Immunization With Autologous Dendritic Cells is Associated With Extended Survival in Glioblastoma Patients

Glioblastoma Drug Development Summit

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Overview

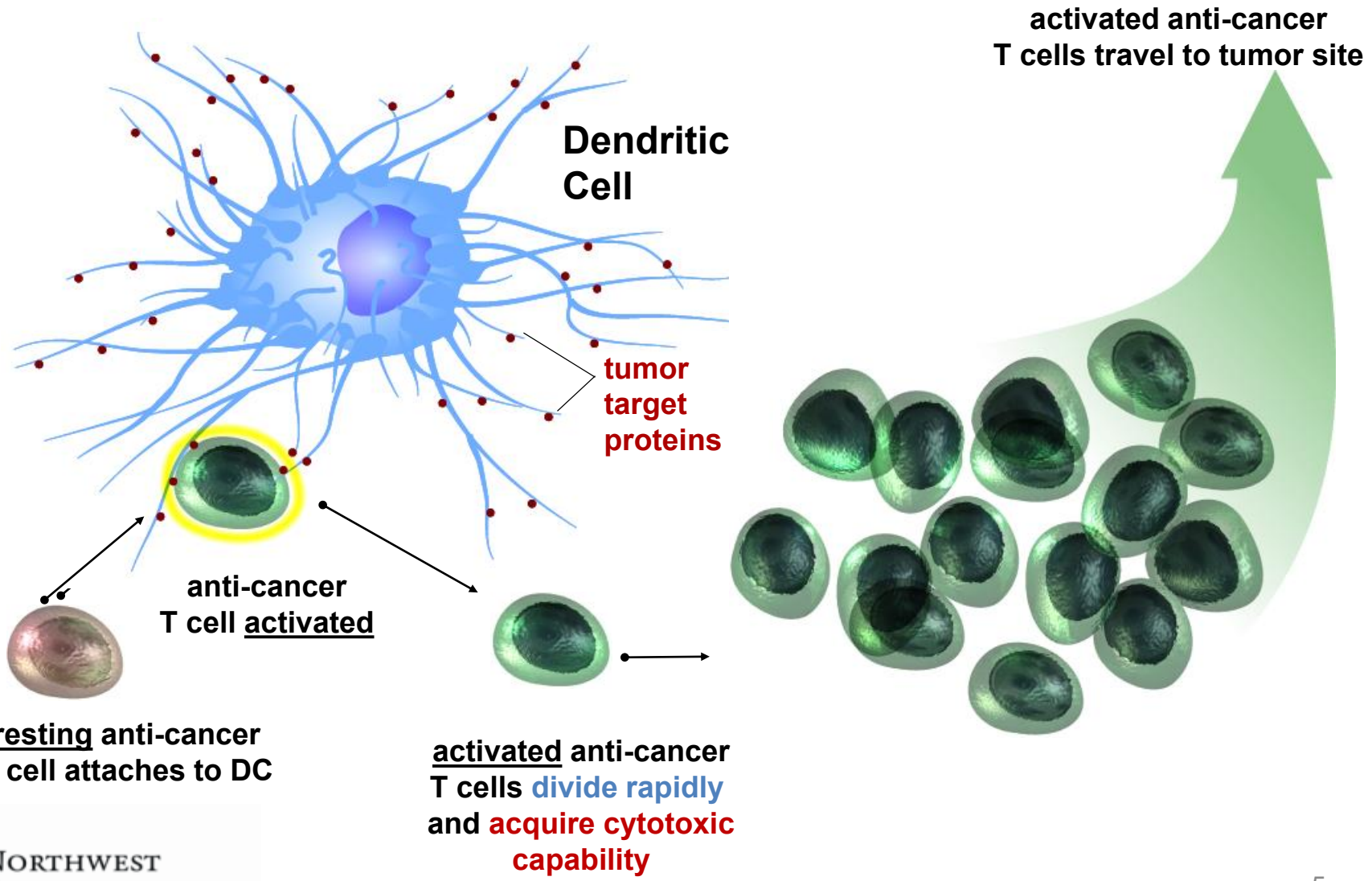
Presentation overview

1. Introduction to DCVax®-L
2. DCVax®-L Mechanism of Action
3. Clinical Results
   a) Phase III trial results
   b) Compassionate use cases
4. Conclusions

DCVax®-L Introduction

- DCVax®-L is 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
- DCVax®-L treatment is intended as adjuvant treatment following surgery
- A Phase III trial showing association between DCVax-L treatment and extended survival was recently reported on (L. Liau et al., JAMA Oncology, January 2023)
- The product is manufactured for each patient separately. Manufacturing takes 8 days, plus release testing

DCVax-: Mechanism of Action



Mechanism of Action (1)

Antigen Uptake

Proteomics analyses were conducted on the following materials:

