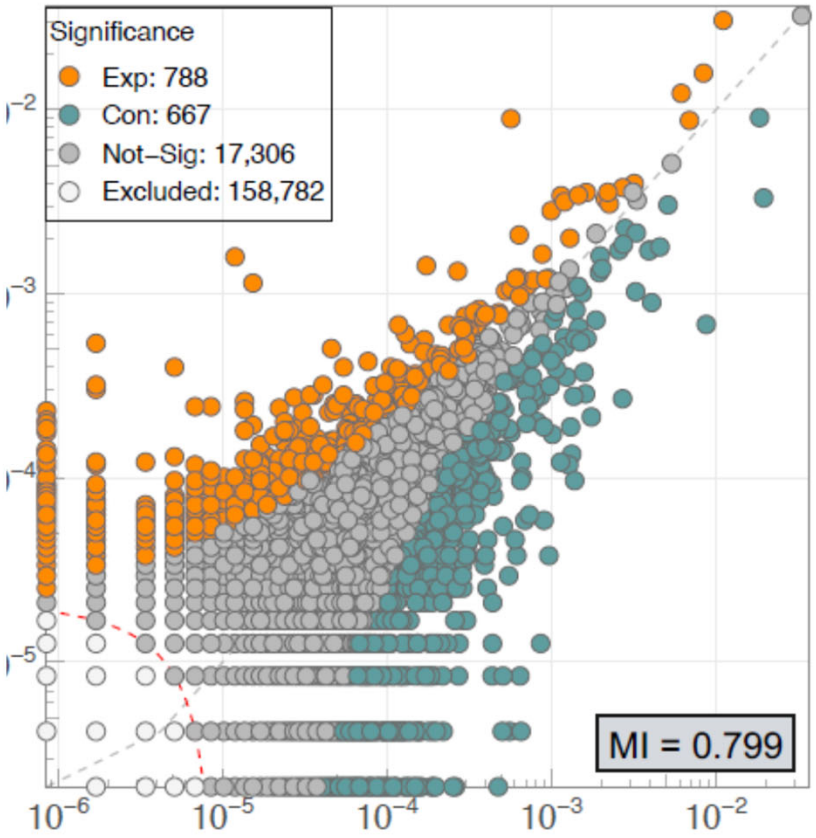
T Cell Repertoire Dynamics



This is your ~~brain~~ blood
from an untreated person



This is your blood
on DCVax-L

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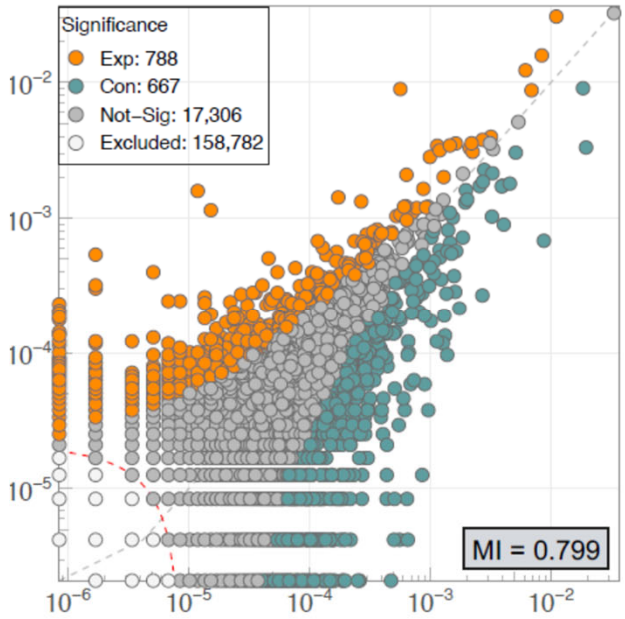
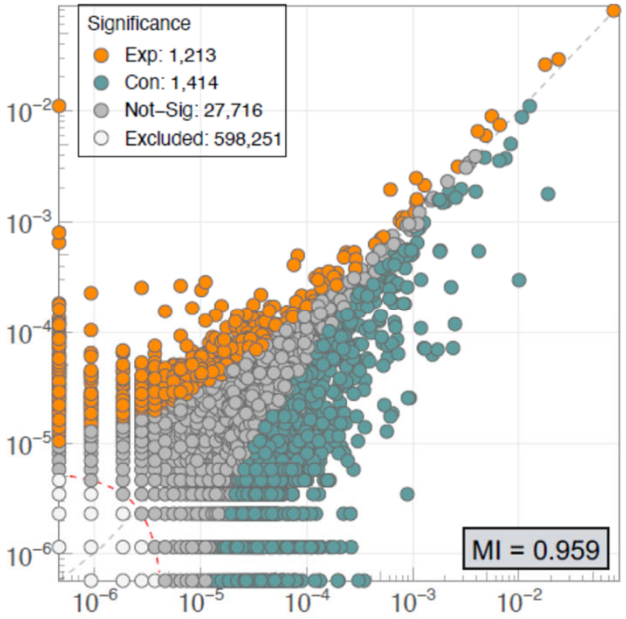
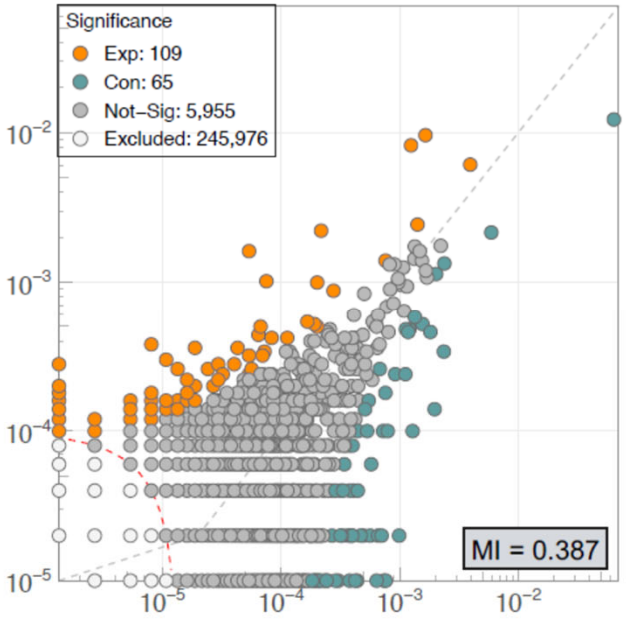
