NORTHWEST BIOTHERAPEUTICS

DCVax®-L Personalized Immune Therapies

Phacilitate Conference
"The Next Breakthrough: Challenging the Status Quo"

January 23, 2019

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Solid Tumors Remain A Challenge For Immunotherapies

DCVax®-L Is Designed To Meet This Challenge

Key Challenge for Immune Therapies: Solid Tumors

Solid Tumors Comprise At Least 80% of All Cancers
and
Solid Tumors Are Highly Variable – A Personalized Disease

- Extensive variations **among cancers**
- Extensive variations **among patients**, even with "same" cancer
- Significant variations **within a single patient** as disease progresses
- Significant variations even **within a single tumor**

DCVax® is tailored to address this extensive variability

Scientific Knowledge Growing Rapidly, But Survival Improvements Limited In Many Solid Tumors

Example: Glioblastoma brain cancer.

Standard of care chemo approved in 2005 (to be added to surgery and radiation) based on adding 10 weeks of survival

In the 14 years since then….

- **extensive genomic and epigenetic profiling** (e.g., Cancer Genome Atlas)
- **identification of tumor subtypes, patient subgroups, pseudoprogression**
- **over 400 clinical trials, over 31,000 patients, many diverse treatments**

BUT, little change in median survival: was ~14.6 mos, now ~15-17 mos

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*

2005-2016

- 417 clinical trials for Glioblastoma
- 31,952 patients
- only 16 Phase 3 trials – only 1 Phase 3 trial positive result

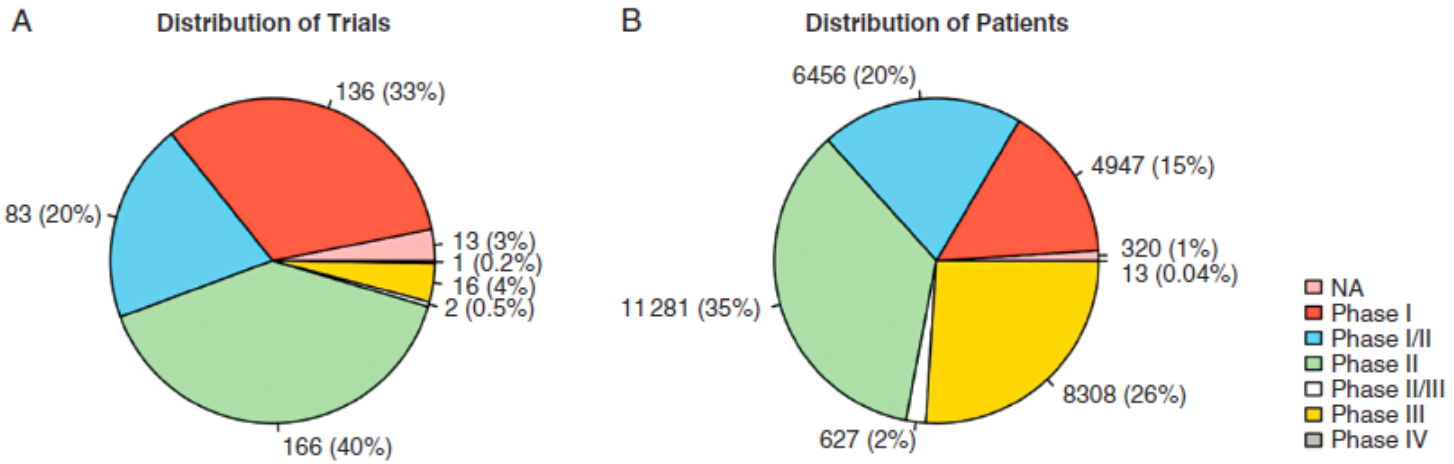

Fig. 2 Distribution of trials (A) and patients (B) among phases.