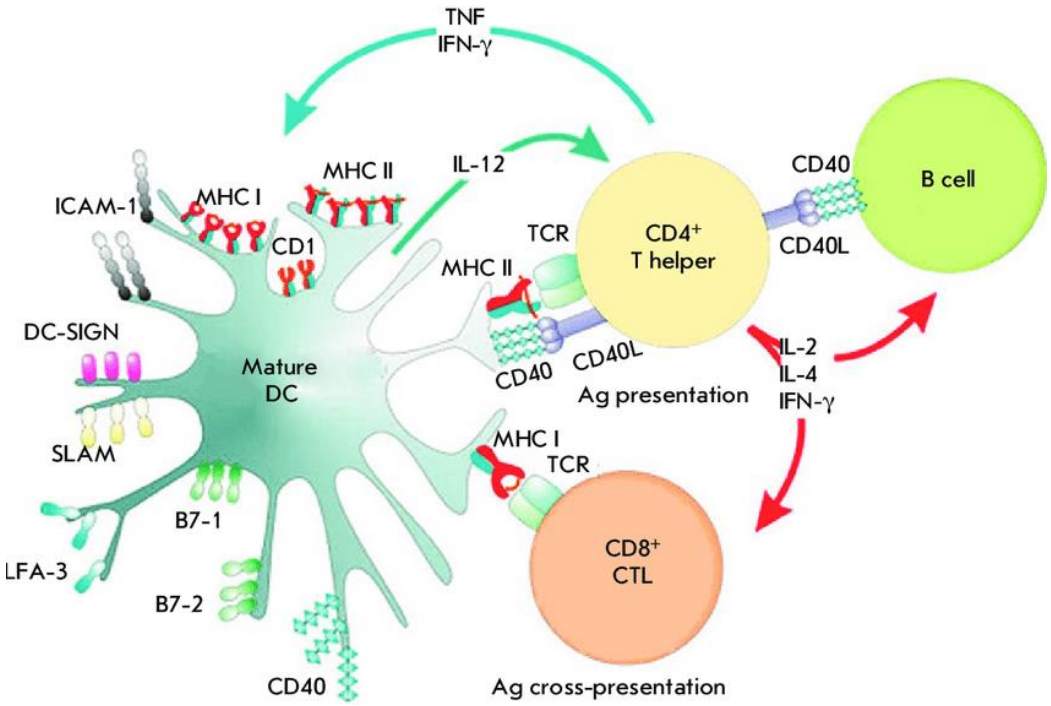
- Tumor lysate
- Unpulsed DCs
- DCs pulsed with tumor lysate
- Peptides eluted from pulsed DCs

Conclusion: The dendritic cells in DCVax-L take up (tumor) antigens from tumor cell lysate and express those on the surface in the context of both class I and class II MHC antigens

Mechanism of Action (2)

T cell stimulation

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



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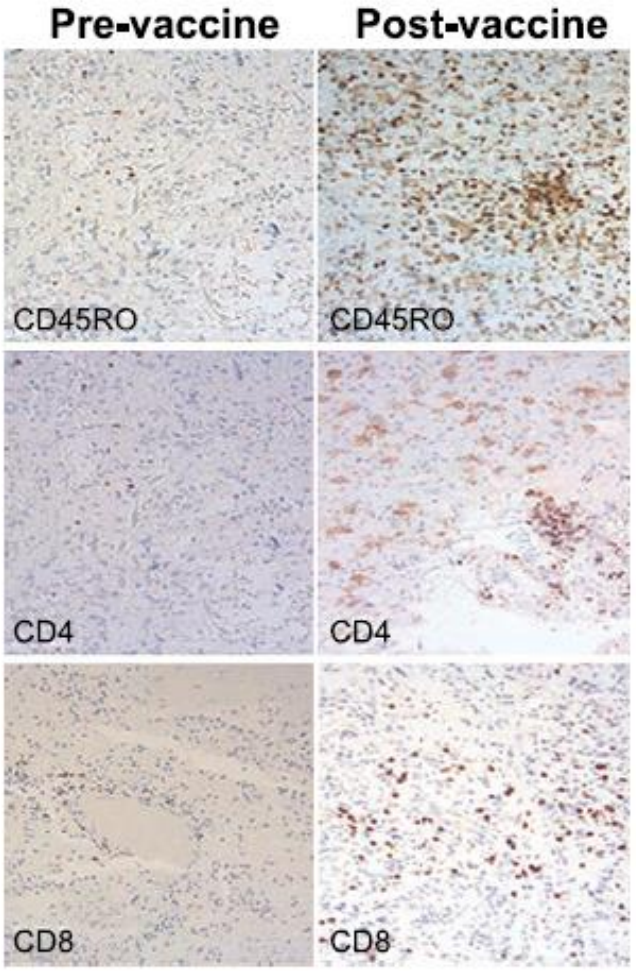
Mechanism of Action (3)
T cell Infiltration in GBM Post Vaccination



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.

Phase III Trial Overview

JAMA Oncology | Original Investigation

Association of Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination With Extension of Survival Among Patients With Newly Diagnosed and Recurrent Glioblastoma

A Phase 3 Prospective Externally Controlled Cohort Trial

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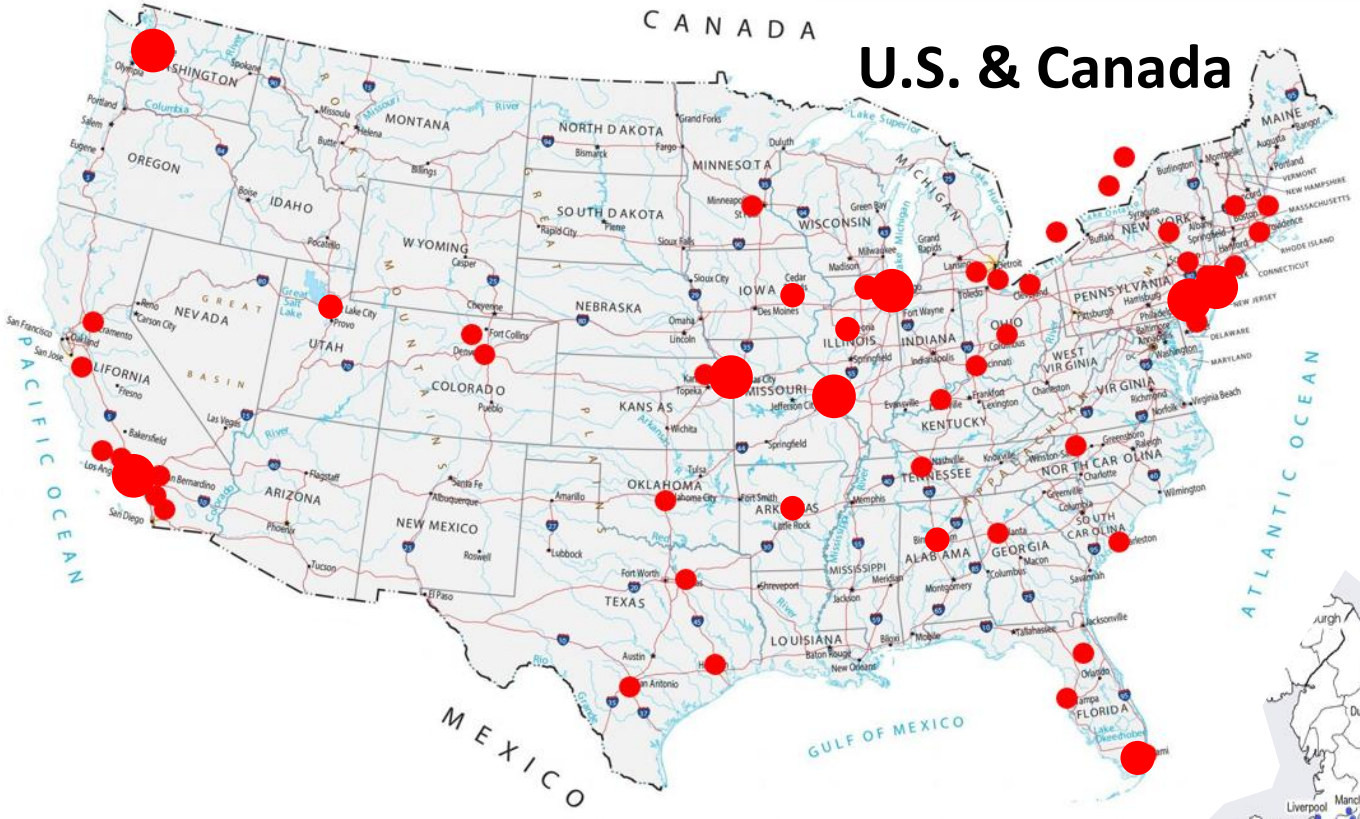
DCVax-L Trial Sites



