Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination for Glioblastoma

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May 10, 2022

Presentation Overview

Innovative Trial Design of DCVax®-L Phase 3 Trial

Results of DCVax®-L Phase 3 Trial

GBM Is a Particularly Difficult Cancer

Most common and lethal primary brain cancer

- Aggressive
- Immunologically "cold"
- Extremely heterogeneous
- Invasive phenotype; difficult to resect
- Nearly 100% recurrence rate

Standard of Care (SOC)

Surgery + 6 weeks daily chemo/radiation + monthly chemo

Survival

Newly diagnosed GBM patients: mOS ~15-17 months from surgery

Time to tumor recurrence: ~7-8 months from surgery

Recurrent GBM patients: mOS ~8 months from recurrence

5-year survival: <5%

GBM Clinical Trials – Years of Failures; Wide Range of Treatments Tested

2005-2016

1034 Neuro-Oncology

20(8), 1034–1043, 2018 | doi:10.1093/neuonc/noy027 | Advance Access date 5 April 2018

The clinical trials landscape for glioblastoma: is it adequate to develop new treatments?

Alyssa M. Vanderbeek, Rifaquat Rahman, Geoffrey Fell, Steffen Ventz, Tianqi Chen, Robert Redd, Giovanni Parmigiani, Timothy F. Cloughesy, Patrick Y. Wen, Lorenzo Trippa,* and Brian M. Alexander*

- **417 clinical trials for Glioblastoma;**
- **31,952 patients**
- **only 16 Phase 3 trials; only 1 positive (TFF device)**

2016-2021 **More failures of large Glioblastoma trials**

- **Checkpoint inhibitors**
- **CAR-Ts**
- **Peptide vaccines**
- **Gene therapy**
- **Chemo**
- **DCs + standardized peptides**

GBM Survival Remains Dismal

- **Temodar approved for newly diagnosed GBM in 2005 based on adding 2.5 months' survival**

- **No systemic treatment has extended newly diagnosed GBM survival in 17 years since then**

- **Gliadel wafer approved for recurrent GBM in 1995 based on adding 2 months' survival**

- **No treatment of any type has extended recurrent GBM survival in 27 years since then**

DCVax®-L Phase 3 Trial: Innovative Trial Design

Trial Overview

Treatment: Autologous dendritic cells (DCs) pulsed with autologous tumor lysate (DCVax®-L). Intra-dermal injections in arm.

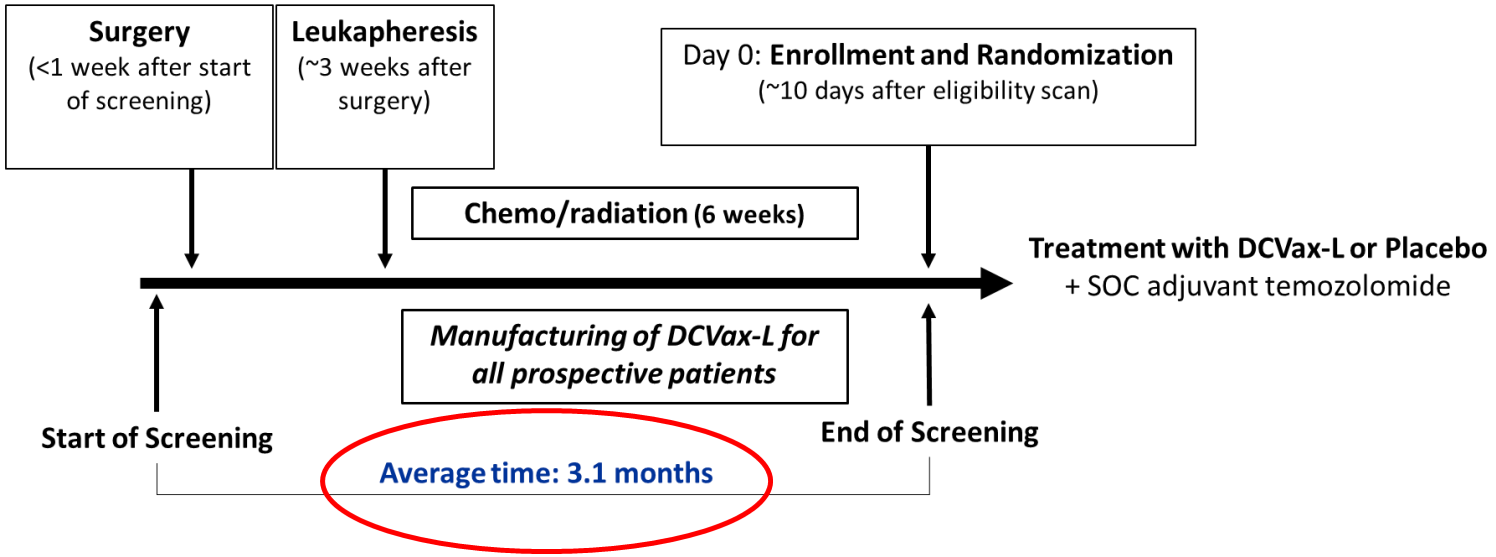
Trial design: Double-blind randomized trial with crossover

331 patients, 94 trial sites in 4 countries
(one of the largest trials of a personalized cell therapy)

Timeline:

- Began 2007
- Enrollment suspended 2008-2011 for financial reasons
- 92% of patients enrolled 2012-2015
- Last patient enrolled November 2015
- Long-term survival follow-up to determine survival tail

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

Crossover Design

All patients could cross over to receive DCVax-L following tumor recurrence

All parties (patients, physicians, sponsor, CRO) **remained blinded** as to what treatment received before crossover

Crossover was necessary for feasibility and ethical reasons:

- **Necessary for enrollment and retention of patients** in era when immune therapies not yet generally viewed as promising for cancer

- Important to justify all patients undergoing **invasive leukapheresis procedure.** No benefit to placebo patients unless they could receive their autologous product made from the leukapheresis.

Progression Free Survival & Pseudo-Progression

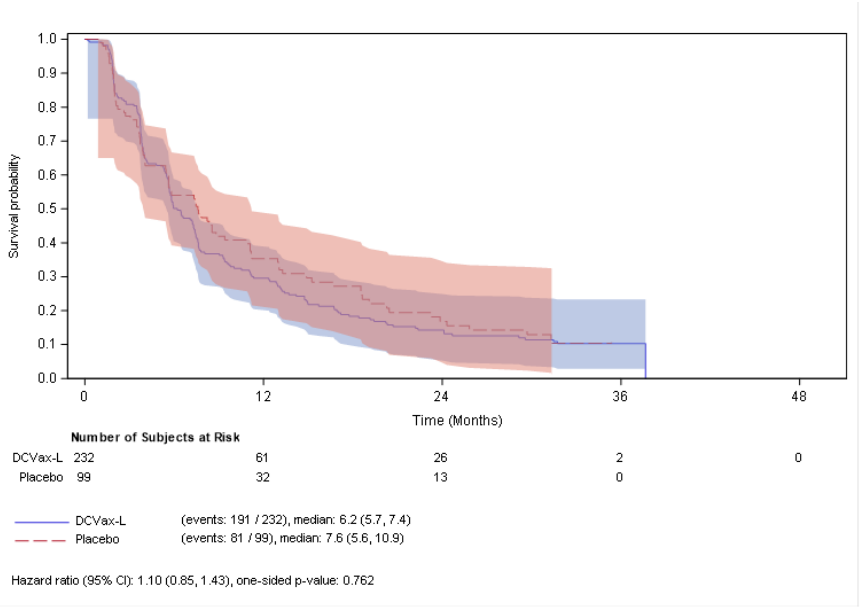
Original primary endpoint, when trial designed in 2007: Progression-Free Survival (PFS)

While the trial was underway, Pseudo-progression (PsPD) became recognized as major issue -- difficulty distinguishing real vs. PsPD

PsPD is an even bigger issue with immune cell therapies: vaccine-induced infiltration of immune cells

PFS endpoint not feasible due to PsPD. So, SAP focused on OS, and specified OS as the primary endpoint before unblinding.