T Cell Repertoire Dynamics







Expansion and **Contraction** of the T cell repertoire in response to DCVax-L (3 example patients)

- X-axis: Baseline
- Y-axis: 8 months

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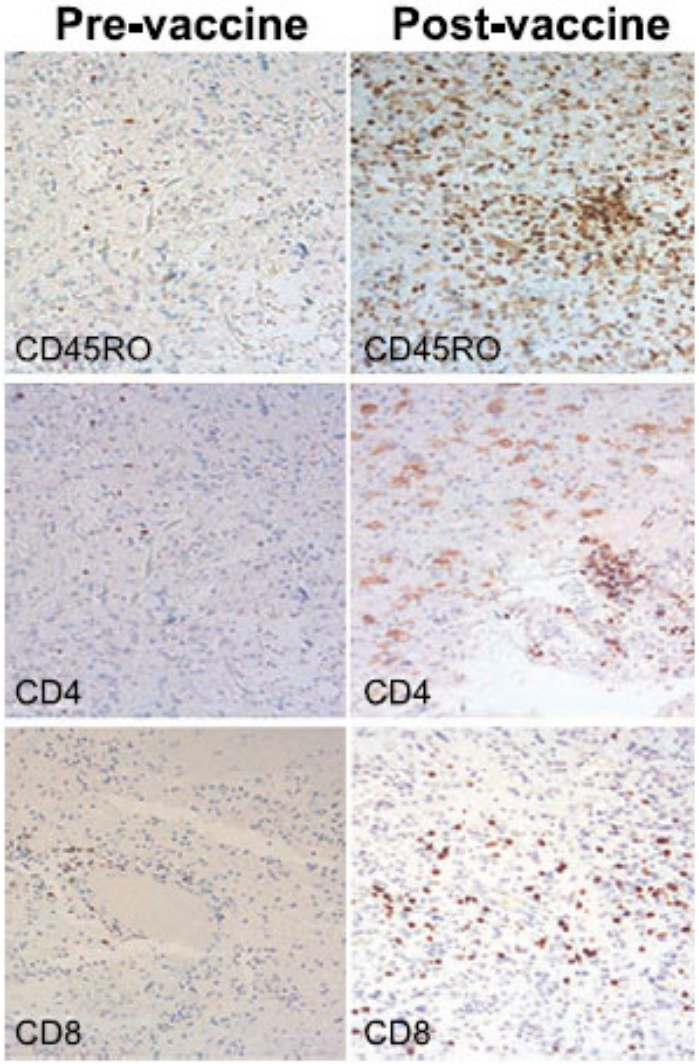
Prediction of (Tumor) Antigens