Cancer Therapies Have Tended to Search for "Silver Bullets"

Cancer therapies typically **1 active agent** ("silver bullet" agent) aimed at **1 or couple of targets** ("silver bullet" target)

- CAR-Ts, TCRs
- Checkpoint inhibitors
- Peptides
- Antibodies
- Targeted therapies

Some therapies in early development are using more targets – but still quite limited (e.g., bi-specific, tri-specific or half-dozen targets)

Some therapies hope for "epitope spreading" to reach a few additional targets that are similar, but that is uncertain and still very limited if it occurs

How Realistic Are "Silver Bullets" Against Enormous (and Dynamic) Complexity and Heterogeneity??

(examples of Cancer Genome Atlas Project findings….
initial publication on GBM in 2008)

Vol 455|23 October 2008|doi:10.1038/nature07385 nature

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

Patterns of somatic nucleotide alterations in glioblastoma

A total of 91 matched tumour–normal pairs (72 untreated and 19 treated cases) were selected from the 143 cases for detection of somatic mutations in 601 selected genes (Supplementary Table 5). The resulting sequences, totalling 97 million base pairs (1.1 ± 0.1 million bases per sample), uncovered 453 validated non-silent somatic mutations in 223 unique genes, 79 of which contained two or more events (Supplementary Table 6; see also http://tcga-data.nci.nih.gov/docs/somatic_mutations/tcga_mutations.htm). The background mutation rates differed markedly between untreated and treated glioblastomas, averaging 1.4 versus 5.8 somatic silent muta-

How Realistic Are "Silver Bullets" Against Enormous (and Dynamic) Complexity and Heterogeneity??

(larger sample set in 2013 Cancer Genome Atlas Project publication)

Cell

The Somatic Genomic Landscape of Glioblastoma

Cameron W. Brennan,[1,2,40,*] Roel G.W. Verhaak,[3,11,40] Aaron McKenna,[4,40] Benito Campos,[5,6] Houtan Noushmehr,[7,8] Sofie R. Salama,[9] Siyuan Zheng,[3] Debyani Chakravarty,[1] J. Zachary Sanborn,[9] Samuel H. Berman,[1] Rameen Beroukhim,[4,5] Brady Bernard,[10] Chang-Jiun Wu,[11] Giannicola Genovese,[11] Ilya Shmulevich,[10] Jill Barnholtz-Sloan,[12] Lihua Zou,[4] Rahulsimham Vegesna,[3] Sachet A. Shukla,[5] Giovanni Ciriello,[13] W.K. Yung,[14] Wei Zhang,[15] Carrie Sougnez,[4] Tom Mikkelsen,[16] Kenneth Aldape,[15] Darell D. Bigner,[17] Erwin G. Van Meir,[18] Michael Prados,[19] Andrew Sloan,[20] Keith L. Black,[21] Jennifer Eschbacher,[22] Gaetano Finocchiaro,[23] William Friedman,[24] David W. Andrews,[25] Abhijit Guha,[26] Mary Iacocca,[27] Brian P. O'Neill,[28] Greg Foltz,[29] Jerome Myers,[30] Daniel J. Weisenberger,[7] Robert Penny,[31] Raju Kucherlapati,[32] Charles M. Perou,[33] D. Neil Hayes,[33] Richard Gibbs,[34] Marco Marra,[35] Gordon B. Mills,[36] Eric Lander,[4] Paul Spellman,[37] Richard Wilson,[38] Chris Sander,[13] John Weinstein,[3] Matthew Meyerson,[4,5] Stacey Gabriel,[4] Peter W. Laird,[7] David Haussler,[9,39] Gad Getz,[4] Lynda Chin,[4,11,*] and TCGA Research Network

cedures). Overall, of the 291 tumor exomes sequenced, 21,540 somatic mutations were identified, with a median rate of 2.2 coding mutations per megabase (lower-upper quartile range, 1.8–2.3). Among the somatic mutations were 20,448 single-nucleotide variants (SNVs), 39 dinucleotide mutations, and 1,153 small insertions and deletions (indels). The SNVs mutations included 5,379 silent, 3,901 missense, 831 nonsense, 360 splice-site and 760 mutations resulting in a frame shift.

Cell *155*, 462–477, October 10, 2013 ©2013 Elsevier Inc.