92% (303 out of 331) patients were enrolled during 2012-2015

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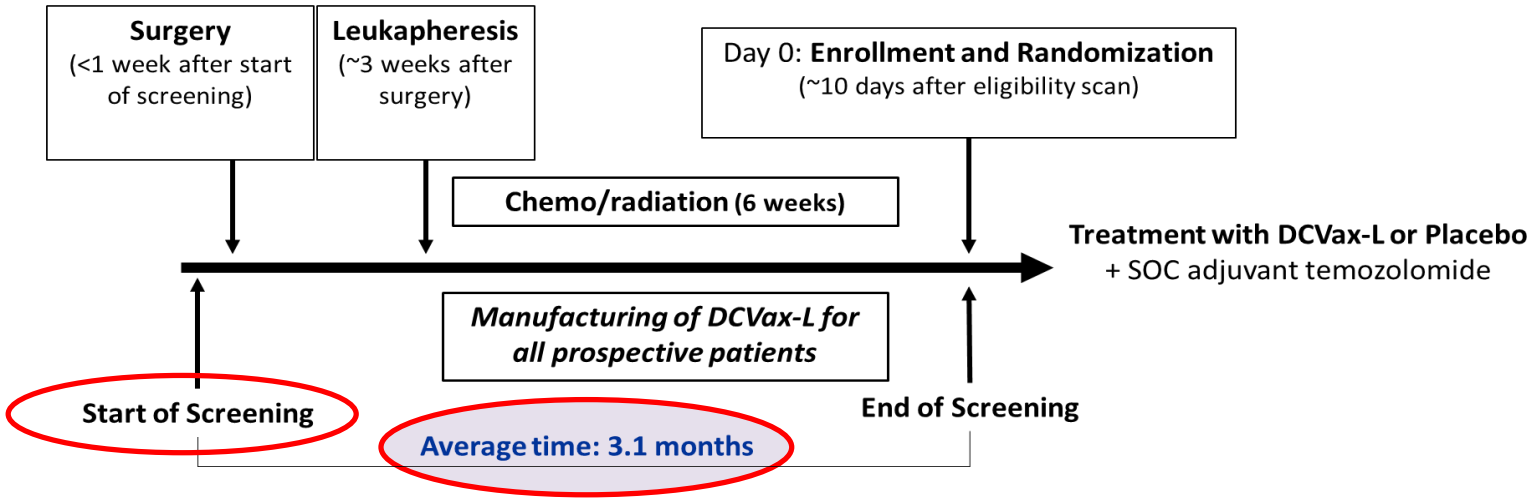
Screening and Enrollment



Treatment Schedule

3 treatments in Month 1: Days 0, 10, 20

3 booster treatments: Months 2, 4, 8

Treatments 2X per year for maintenance

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Trial Design; Statistical Analysis Plan

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)

This SAP and its Endpoints were pre-specified and submitted to regulators before unblinding.

External Controls (ECP)

Criteria used to identify the trials included the following:

- Randomized controlled trials
- Control arm with SOC or physician's choice
- Patients must be 18 years or older
- Contemporaneous with DCVax-L
- KM plots for OS (and subgroups) included for digitization

➢ Independent expert firm evaluated & selected the comparators with no Sponsor involvement

External Control Populations (ECPs)