- Existing databases allow us to predict which antigens the expanded T cells were possibly responding to
- These algorithms are imperfect, and the databases are limited, so at this point predictions are only indicative
- Within these limitations, we made the following observations:
  - The expanding T cell clones respond to a **broad range** of antigens
  - The predicted epitopes included:
    - Several known tumor antigens
      - Some known to be associated with GBM; some not previously identified in GBM
    - Several viral (CMV, EBV) antigens
    - Multiple molecules with unknown functions

Mechanism of Action (3)
T cell Infiltration in GBM Post Vaccination



Infiltration of T cells in the tumor is observed in patients treated with DCVax-L

Both CD4 and CD8 cells are seen

L. Liau et al.

Immune Monitoring - Summary

- T Cell Receptor (TCR) sequencing demonstrated extensive expansion of specific T cell clones following immunization with DCVax-L
- This expansion is responsive to a **broad repertoire** of antigens
- *"This level of clonal expansion, particularly of the newly detected clones, provides strong evidence for a novel stimulus to the immune system during this interval."*
- **These observations support the postulated mechanism of action of DCVax-L**

DCVax-L Phase III Trial
External Controls

Trial Design

Primary Endpoint: OS in newly diagnosed GBM

DCVax-L arm (n=232) vs. External controls (n=1,366)

(control arms of external studies)

Secondary Endpoint: OS in recurrent GBM

Placebo arm crossovers* (n=64) vs. External controls (n=640)

*(Placebo arm patients received only SOC + placebo until recurrence, then DCVax-L)

(control arms of external studies)

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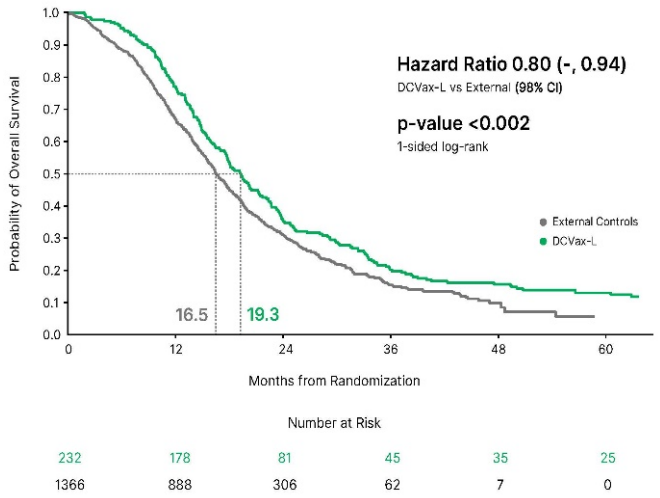
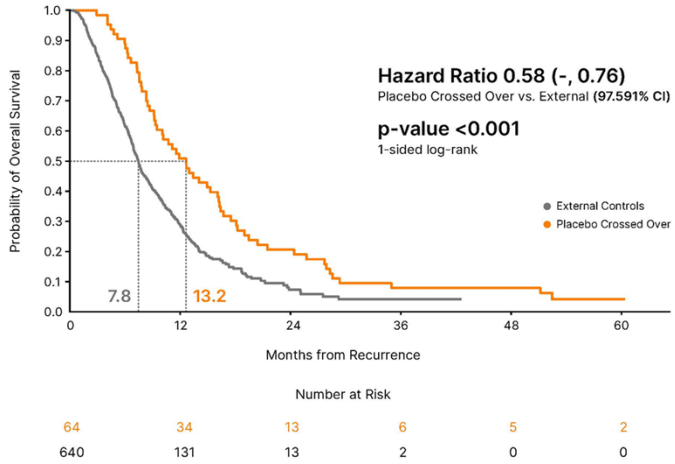
Overall Survival in nGBM and rGBM