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How Realistic Are "Silver Bullets" Against Enormous (and Dynamic) Complexity and Heterogeneity??

(functional aspects -- factors helping to enable tumor escape)

News Release

Posted: October 28, 2013

Genomic Understanding of Glioblastoma Expanded

Glioblastoma multiforme (GBM) was the first cancer type to be systematically studied by The Cancer Genome Atlas Research Network (TCGA) in 2008. In a new, complementary report, TCGA experts examined more than 590 GBM samples--the largest to date utilizing genomic characterization techniques and nearly 400 more than were examined in 2008….

….In 2013, it is now evident that glioblastoma growth is driven by large signaling networks that have a functional redundancy that permit adaptation of the tumor in response to targeted molecular treatments…

DCVax®-L Takes A Different Approach: Many Active Agents Against Many Tumor Targets

The Opposite of “Silver Bullets”

Key Characteristics of DCVax®-L

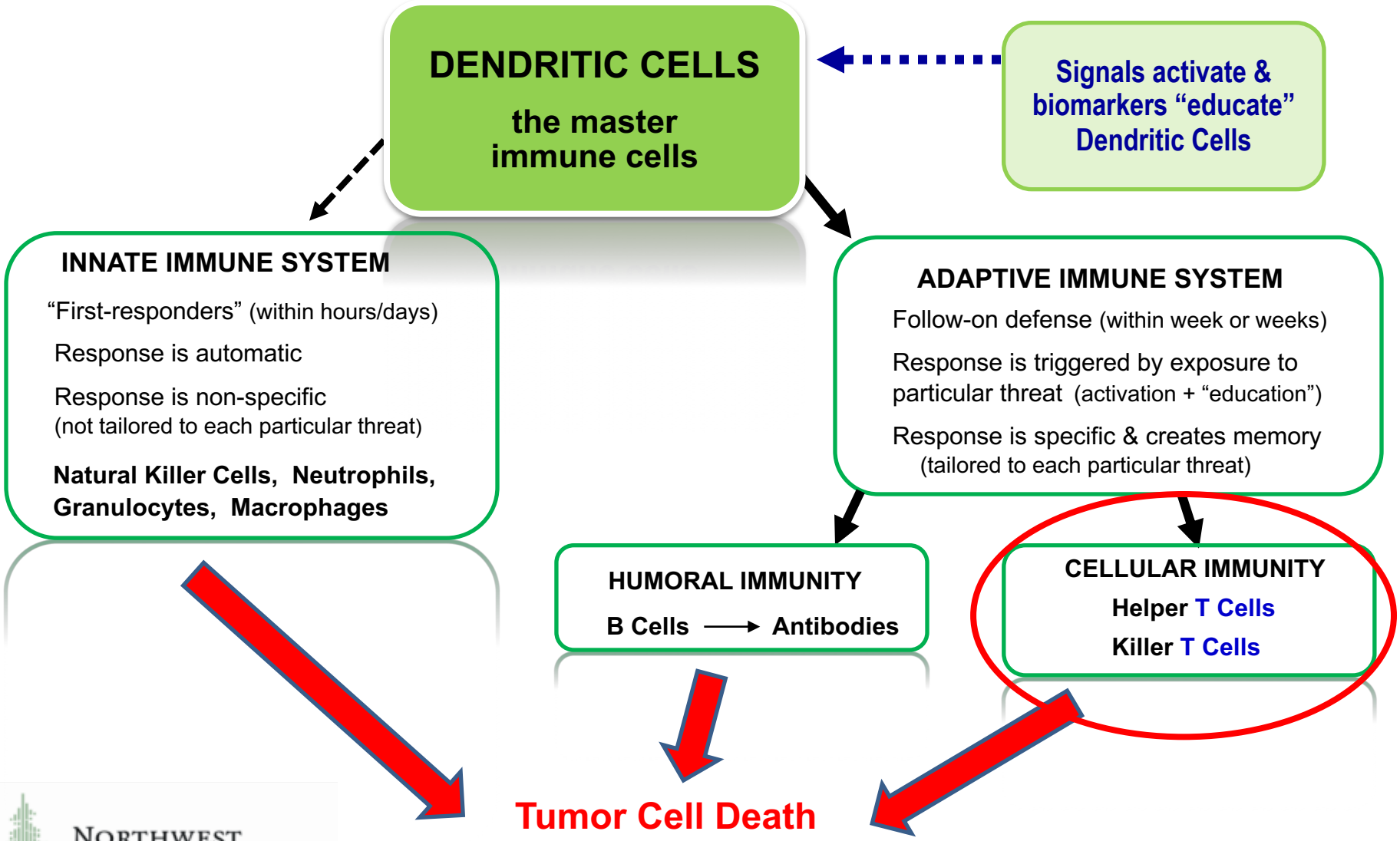
1. **Uses master cell of immune system: dendritic cells**
   - Mobilizes *many* active agents – whole immune system, both T cells and others.