Survival outcomes

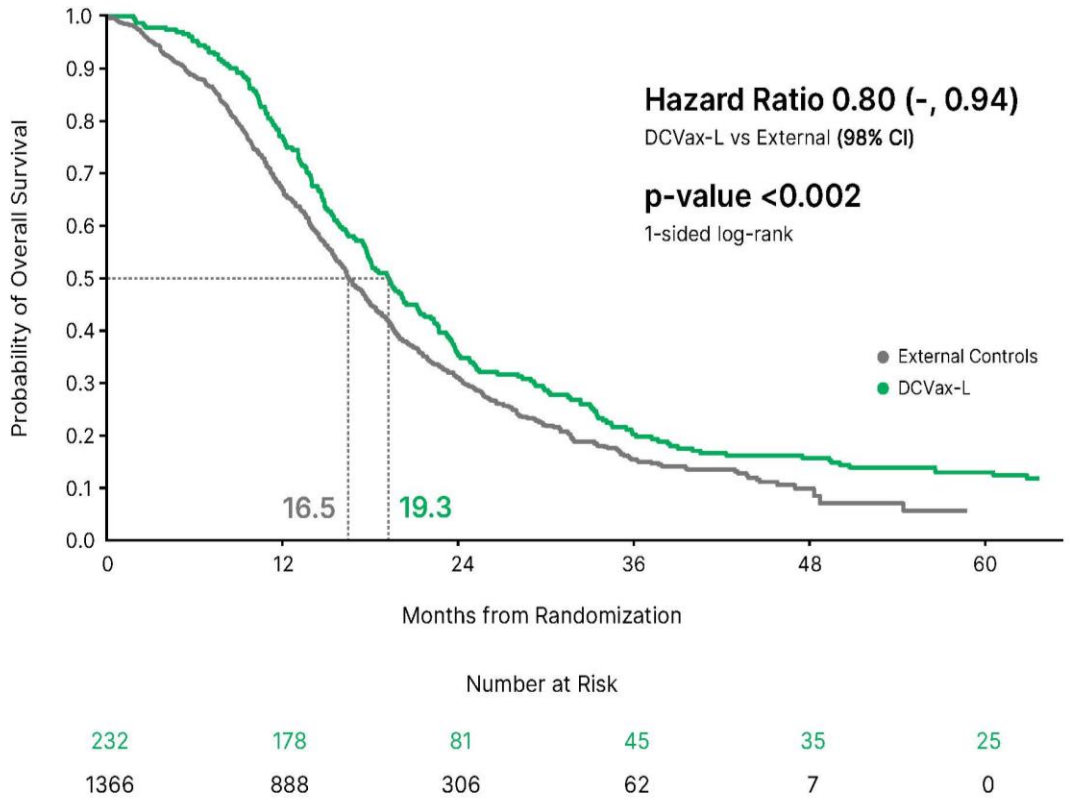
Newly Diagnosed Glioblastoma				
Study	**Agent under study**	**n**	**Median OS (months)**	**95% CI (months)**
Gilbert et al 2013	dose-dense tmz	411	16.6	14.9 – 18.0
Gilbert et al. 2014	bevacizumab	309	16.1	14.8 – 18.7
Weller et al. 2017	rindopepimut	374	17.4	16.2 – 18.8
Stupp et al. 2017	tumor treating 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**

Validation of the ECP

For each comparator study, the treatment arm was compared against the external controls determined for DCVax-L trial. **All results were same as originally reported.**

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

Overall Survival in Newly Diagnosed GBM



mOS of DCVax arm = **19.3 mos** from randomization; **22.4 mos from surgery**

mOS of controls = 16.5 mos from randomization

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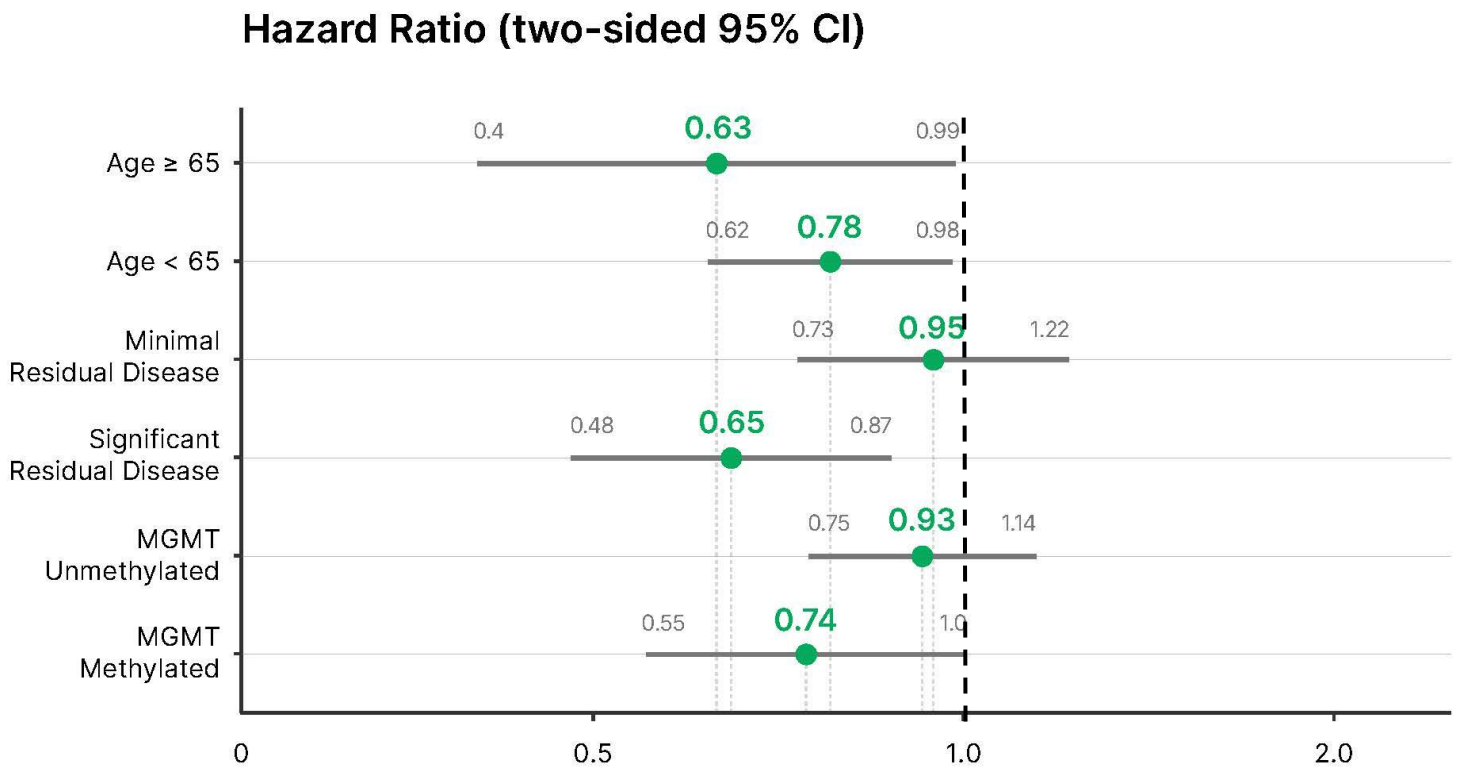
Overall Survival in Subgroups