Progression Free Survival



- PFS was not significantly different between the DCVax-L arm and placebo arm: p=0.47

- mPFS was 6.2 months (95% CI: 5.7-7.4 months) for DCVax-L patients; mPFS was 7.6 months (95% CI: 5.6-10.9 months) for placebo patients

- **The results in DCVax-L patients may reflect vaccine-induced PsPD.**

Overall Survival Endpoints & External Controls

Since PFS was not feasible as the primary endpoint, due to PsPD, the **SAP focused OS endpoints**.

OS endpoints **could not be within-study comparisons** of DCVax-L patients vs. placebo patients, because placebo patients received DCVax-L following crossover.

So, the OS endpoints compared DCVax-L patients with **external controls**.

This approach fits well with growing commentary in support of streamlined trial designs and use of external controls where classic within-study comparisons are not feasible.

This approach also enabled *two* OS endpoints: nGBM and rGBM.

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: Sources and Validation

External Controls: Process & Selection Criteria

Independent expert firm (not sponsor) evaluated other GBM trials, and selected the most closely matched using 14 criteria:

- Contemporaneous, same patient population, same SOC, RCT design, etc.

The independent expert selected 5 nGBM trials & 10 rGBM trials

The **control arm** patients from these comparator trials served as the external controls for the DCVax-L trial

- Controls from nGBM trials => controls for nGBM DCVax-L patients
- Controls from rGBM trials => controls for rGBM DCVax-L patients

These external controls were **pre-specified in the Statistical Analysis Plan** (SAP) for the DCVax-L trial

External Controls: Validation

4 sets of analyses were conducted to obtain controls rigorously matched to the DCVax-L study population, minimize potential biases and confirm the robustness of the survival results.

1. **Matching of the DCVax-L trial and the comparator trials**
   Matching of the trials whose control arm patients served as external controls for DCVax-L trial, using 14 criteria as described above.

2. **Validation of the external controls approach**
   For each comparator study, the treatment arm was compared against the external controls determined for DCVax-L trial. For each of the 15 comparator studies, results were same as originally reported.

External Controls – Validation (cont'd)

3. Sensitivity analyses to check for comparator differences

5 sensitivity analyses conducted, removing each of the 5 comparator studies for nGBM, one at a time. No change in comparison with DCVax-L trial seen.

6th sensitivity analysis removed 2 of the 5 comparator trials, in which it was unclear whether they excluded patients with early progression as did other 3 comparators and the DCVax-L trial. No change in comparison seen.

4. Adjustments for individual patient characteristics

Matching Adjusted Indirect Comparison (MAIC) methodology used to adjust for even small differences in individual patient characteristics. Comparison of DCVax-L vs. external controls OS remained statistically significant. (Propensity score matching was not feasible with the available data.)

External Controls for nGBM – 5 Comparator RCTs

Newly Diagnosed Glioblastoma			
Study	n	Median OS (months)	95 CI (months)
Gilbert et al 2013	411	16.6	14.9 – 18.0
Gilbert et al. 2014	309	16.1	14.8 – 18.7
Weller et al. 2017	374	17.4	16.2 – 18.8
Stupp et al. 2017	229	16.0	14.0 – 18.4
Wen et al. 2019	43	15.0	12.3 – 23.1
Aggregate Newly Diagnosed[1]	**1,366**	**16.5**	**16.0 – 17.5**

1) Based on reconstructed individual patient data (IPD)

These are leading contemporaneous studies in the field; well known.

External Controls for nGBM – Patient Demographics and Prognostic Factors

		Age				Sex		KPS			MGMT			IDH-1			Resection			Res. Disease		
	n	<50	≥50	<65	≥65	Male	Female	<90	≥90	Missing	Methylated	Unmethylated	Missing	Mut	WT	Missing	Comp	Part	Other/Missing	Minimal	Significant	Missing
Newly Diagnosed GBM (nGBM)																						
Gilbert 2013	411	27	73			58	42	34	66	0	30	62	9				56	41	3			
Gilbert 2014	309	21	79			63	37	39	62	0	28	69	3				59	39	3			
Stupp 2017	229			80	20	69	31	32	65	3	34	42	25	3	49	48	54	34	13			
Weller 2017	374			77	23	61	39				35	58	7							56	44	0
Wen 2019	43	28	72	67	33	72	28	40	61	0	42	56	2				74	26	0			
All nGBM ECP	**1366**	**25**	**75**	**77**	**23**	**62**	**38**	**35**	**64**	**1**	**32**	**59**	**9**	**3**	**49**	**48**	**57**	**38**	**5**	**56**	**44**	**0**
nGBM DCVax	**232**	**25**	**75**	**78**	**22**	**59**	**41**	**30**	**69**	**1**	**39**	**56**	**5**	**3**	**88**	**9**	**63**	**37**	**0**	**63**	**37**	**0**

External Controls for rGBM – 10 Comparator RCTs

Recurrent Glioblastoma at First Relapse			
Study	n	Median OS (months)	95 CI (months)
Wick et al. 2010	92	7.1	6.0 – 8.8
Taal et al. 2014	46	8.0	6.0 – 11.0
Brandes et al. 2016	40	7.5	5.6 – 10.3
Cloughesy et al. 2017	65	12.6	n.a.[2]
Wick et al. 2017	149	8.6	7.6 – 10.4
Brandes et al. 2018	62	5.5	3.9 – 7.2
Galanis et al. 2019	38	7.7	n.a.[2]
Lombardi et al. 2019	60	5.6	4.7 – 7.3
Narita et al. 2019	30	8.0	4.8 – 12.9
Lee et al. 2020	58	11.5	8.4 – 14.2
Aggregate Recurrent GBM[1]	**640**	**7.8**	**7.2 – 8.2**

1) Based on reconstructed individual patient data (IPD);
2) not available from referenced publication

External Controls for rGBM – Patient Demographics and Prognostic Factors

		Age			Sex		Race			MGMT			IDH-1		
	n	Median	<50	≥50	Male	Female	White	Non-White	Other/Missing	Methylated	Unmethylated	Missing	Mut	WT	Missing
Cloughesy 2017	65	55	26	74	60	40	99	0	2	40	39	22	9	91	0
Wick 2010	92		30	70	61	39									
Brandes 2016	40				58	43	73	3	25				3	73	25
Wick 2017	149	60	20	80	61	39				25	26	50			
Narita 2019	30	59			63	37									
Brandes 2019	62	59			73	27				19	40	40			
Taal 2014	46	56			57	43				50	44	6	7	93	0
Lombardi 2019	60	59			72	28				46	54	1	0	100	0
Lee 2020	58	58	29	71	62	38	91	3	5				0	100	0
Galanis 2019	38	57			58	42									
All rGBM ECP	**640**		**25**	**75**	**63**	**38**	**90**	**2**	**8**	**33**	**37**	**31**	**4**	**93**	**4**
rGBM DCVax	**64**	**56**	**27**	**73**	**66**	**34**	**84**	**0**	**16**	**44**	**52**	**5**	**3**	**84**	**12**

020221 Study Results

Overall Results

- **Primary endpoint met (mOS in nGBM),** with statistical significance
- **Secondary endpoint met (mOS in rGBM),** with statistical significance
- **Excellent safety profile:**
  - 2,193 doses of DCVax®-L administered
  - only 5 SAEs at least possibly related
  - No autoimmune reactions
  - No cytokine storms

Overall Results – 5 Key Data 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

Innovation

- **First Phase 3 trial of a systemic treatment in 17 years to show a significant extension of mOS in nGBM.**

- **First Phase 3 trial of any type of treatment in 27 years to show a significant extension of mOS in rGBM.**

- **One of the first, if not the first, Phase 3 trial to show meaningful increases in the long-term tails of the survival curves in both nGBM and rGBM.**