<u>mOS of DCVax patients</u>:
19.3 months from randomization;
22.4 months from surgery

<u>mOS of controls</u>:
16.5 months from randomization

<u>mOS of DCVax patients</u>:
13.2 months from recurrence

<u>mOS of controls</u>:
7.8 months from recurrence

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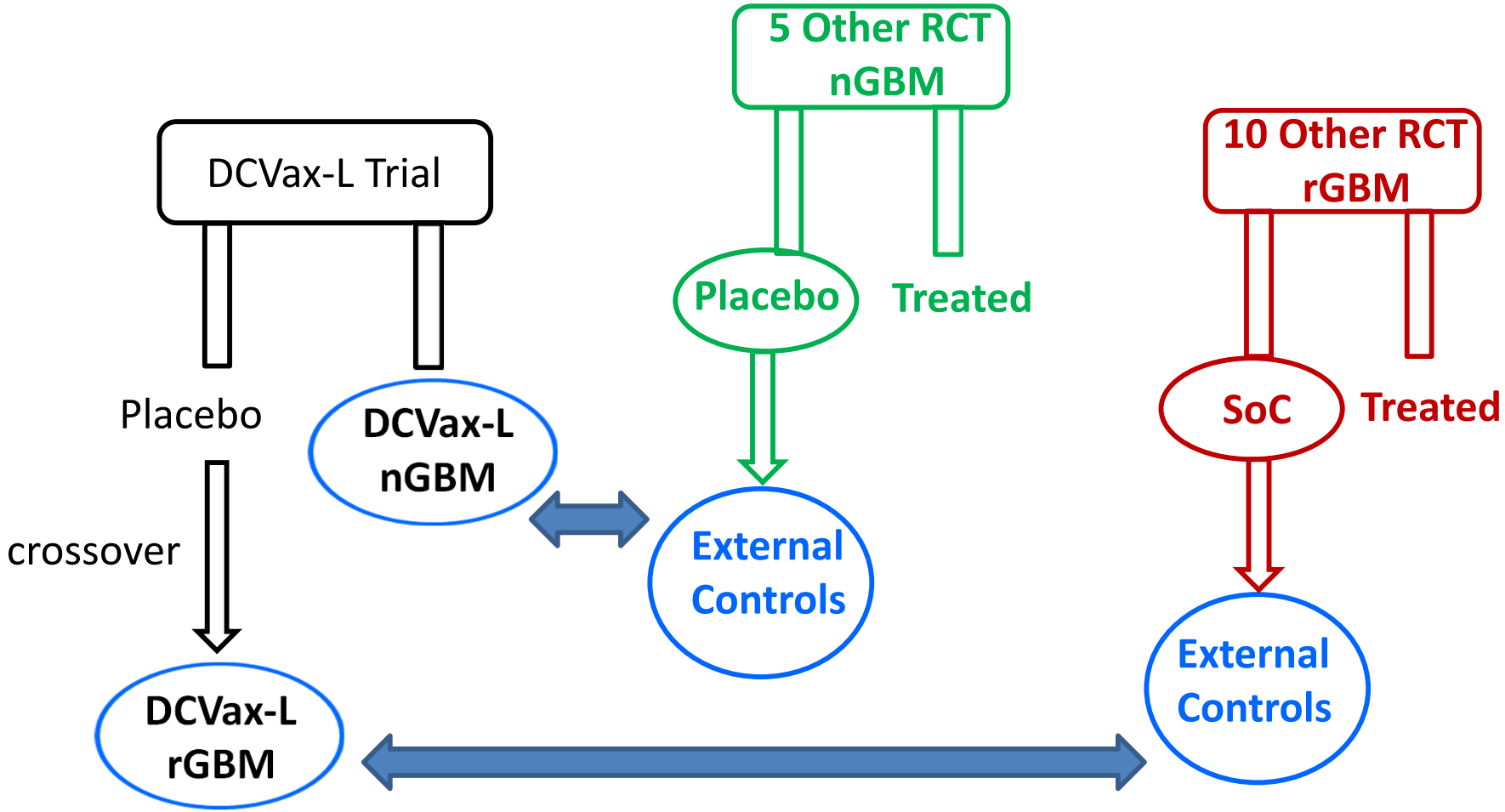
Landmark Survival Data