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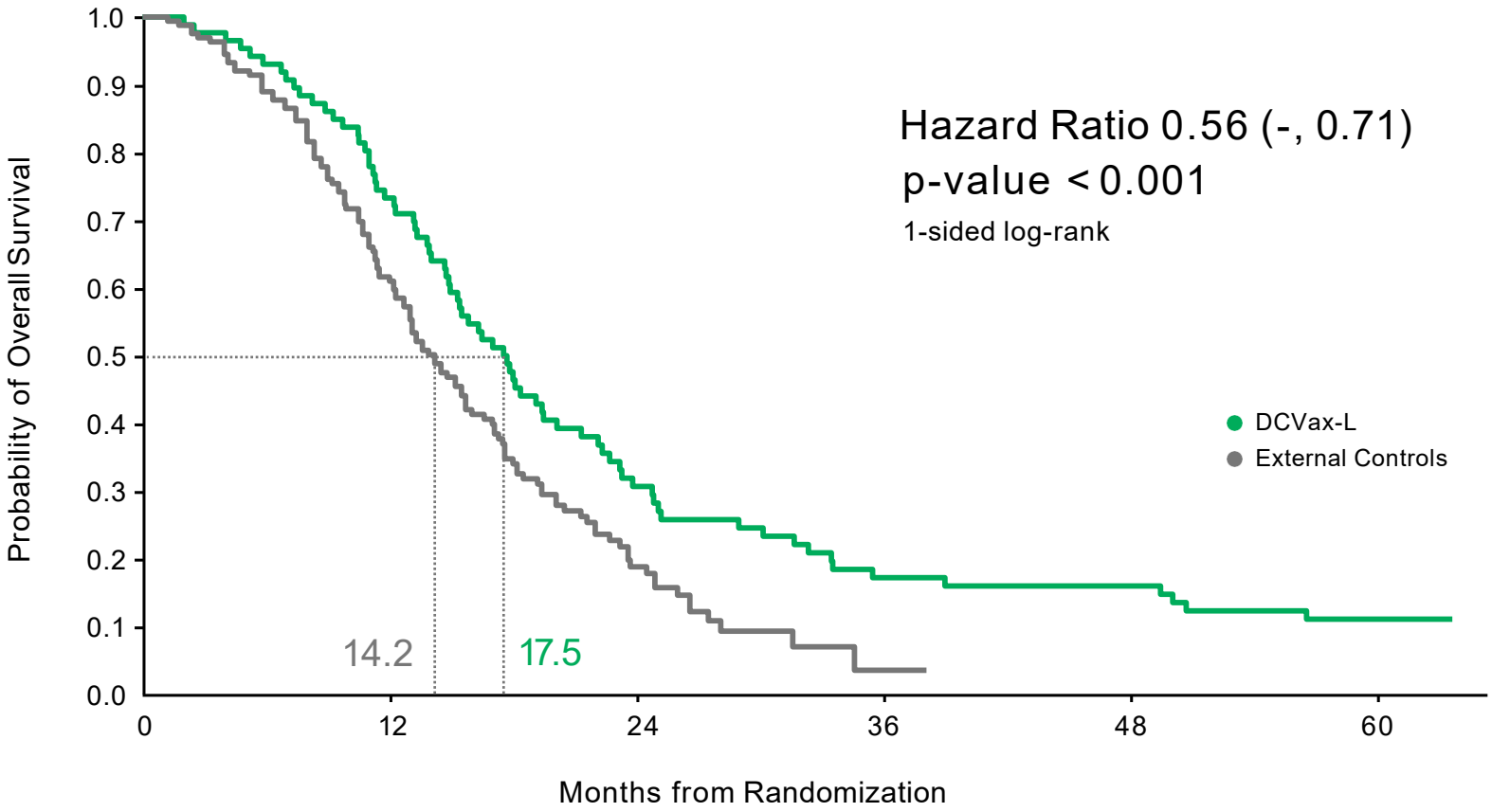
Significant Residual Disease