Broader Perspective

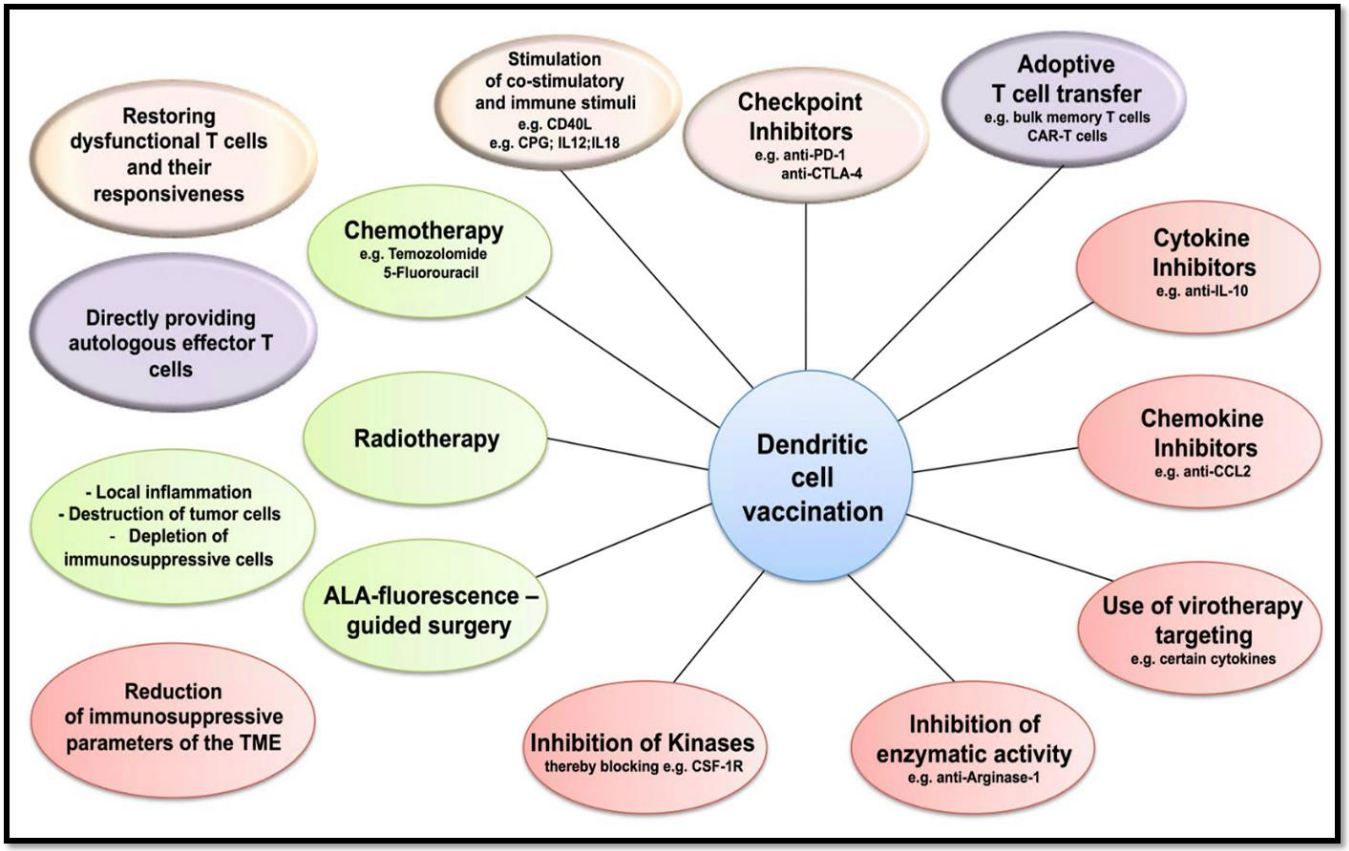
- **DCVax-L suitable for combinations with wide range of other treatments**
  (checkpoint inhibitors, oncolytic viruses, cytokines, chemo, etc.)

- **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.**

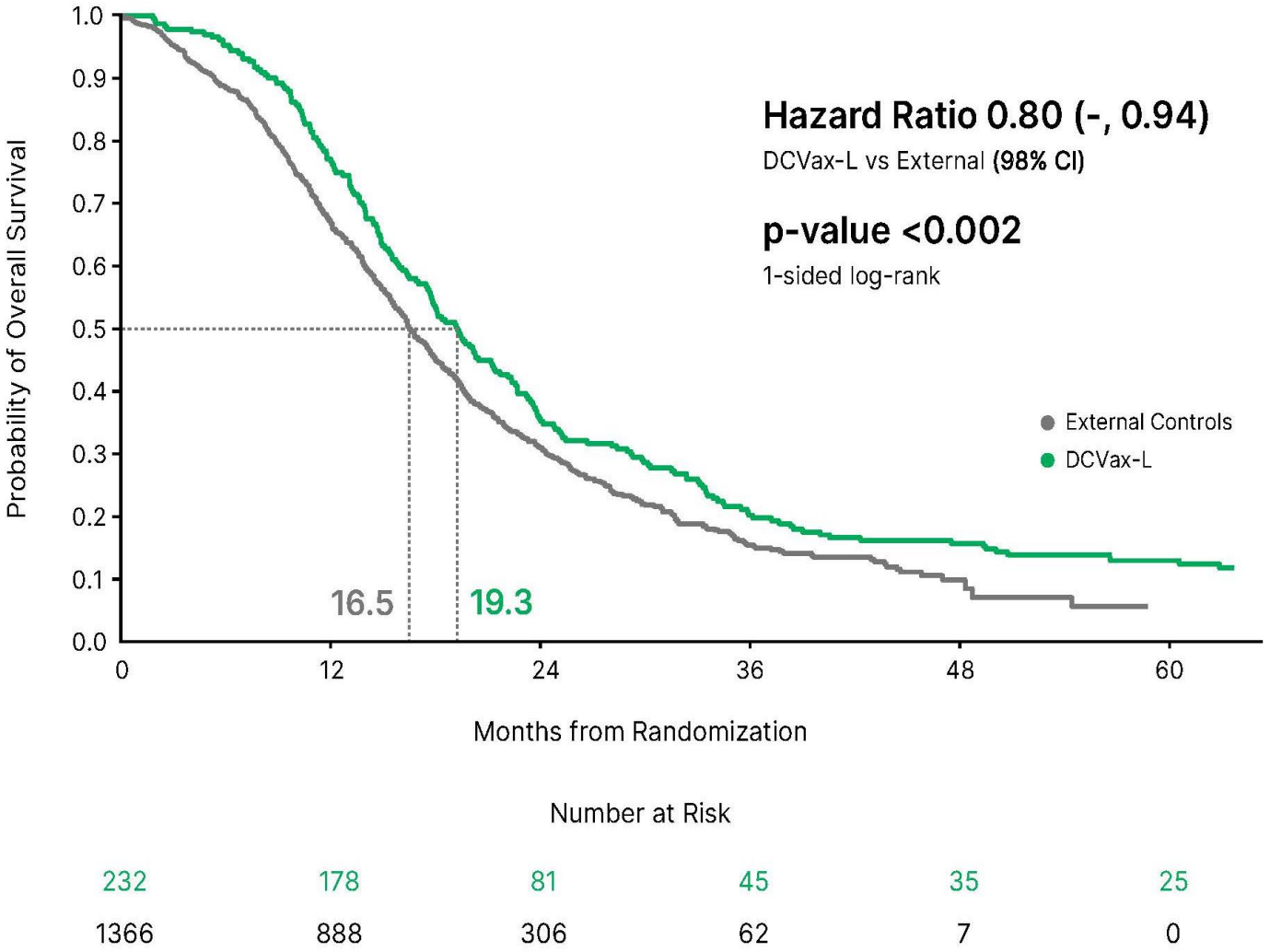
Future Opportunities for Combination Therapies