nGBM Landmark survival rate			
	ECP	DCVax-L	Relative Rate
36 mo	15.5%	20.2%	130%
48 mo	9.9%	15.7%	159%
60 mo	5.7%	13.0%	228%
rGBM Landmark survival rate post progression			
	ECP	DCVax-L	Relative Rate
6 mo	64.0%	90.6%	142%
12 mo	30.8%	54.1%	175%
18 mo	15.9%	31.8%	200%
24 mo	9.6%	20.7%	215%
30 mo	5.1%	11.1%	217%

External Controls Drawn From Other Randomized Controlled Trials



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External Control Population (ECP)

4 Layers of Statistical Methods Used to:

- Closely match the ECP and DCVax-L patients
- Address and minimize known and unknown biases

1. **Matching of comparator clinical trials** from which the ECP was drawn
2. **Validation of this ECP approach**: check that trial outcomes remain same
3. **Sensitivity analyses**: check for both known and unknown biases
4. **Adjustment for individual patient characteristics** (MAIC)

1. Matching of Comparator Trials

Comparator trials **selected by independent experts;** no Company involvement

Selection made using **14 criteria for matching** (7 for nGBM and 7 for rGBM)

nGBM:
1) contemporaneous study time period;
2) reported outcomes (including survival);
3) same standard of care used (radiation and temozolomide);
4) randomized study design;
5) patients aged >18;
6) KM curves available for survival and for subgroups; and
7) publication in English.

High quality data: ≤2% patients lost to follow up (LTFU) in the comparator trials
<2% LTFU in DCVax-L trial

Comparator studies were "**fit for purpose**"

The specific selected comparator trials (not just the criteria) were **pre-specified** in the Statistical Analysis Plan (SAP).

1. Matching of Comparator Trials (cont'd)

Newly Diagnosed Glioblastoma				
Study	**Agent under study**	**n**	**Median OS (months)**	**95% CI (months)**
Gilbert et al 2013	dose-dense tmz	411	16.6	14.9 – 18.0
Gilbert et al. 2014	bevacizumab	309	16.1	14.8 – 18.7
Weller et al. 2017	rindopepimut	374	17.4	16.2 – 18.8
Stupp et al. 2017	tumor treating fields	229	16.0	14.0 – 18.4
Wen et al. 2019	ICT-107	43	15.0	12.3 – 23.1
Aggregate Newly Diagnosed		**1,366**	**16.5**	**16.0 – 17.5**
Recurrent Glioblastoma at First Relapse				
Study	**Agent under study**	**n**	**Median OS (months)**	**95% CI (months)**
Wick et al. 2010	enzastaurin	92	7.1	6.0 – 8.8
Taal et al. 2014	bevacizumab	46	8.0	6.0 – 11.0
Brandes et al. 2016	galunisertib	40	7.5	5.6 – 10.3
Cloughesy et al. 2017	onartuzumab	65	12.6	n.a.[2]
Wick et al. 2017	bevacizumab	149	8.6	7.6 – 10.4
Brandes et al. 2018	bevacizumab	62	5.5	3.9 – 7.2
Galanis et al. 2019	bev + dasatinib	38	7.7	n.a.[2]
Lombardi et al. 2019	regorafanib	60	5.6	4.7 – 7.3
Narita et al. 2019	peptide vaccine	30	8.0	4.8 – 12.9
Lee et al. 2020	bev + trebananib	58	11.5	8.4 – 14.2
Aggregate Recurrent GBM		**640**	**7.8**	**7.2 – 8.2**