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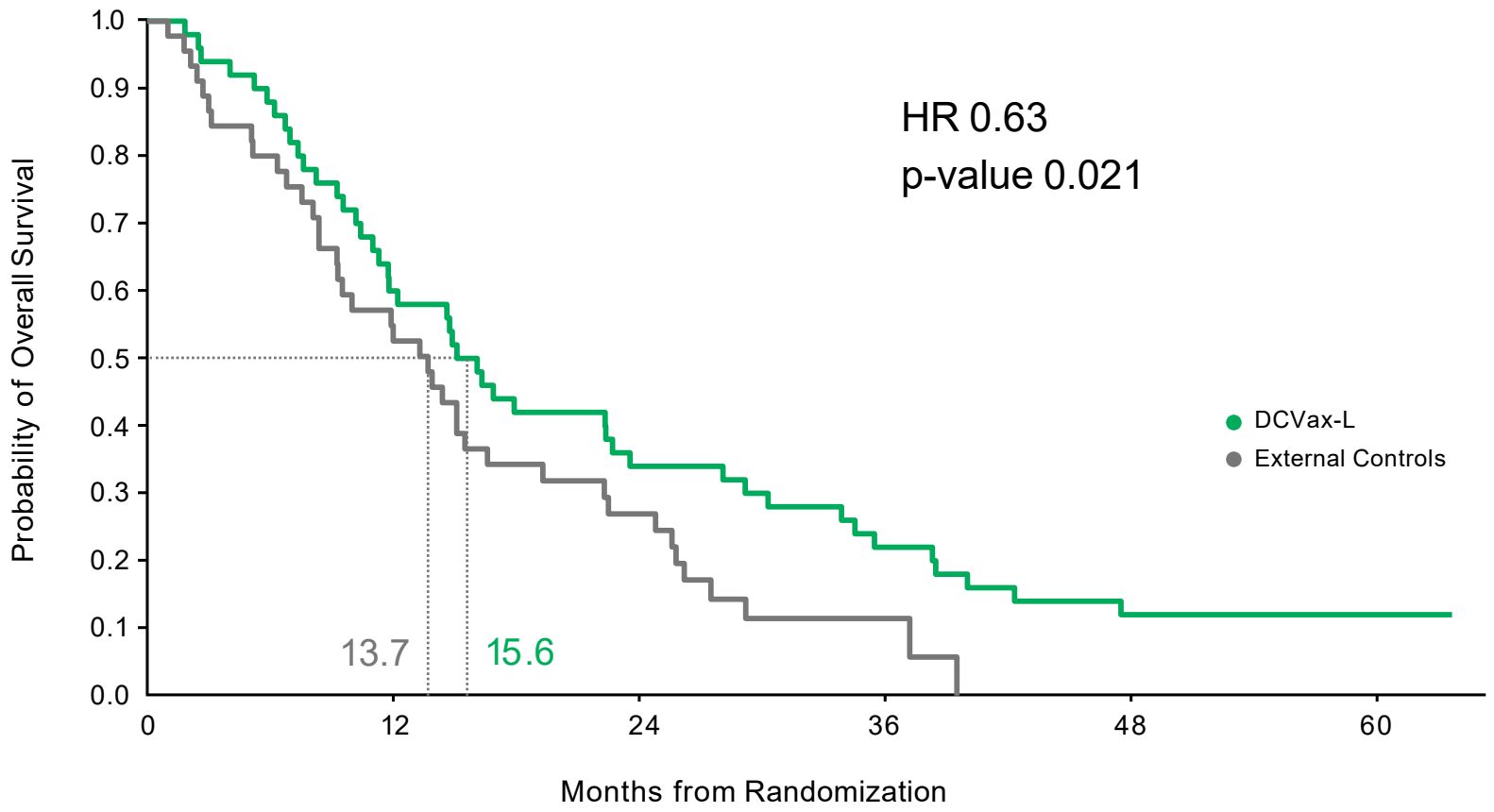
Overall Survival - Age ≥ 65



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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	**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	**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

External Controls: Individual Matching

Adjustments for individual patient characteristics: MAIC

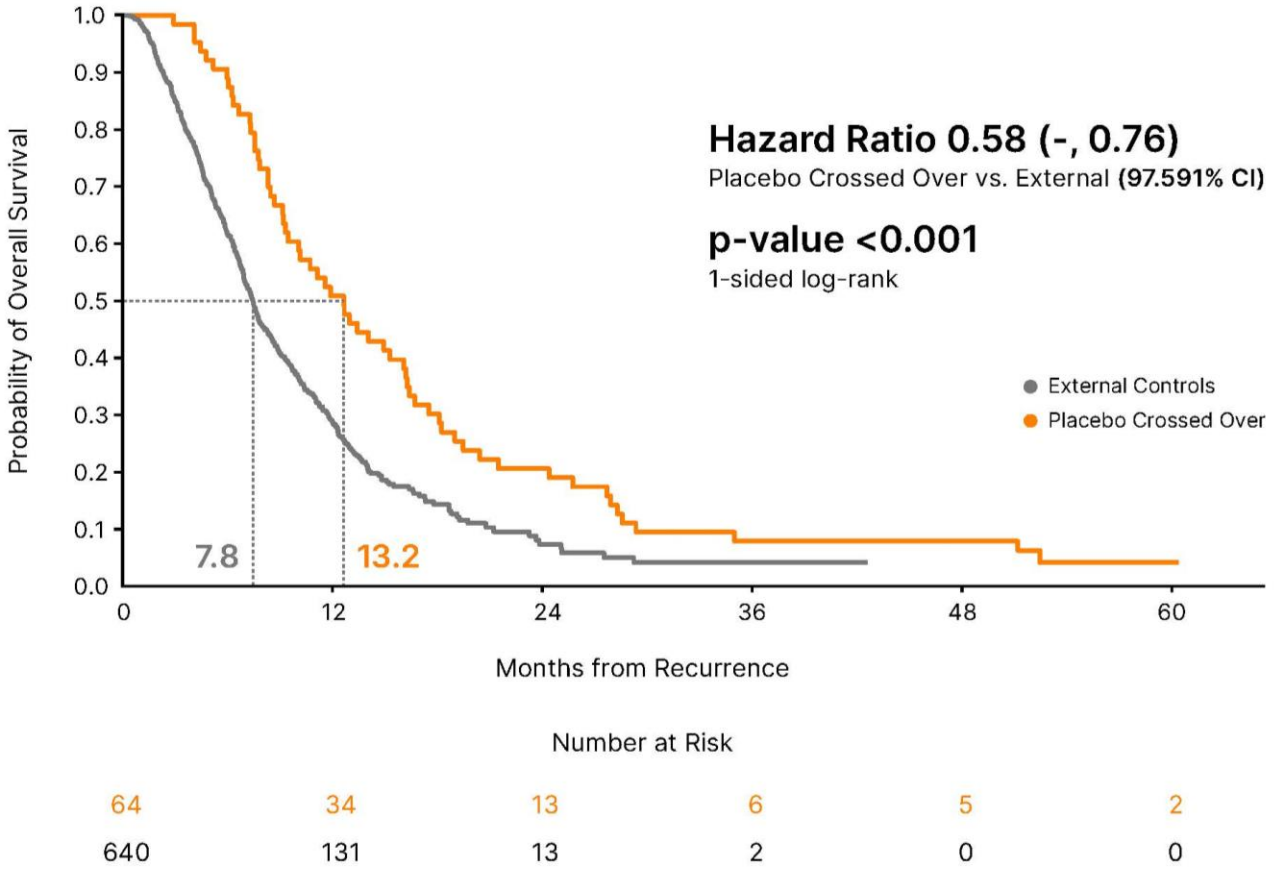
(Matching Adjusted Indirect Comparison)

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.