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

Newly Diagnosed GBM

Overall Survival in Newly Diagnosed GBM



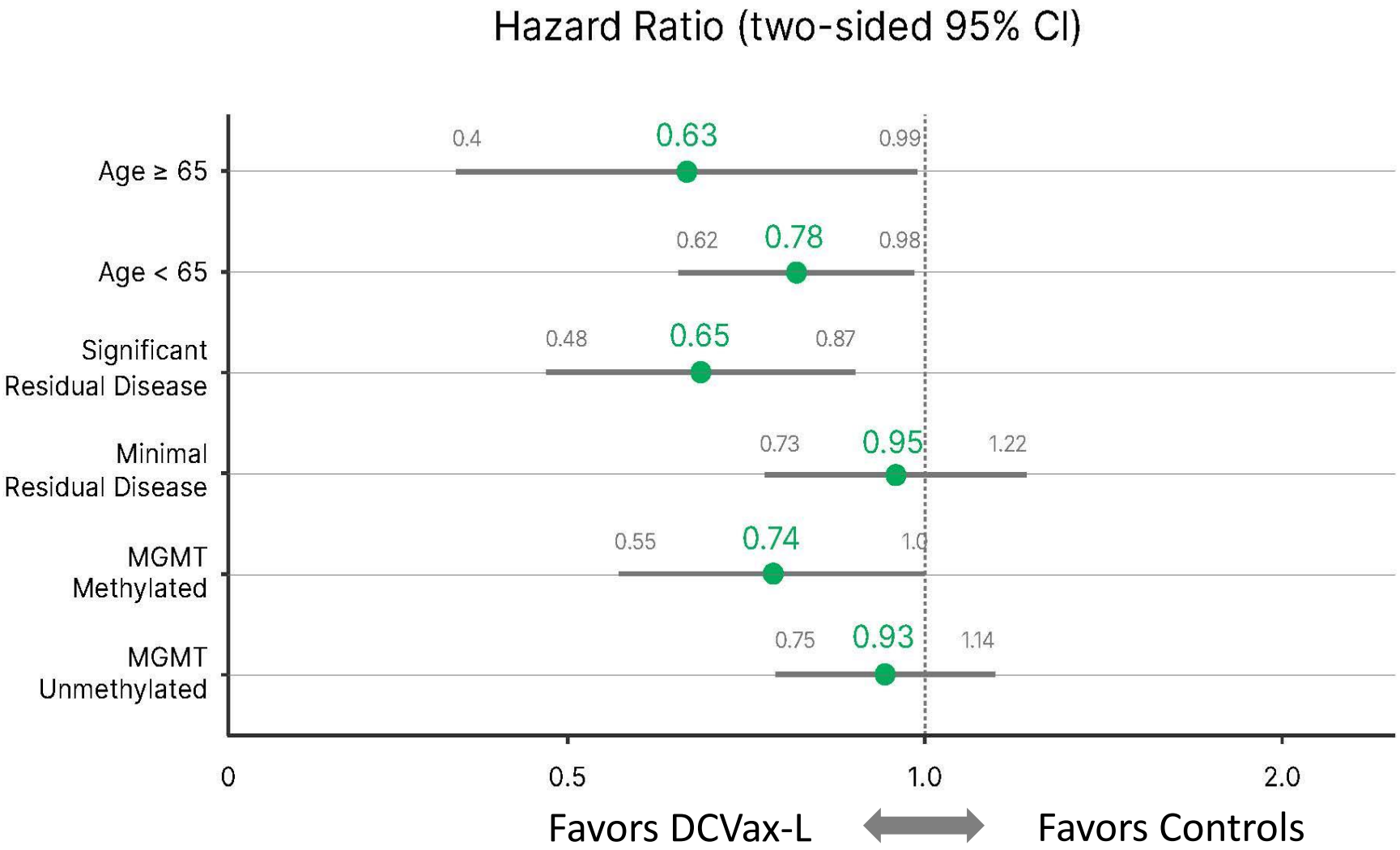
mOS of DCVax arm = **19.3 mos** from randomization; **22.4 mos from surgery**

mOS of controls = 16.5 mos from randomization

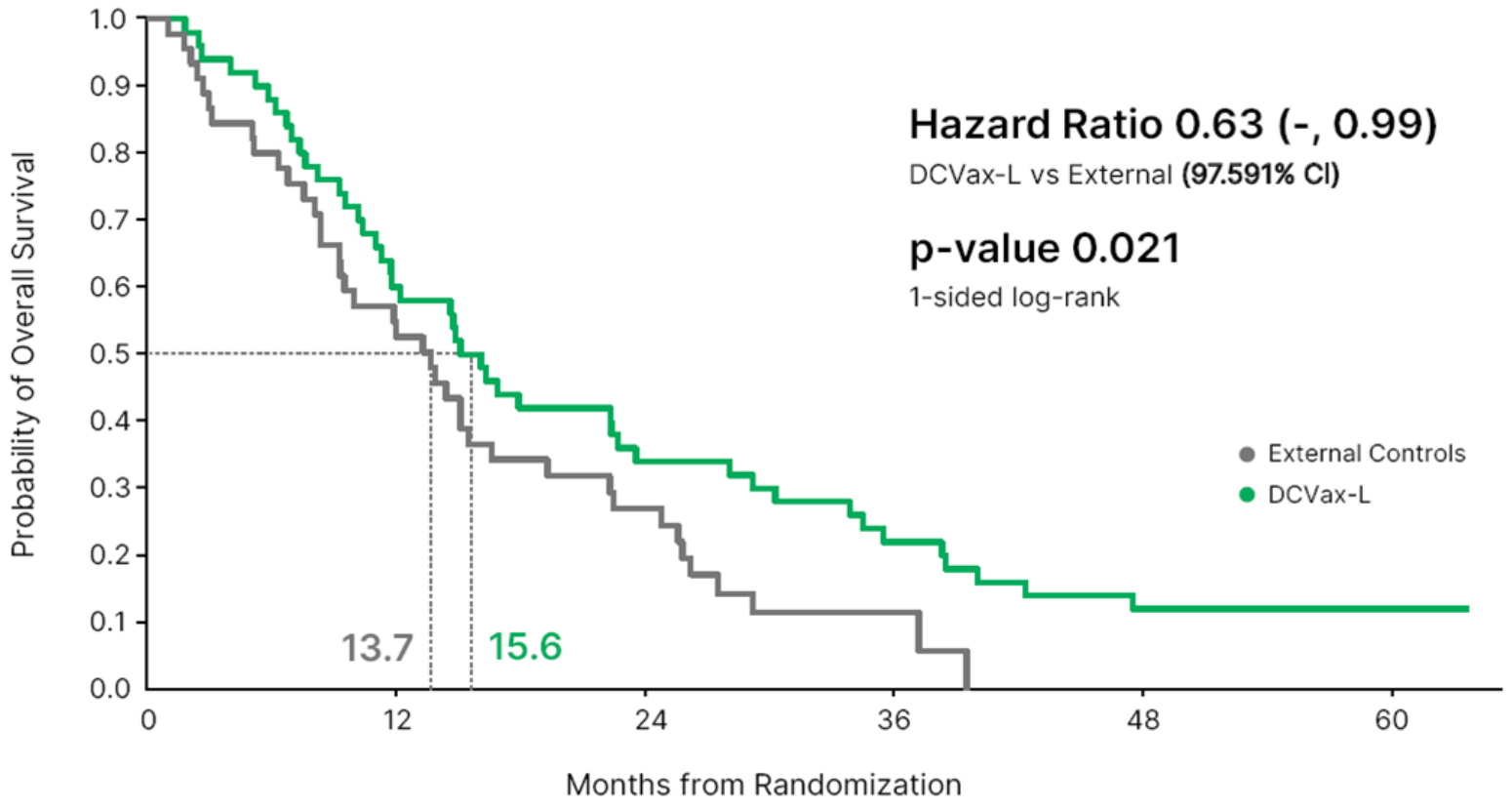
Survival Tail In Newly Diagnosed GBM

Landmark Survival Rate (%) in nGBM measured from date of randomization* *(3 months after surgery)			
	External (n = 1366)	**DCVax-L (n=232)**	**Comparative Increase**
36 months	**15.5%**	**20.2%**	**130%**
48 months	**9.9%**	**15.7%**	**159%**
60 months	**5.7%**	**13.0%**	**>228%**