2. **Fully personalized**
   - Avoids Russian roulette at the outset, as to whether patient's tumor expresses the treatment target -- fits the patient's version of the cancer.

3. **Uses ALL tumor antigens, not just 1 or a few**
   - Minimizes tumor escape after treatment. When treatments target just 1 or a couple of antigens, the tumor stops expressing those.

DCVax® uses Nature's system: many weapons against many targets to address extensive complexity and variability of solid tumors

Dendritic Cells Mobilize Overall Immune System



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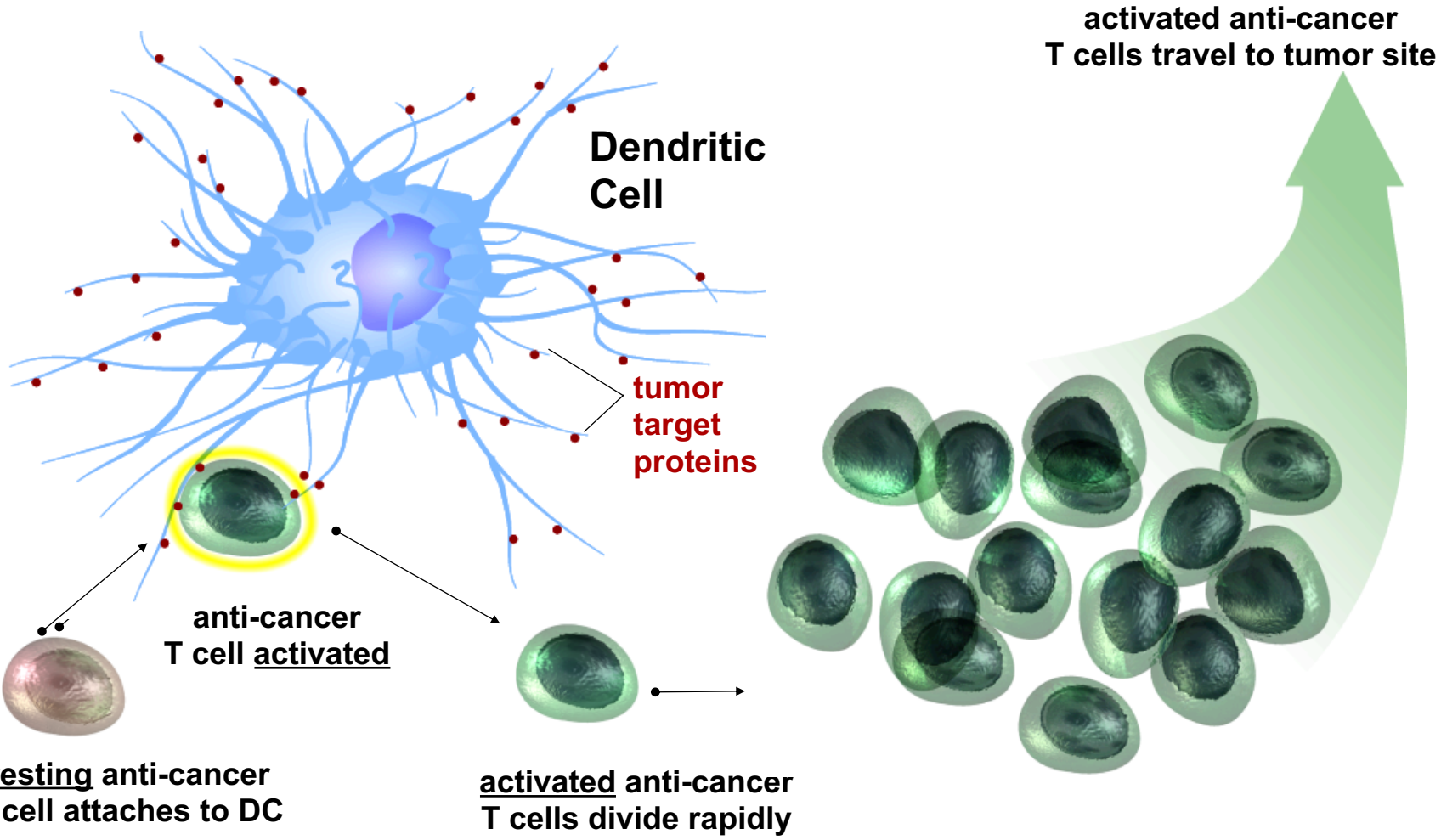
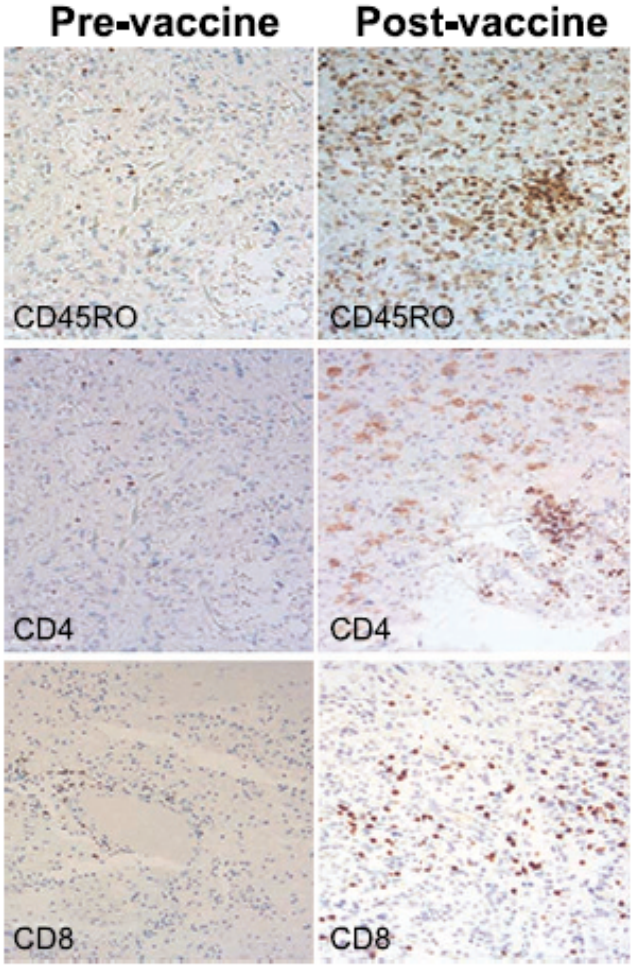
Large Multiplier: Each Dendritic Cell Activates *Hundreds* of T Cells, *Diverse* T Cells and Others



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.

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Clinical Results To Date With the DCVax®-L Approach Are Encouraging

International Phase 3 Trial of DCVax®-L for Newly Diagnosed Glioblastoma Is Nearing Completion

- 331-patients in Intent to Treat (ITT) population (one of the largest late-stage trials of a cell therapy)
- Over 80 sites in US, Canada, UK and Germany
- Randomized 2:1 (SOC + DCVax®-L vs. SOC + placebo)
- Primary endpoint: Progression Free Survival (PFS)
  Secondary endpoint: Overall Survival (OS)
- Crossover allowed at tumor recurrence for all patients; all parties remain blinded about which arm of trial patient in before recurrence
- Due to crossover, 90% of patients have received DCVax®-L
- Last enrollment in November 2015; data has matured
- Key focus: "long tail" of survival curve, as with all immunotherapies
- Company remains blinded, working with experts towards data lock & unblinding

Blinded Interim Data From DCVax®-L Phase 3 Trial Published & Presented

Initial (2017) blinded interim data published in JTM in May 2018.