- Adjusts for even small differences in individual patient characteristics.
- Reduces the sample size for DCVax-L, but not for the ECP

OS difference vs. ECP remained statistically significant.

Overall Survival in Recurrent GBM



mOS = **13.2 months** from recurrence with DCVax-L **vs. 7.8 months** in controls

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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%

Overall Survival (OS) Results – Key Points

NEWLY DIAGNOSED GBM:

- **mOS:** 19.3 mos from randomization (22.4 mos from surgery) vs. 16.5 mos from randomization in controls
- **mMGMT mOS:** 30.2 mos from randomization (33 mos from surgery) vs 21.3 mos from randomization in controls
- **Survival Tail:** 13% vs 5.7% at 5 years

RECURRENT GBM:

- **mOS:** 13.2 mos vs. 7.8 mos from recurrence
- **Survival Tail:** 20.7% vs. 9.6% at 24 mos after recurrence
  11.1% vs. 5.1% at 30 mos after recurrence

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Safety Profile

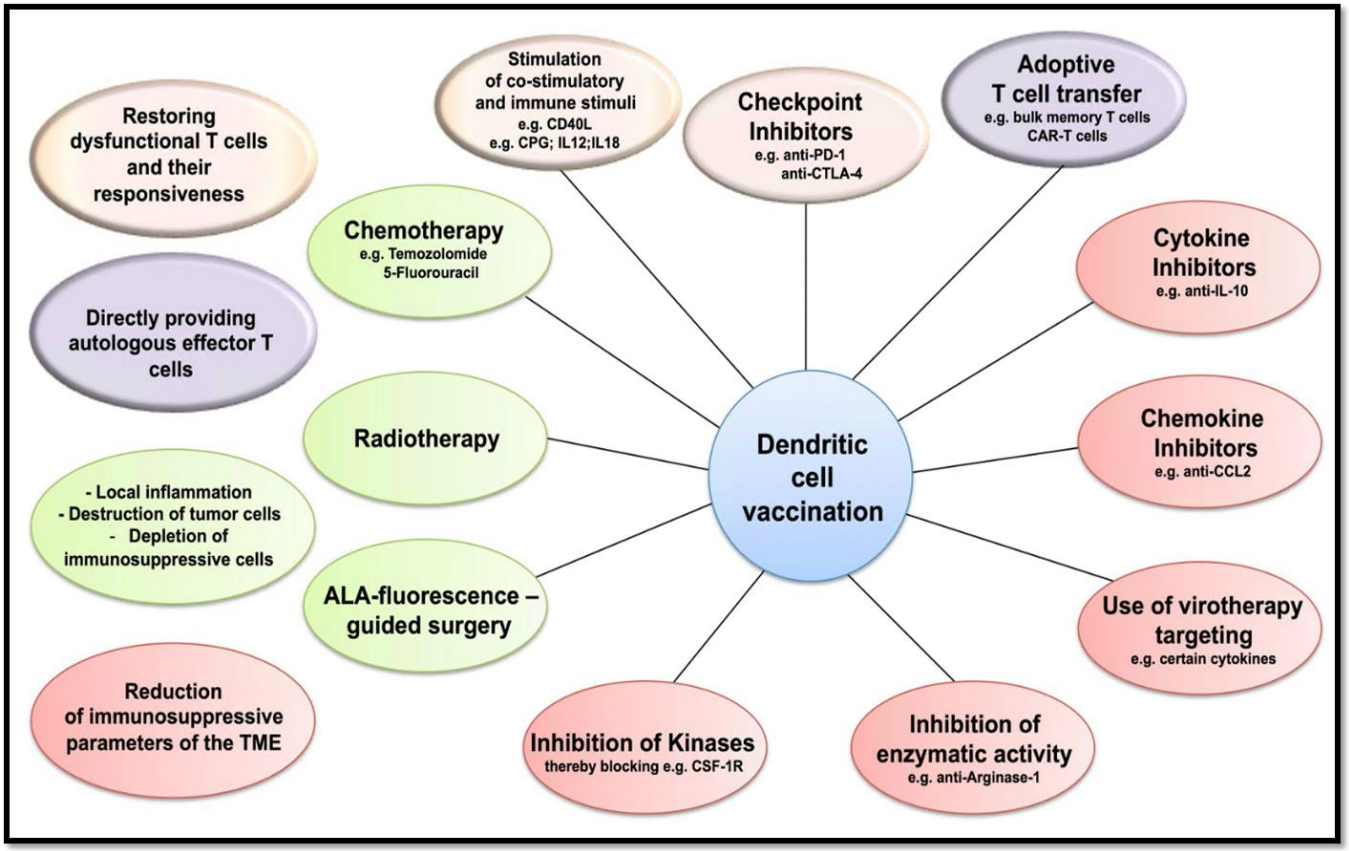
>2,100 doses were administered during the DCVax-L trial

Only 5 SAEs at least "possibly related" to DCVax-L treatment

- 3 cases of intracranial edema (grades 2 and 3)
- 1 case of nausea (grade 3)
- 1 case of lymph node infection (grade 3)

Overall safety profile in DCVax-L patients is similar to that experienced with standard of care treatment