Pre-Defined Sub-Groups: Summary



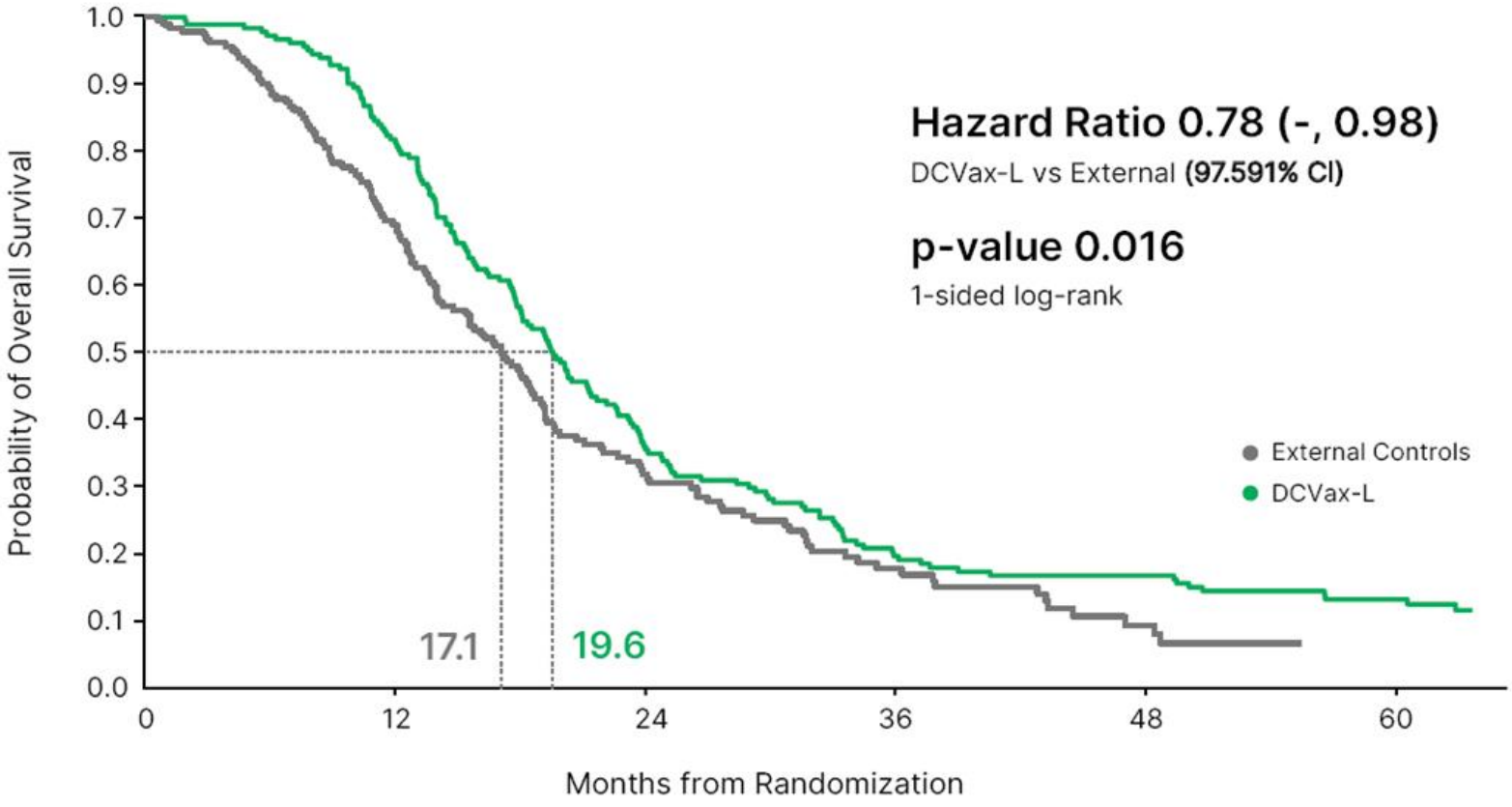
Newly Diagnosed GBM: Age ≥ 65



Number at Risk

50	30	17	11	6	5
45	24	11	2	0	0

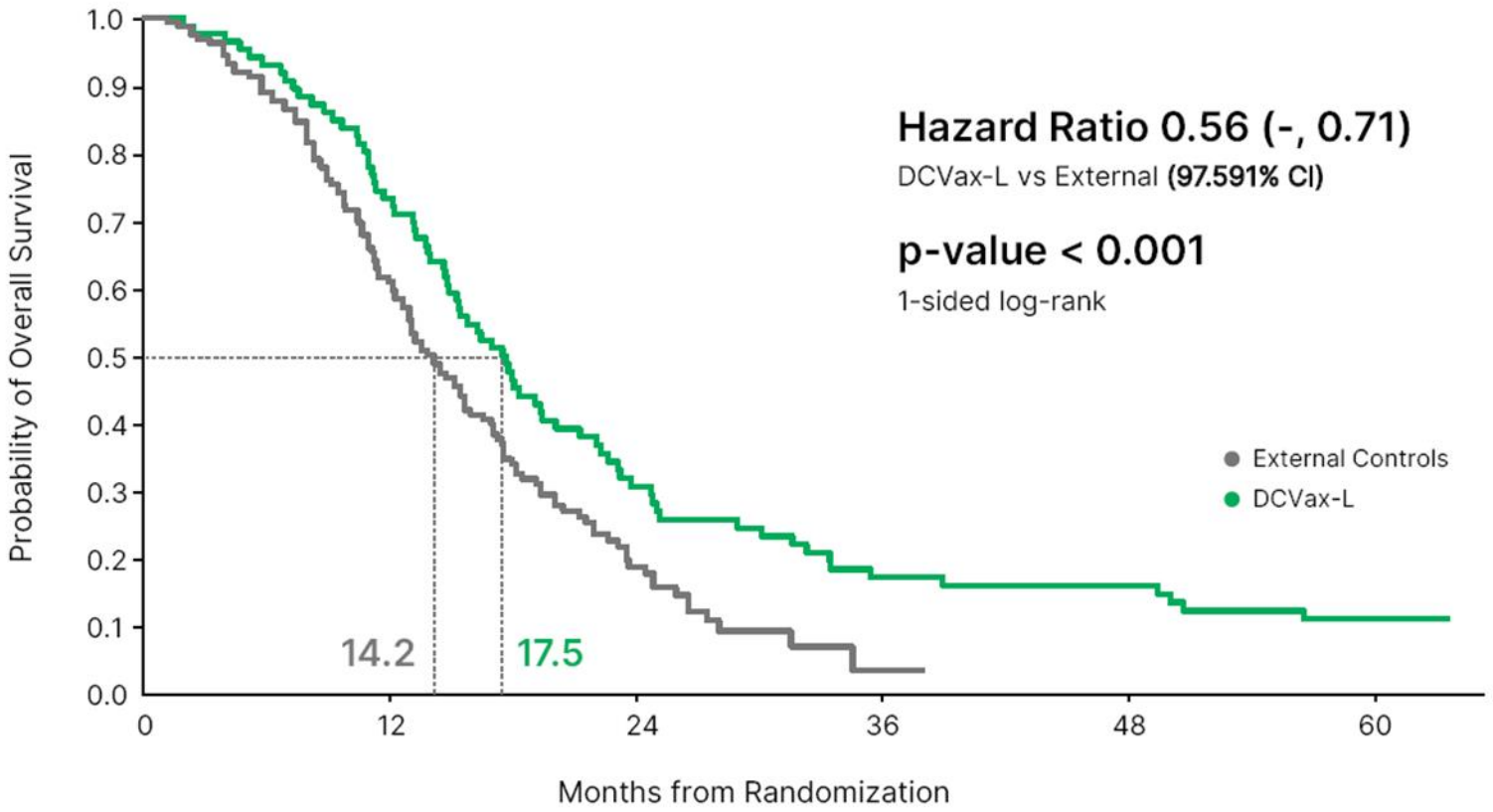