These clinical trials are the major studies in the field during his time period

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2. Validation of the ECP

Indication	Study	HR vs. ECP	Lower bound	Upper bound
Newly diagnosed GBM	Gilbert 2013	1.01	0.89	1.14
	Gilbert 2014	1.13	0.72	1.33
	Weller 2017	0.9	0.78	1.03
	Stupp 2017	0.73	0.65	0.83
	Wen 2019	0.98	0.72	1.33
Recurrent GBM	Wick 2010	1.17	0.94	1.45
	Brandes 2016	1.01	0.78	1.31
	Wick 2017	0.94	0.80	1.10
	Cloughesy 2017	0.92	0.65	1.29
	Brandes 2018	1.52	1.14	2.02
	Galanis 2019	1.12	0.88	1.44
	Lombardi 2019	0.84	0.62	1.15
	Narita 2019	0.92	0.68	1.23
	Taal 2019	0.91	0.65	1.29
	Lee 2020	0.93	0.68	1.28

For each **comparator** trial, the **treatment arm** was compared against the **external controls** (ECP) determined for the DCVax-L trial….

….to check whether the result was the same as originally reported from the within-study comparison in that comparator trial.

All results were the same as originally reported for each of the comparator trials.

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3. Sensitivity Analyses

Known bias: not all trials excluded patients with evidence of progression post chemoradiation. Removing those trials yields the following result:

Studies removed	n ECP	HR	98% CI	p
None removed	**1366**	**0.80**	**0.00, 0.94**	**0.002**
Gilbert 2013, 2014	646	0.77	0.00 – 0.92	0.001

Unknown biases: specific inclusion criteria for each trial may have influenced outcomes. Removing each trial individually yields the following results:

Study removed	n ECP	HR	98% CI	p
None removed	**1366**	**0.80**	**0.00, 0.94**	**0.002**
Gilbert 2013	955	0.77	0.00, 0.92	<0.001
Gilbert 2014	1057	0.80	0.00, 0.94	0.002
Weller 2017	992	0.79	0.00, 0.94	0.002
Stupp 2017	1137	0.82	0.00, 0.97	0.007
Wen 2019	1323	0.80	0.00, 0.94	0.002

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4. Adjustments for Individual Patient Characteristics

Matching Adjusted Indirect Comparison: MAIC

The MAIC methodology **applies a weight** to each individual patient in the DCVax-L population in such a way that the sum of the weights for patients in **each category** for a characteristic **achieves a match with the external** control population, thereby making the patient populations comparable, while reducing the sample size.

- **Well established and widely used** in health economics analyses and reimbursement decisions
- **Adjusts for even small differences** in individual patient characteristics.
- Reduces the sample size for DCVax-L, but not for the ECP
- **MAIC matching was done for age, sex, race, MGMT methylation status, KPS score and extent of resection or residual disease.**

OS difference vs. ECP remained statistically significant…

- **Against the pooled controls, and also**
- **Against each comparator study individually**