Future Opportunities for Combination Therapies



Datsi A, Sorg RV. *Frontiers in Immunology,* 2021

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Broader Perspective

- **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.**

Compassionate Case #1:
70 yr old male with GBM

confusion and seizure

First course of DCVax-L

Second course of DCVax-L

Patient is alive and doing well

2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023

First resection: GBM diagnosis

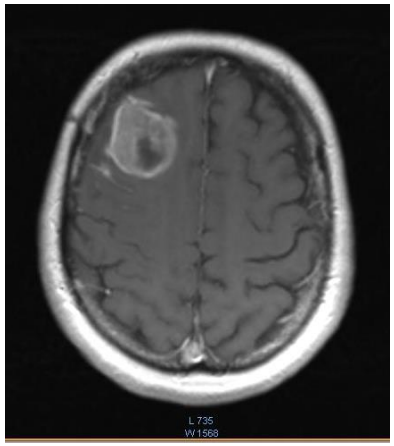
Chemoradiation + <1 cycle temozolomide

Recurrence: 2nd resection

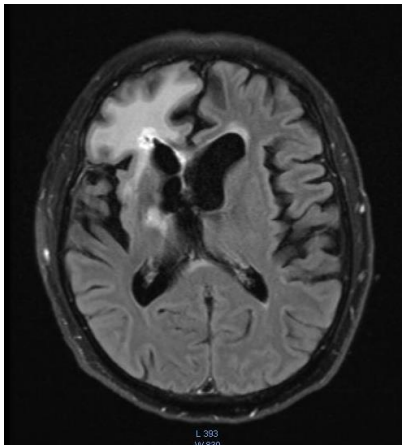
Recurrence: 3rd resection

Recurrence: 4th resection

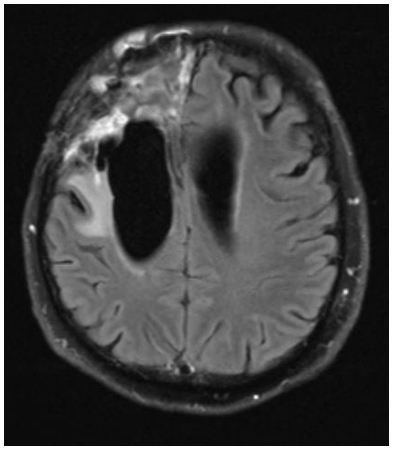
Here DCVax-L was given as monotherapy



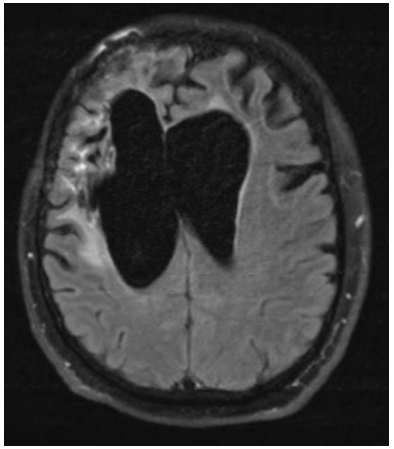
July 2014



Dec 2018



Apr 2019



Dec 2022

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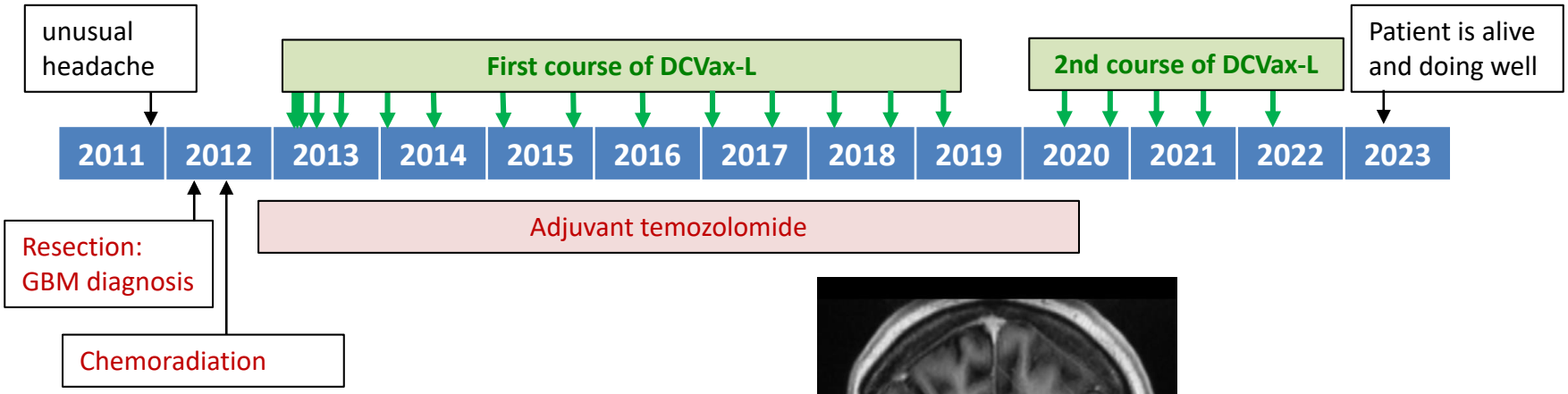
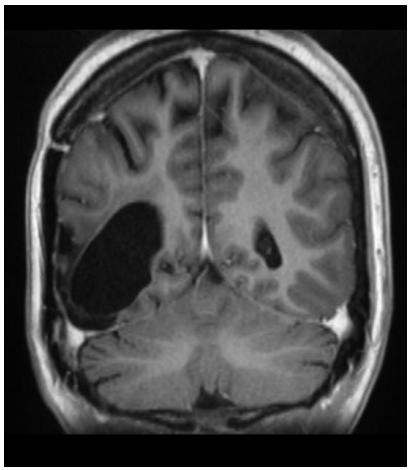
Compassionate Case #2
46 yr. old female with GBM



Notes:

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



August 2019

Observations From Compassionate Use Cases

Anecdotal observations:

- DCVax-L is well tolerated and can be effective in older patients, 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, with extended survival
- When patients experience recurrence before all doses are used, continuing treatment with the original DCVax-L batch can still extend survival

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
- Mechanism of action studies demonstrate uptake and presentation of a broad range of antigens which may be important to prevent tumor escape

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