Newly Diagnosed GBM: Age < 65



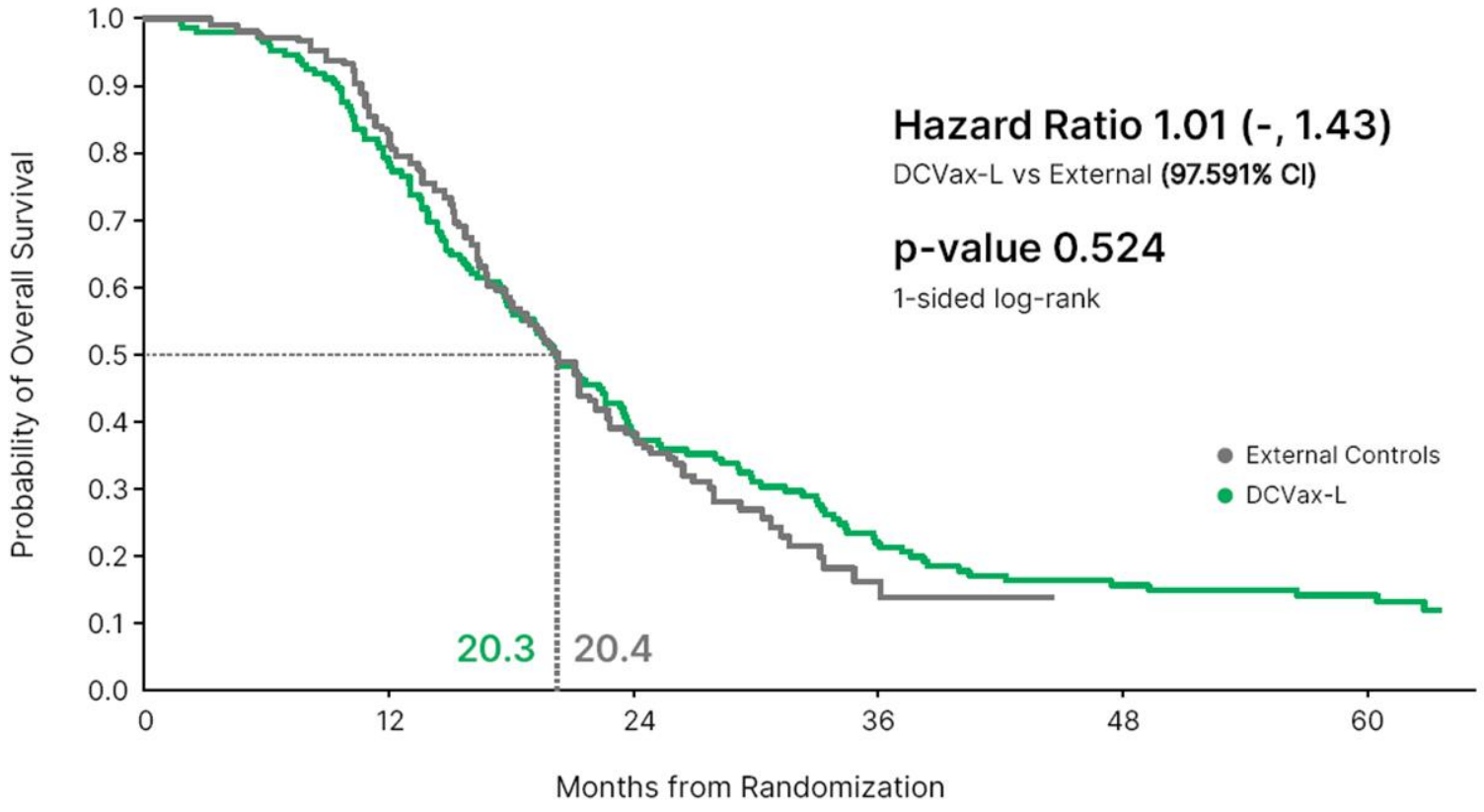
Number at Risk

182	148	64	34	29	20
184	120	49	20	7	0

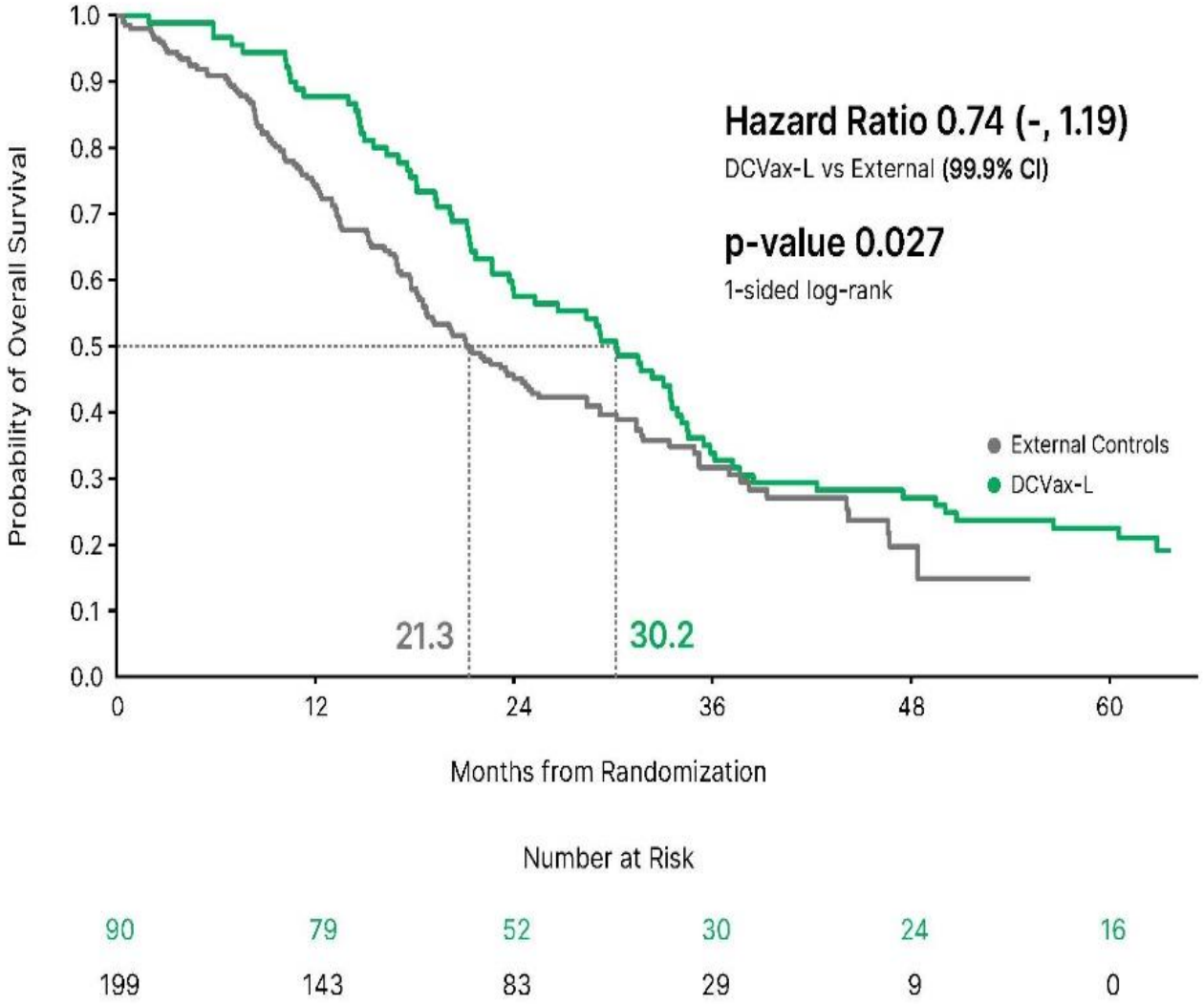
Newly Diagnosed GBM: Significant Residual Disease