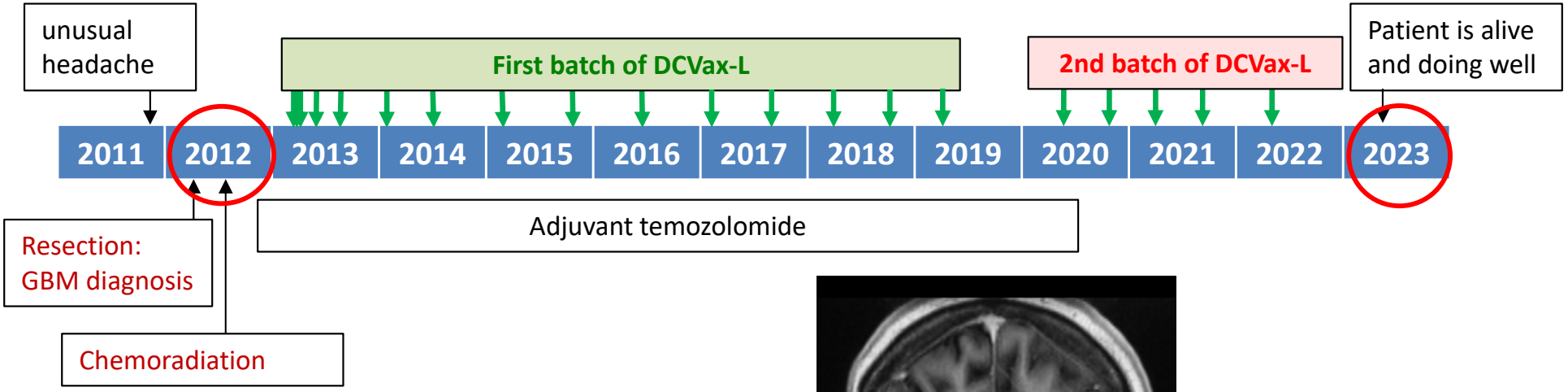
Phase III External Controls

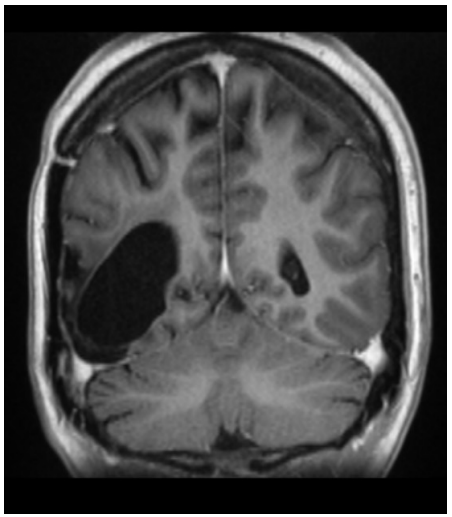
Conclusions

- Survival of GBM patients participating in clinical trials as control subjects is remarkably consistent, creating a landscape in which ECPs can be used as synthetic control arms
- Against this background, treatment with DCVax-L is associated with statistically significant and clinically meaningful extended survival, both in newly diagnosed and recurrent GBM
- The results are robust and hold up well against multiple analyses to address known and unknown sources of bias

Compassionate Use – Observations

Compassionate Case #2
46 yr. old female with GBM





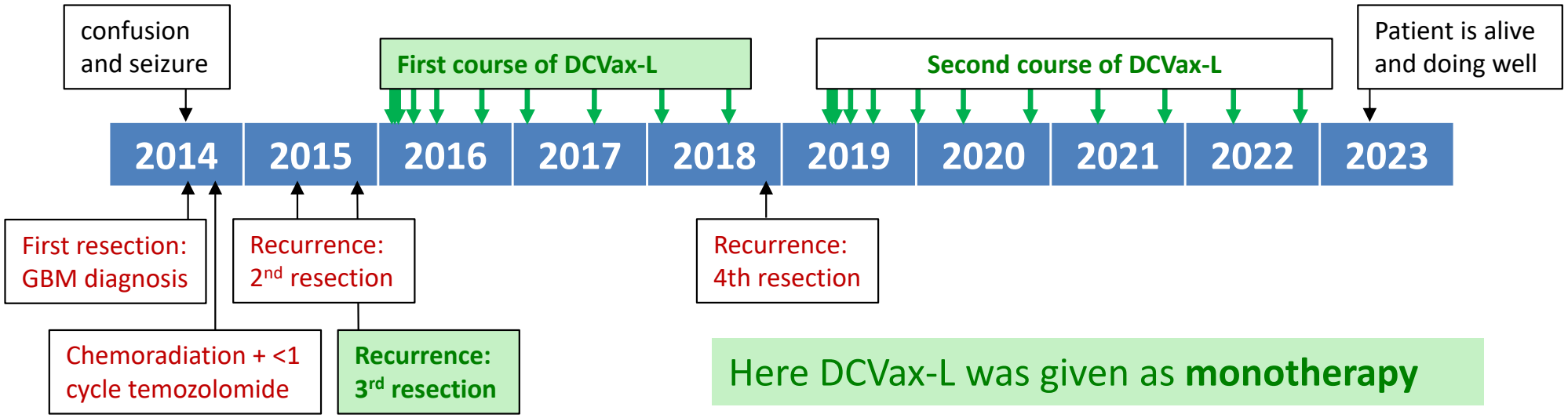
August 2019

Notes:

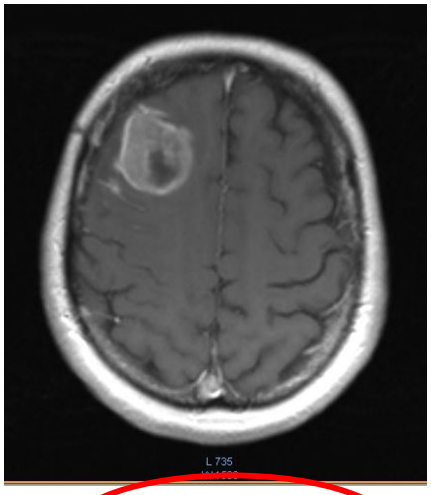
- Patient was diagnosed with GBM with oligodendrioglioma component
- MGMT methylated
- Scans are done every 6 months, with no evidence of progression to date

Northwest Biotherapeutics

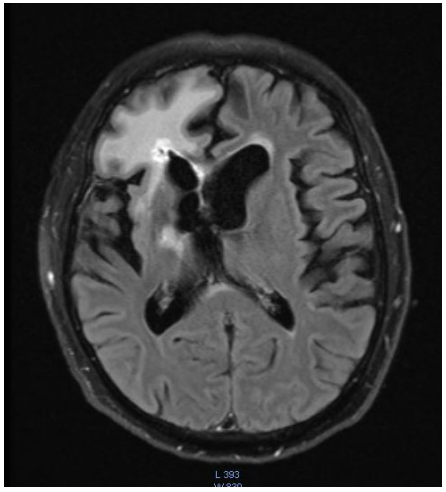
Compassionate Case #1:
70 yr old male with GBM



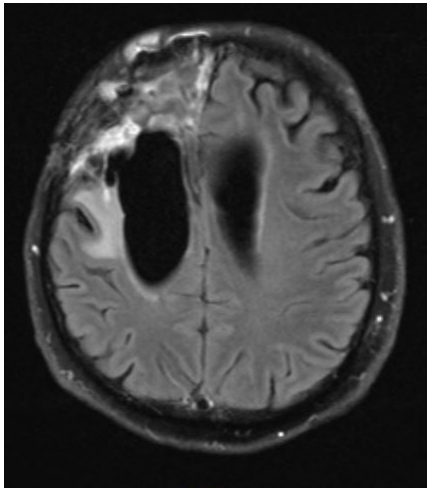
Here DCVax-L was given as **monotherapy**



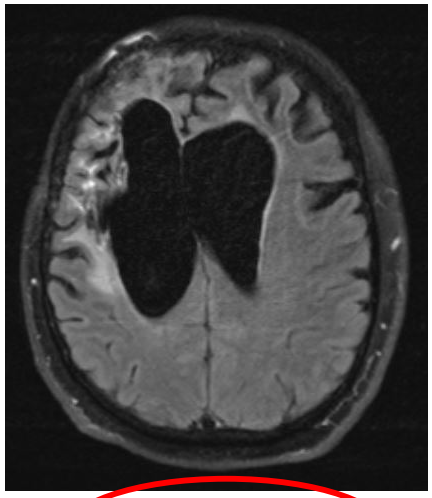
July 2014



Dec 2018



Apr 2019



Dec 2022

NORTHWEST BIOTHERAPEUTICS

Observations From Compassionate Use Cases

Anecdotal observations:

- DCVax-L is well tolerated and can be **effective in older patients**, including patients with substantial co-morbidities, at least through late 80s ages
- When patients experience recurrence, and have an **additional resection, a new batch of DCVax-L** can be made and patients can **respond again** (unlike targeted therapies), with extended survival
- When patients experience recurrence before all doses are used, continuing treatment with the **original DCVax-L batch can still exten**d **survival**

Broader Perspective

- **DCVax-L induces a broad-spectrum immune response**
- **DCVax-L suitable for combinations with wide range of other treatments**
  (checkpoint inhibitors, oncolytic viruses, cytokines, chemo, etc.)
- **When a DCVax-L patient has recurrence(s), new batch(es) of DCVax-L can be made**
  (treatment targets not lost, as they are with targeted therapies)
- **DCVax-L can potentially apply to any type of solid tumor**
  (multiple other cancers treated in compassionate uses cases and a prior small pilot trial)
- **DCVax-L can be administered in community settings as well as major cancer centers.**

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