Newly Diagnosed GBM: Minimal Residual Disease



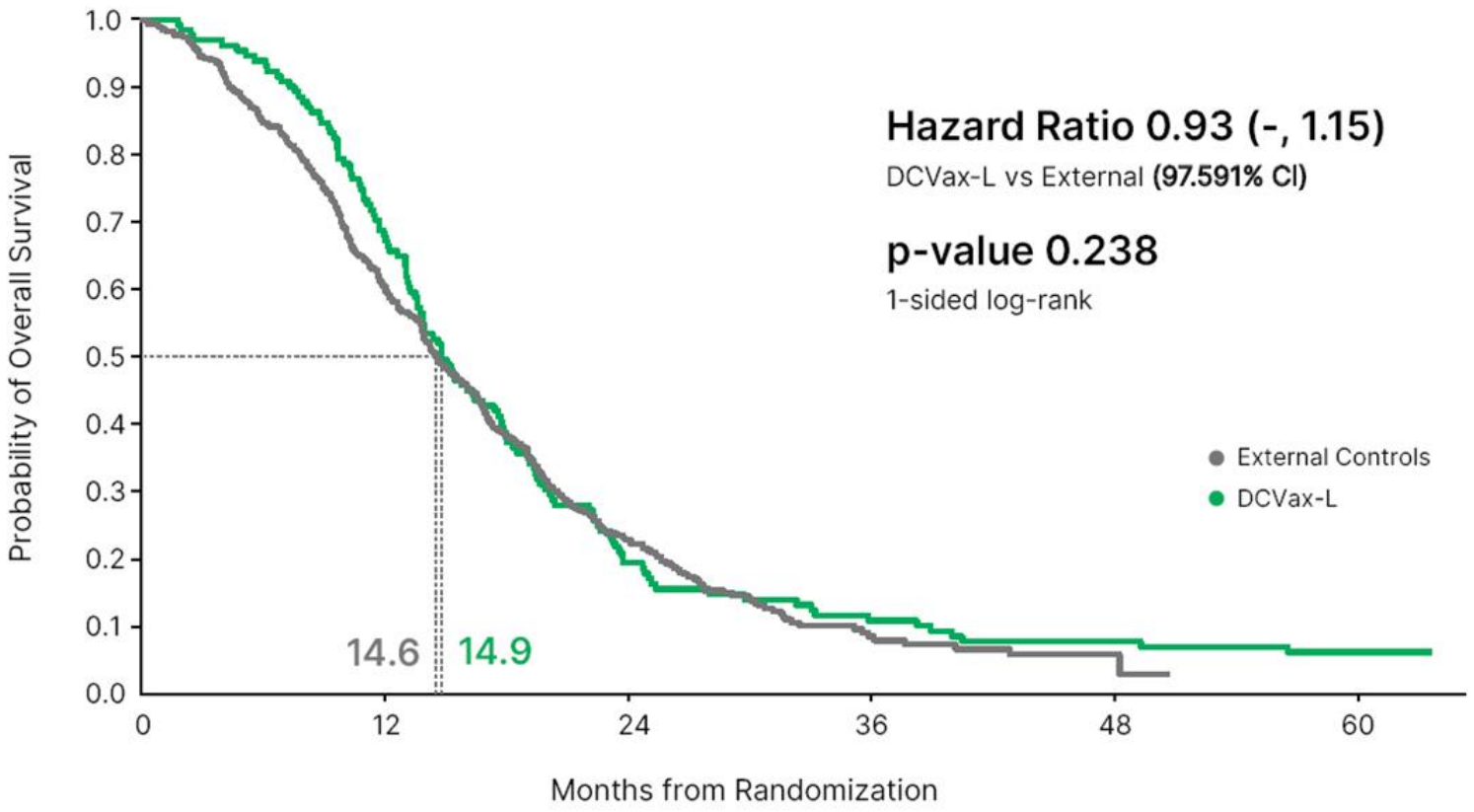
Newly Diagnosed GBM: MGMT Methylated



mMGMT DCVax-L patients mOS = **30.2 mos** from randomization; **33 mos from surgery**

mMGMT control patients mOS = 21.3 mos from randomization

Newly Diagnosed GBM: MGMT Unmethylated

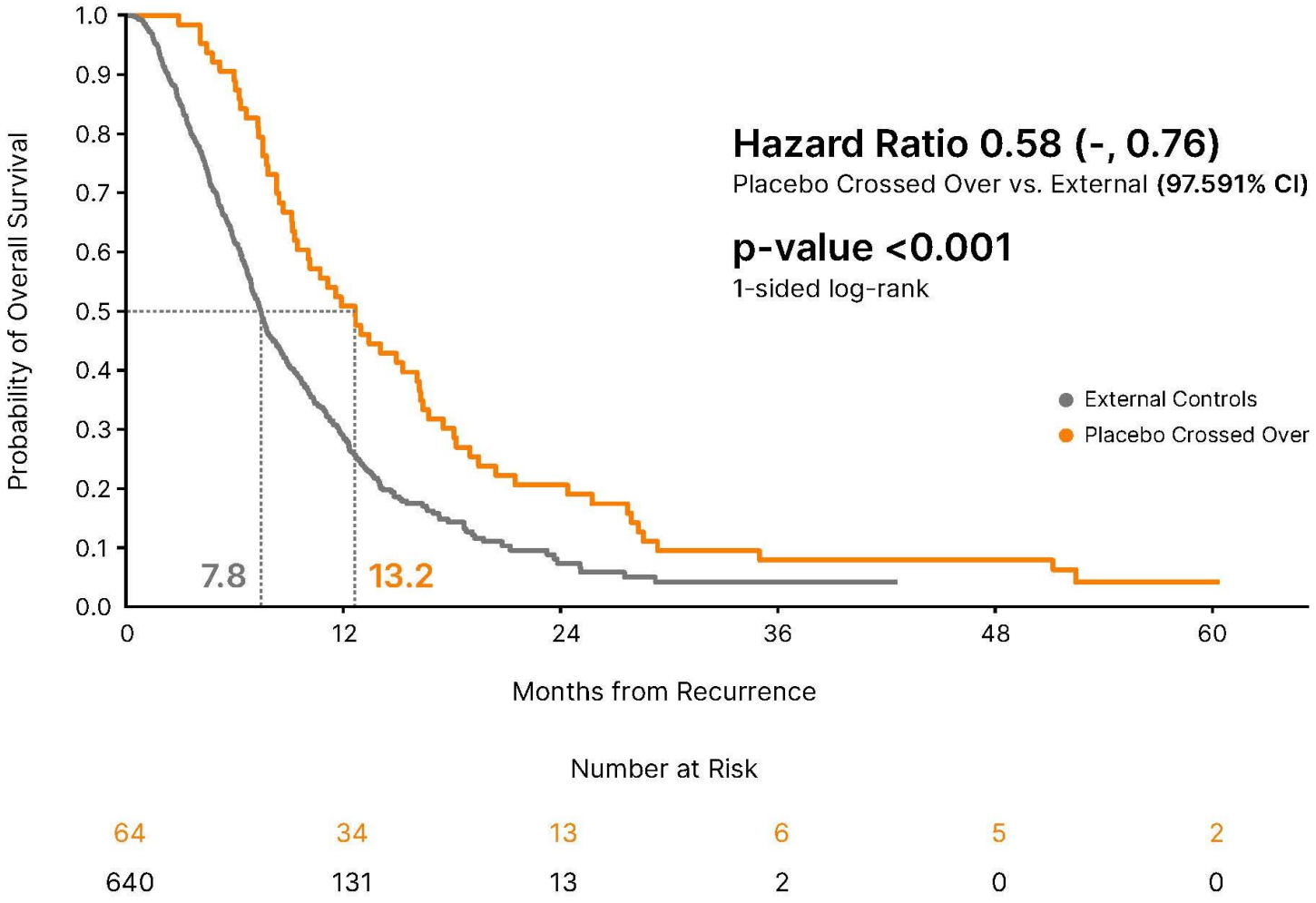


Number at Risk

131	90	25	14	10	8
349	207	73	15	4	0

Recurrent GBM

Overall Survival in Recurrent GBM



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

Survival Tail In Recurrent GBM

Landmark survival rate (%) in rGBM measured from date of recurrence			
	External* (N = 640)	DCVax-L (N = 64)	Comparative Increase
6 months	64.0%	90.6%	142%
12 months	30.8%	54.1%	175%
18 months	15.9%	31.8%	200%
24 months	9.6%	20.7%	215%
30 months	5.1%	11.1%	217%

Why/How Does DCVax-L Work?

Key Characteristics of DCVax-L

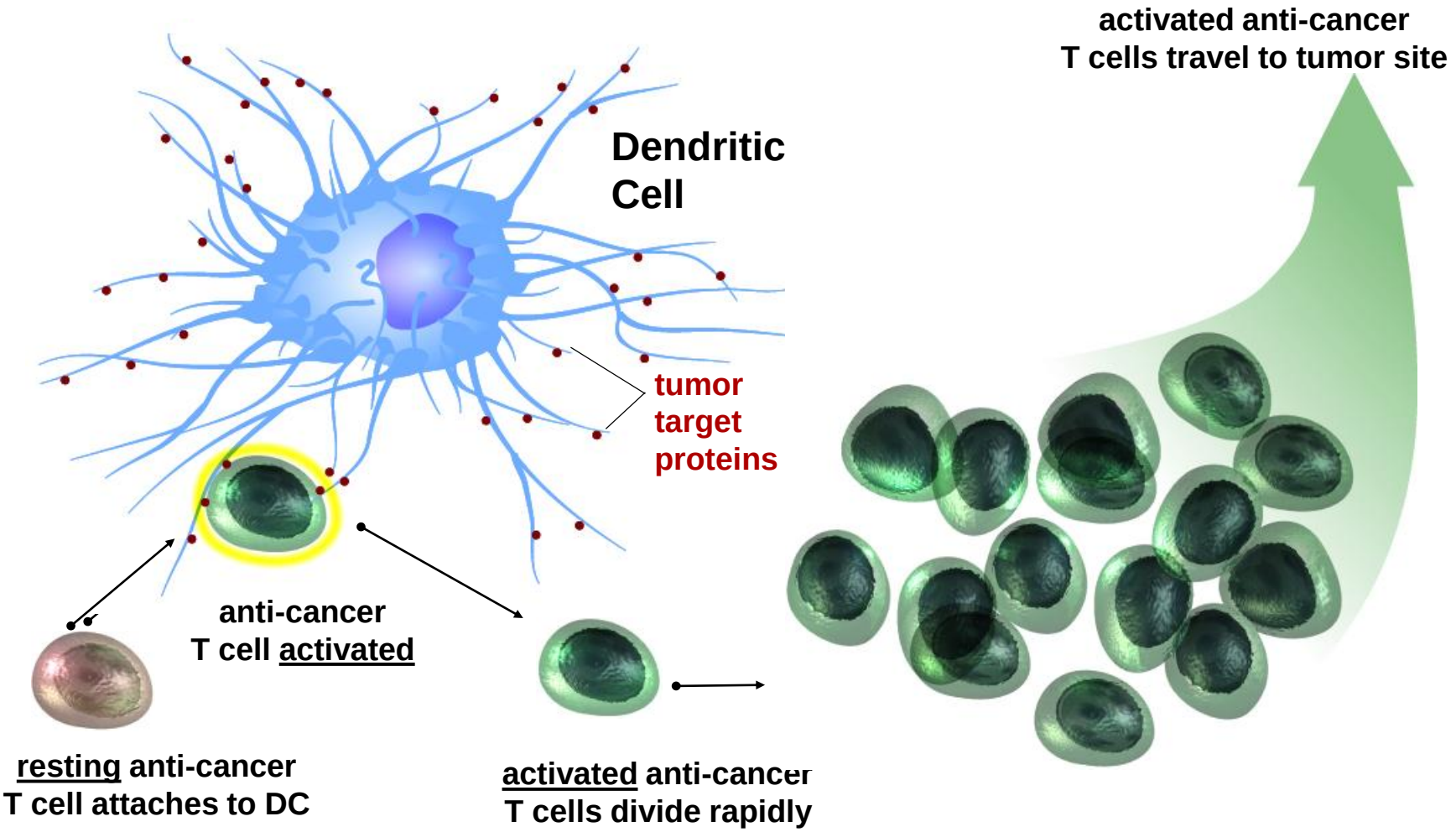
1. **Uses master cells of immune system: dendritic cells**
   - **Mobilizes multiple elements of the immune system**

2. **Fully personalized**
   - **Inherently targets antigens actually on the patient's tumor -- fits the patient's version of the cancer.**

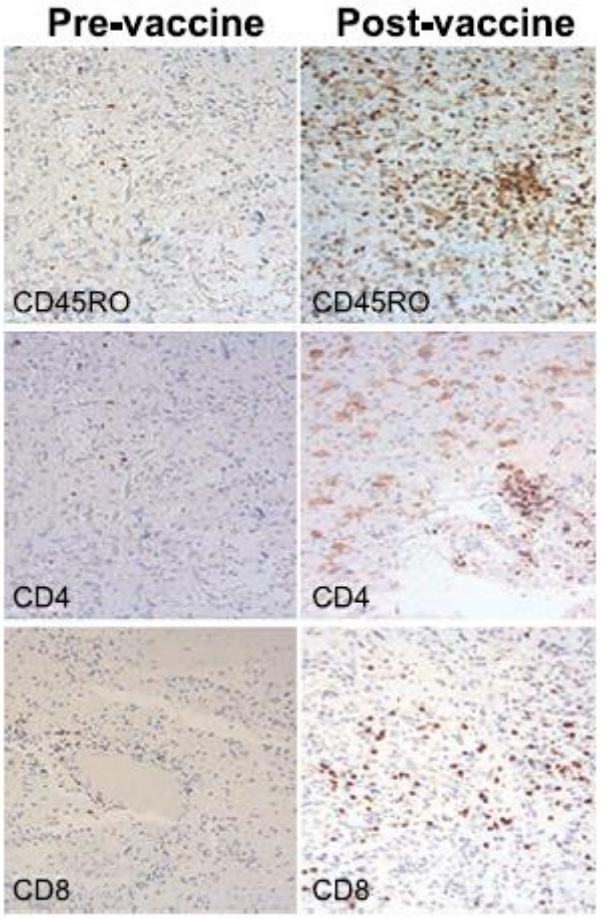
3. **Uses ALL tumor antigens, not just 1 or a few**
   - **Makes it difficult for tumors to mutate around the antigens targeted. Minimizes tumor escape after (or during) treatment.**

Addresses extensive complexity and variability of solid tumors.

Large Multiplier: Dendritic Cell Activates *Hundreds* of T Cells, *Diverse* T Cells & Other Immune Cells



T Cells Can Cross the Blood Brain Barrier; T Cells Infiltrate Glioblastoma Tumors After DCVax-L



Infiltration of T cells into Glioblastoma tumors is observed in patients treated with DCVax®-L

Both CD4 and CD8 T cells are seen

L. Liau et al.

Conclusions (1)

- The completion of a large, phase 3 trial including 331 patients, 94 sites, over 70 clinical investigators, in 4 countries using an autologous, dendritic cell, tumor lysate (DCVax-L) shows efficacy to meet the primary and secondary end-points of an increase in O.S. for nGBM and rGBM
- The vaccine is easily administered and has a favorable safety profile.
- The use of external, contemporaneous clinical trials (n = 5 for nGBM and n =10 for rGBM) is innovative, and going forward, could be transformative given the poor track record and numerous failed trails in neuro-oncology.
- There is a significant percentage of long-term survivors, consistent with an immune memory effect by the T-cells, potentially changing the natural history of GBM from a uniformly fatal to a chronic, manageable disease.

Conclusions (2)

- Specific subpopulations show an unanticipated benefit including; a) older patients, and b) patients with residual disease after surgery. As expected, patients with methylated MGMT promoter fare better than unmethylated group.
- The feasibility of the vaccination process enables widespread application in the community setting, as well as in major academic centers of excellence.
- The use of dendritic cells as the master, professional antigen presenting cells allows for combination therapy using other approaches such as blockade of immunosuppressive cytokines, CAR T cells, viral oncolytic therapy, electric field therapy, DNA vaccines, etc.
- Preliminary data shows evidence of T cell infiltration into the target tissue (Glioblastoma).

Summary

Patients treated with DCVax-L showed a

clinically meaningful and statistically significant extension of survival…

…in both newly diagnosed and recurrent GBM,

…with an excellent safety profile, and

…noteworthy long tails of survival.

Acknowledgments

- **UCLA** (US lead): Prof. Linda Liau and Dr. Robert Prins

- **Kings College Hospital** (Europe lead): Prof. Keyoumars Ashkan

- **Trial Steering Committee**:
  Prof. Steven Brem (UPenn)
  Dr. Jian Campian (Wash. U., now Mayo Clinic)
  Dr. Fabio Iwamoto (Columbia University)
  Dr. John Trusheim (Allina Health)

- **Investigators and sub-investigators** of the 020221 trial

- **Patients and their families**