Liau *et al. J Transl Med* (2018) 16:142
https://doi.org/10.1186/s12967-018-1507-6

Journal of Translational Medicine

RESEARCH Open Access

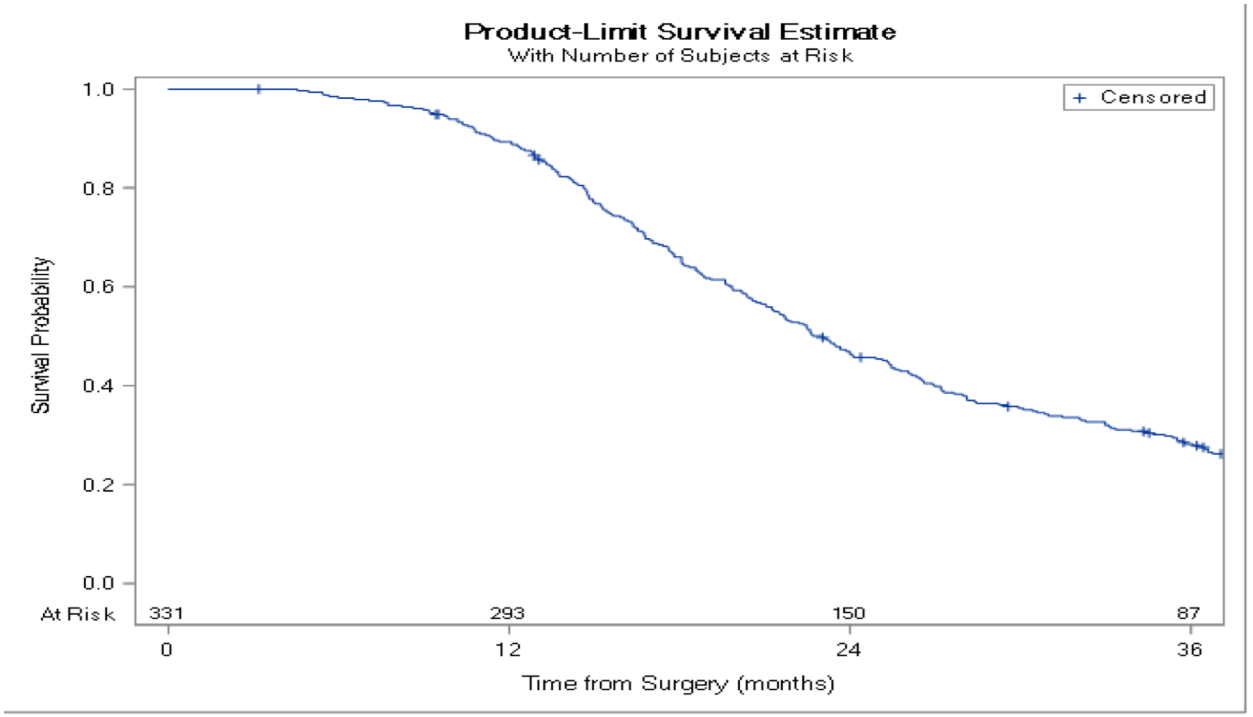
First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma

Linda M. Liau[1*], Keyoumars Ashkan[2], David D. Tran[3], Jian L. Campian[4], John E. Trusheim[5], Charles S. Cobbs[6], Jason A. Heth[7], Michael Salacz[8], Sarah Taylor[8], Stacy D. D'Andre[9], Fabio M. Iwamoto[10], Edward J. Dropcho[11], Yaron A. Moshel[12], Kevin A. Walter[13], Clement P. Pillainayagam[14], Robert Aiken[15], Rekha Chaudhary[16], Samuel A. Goldlust[17], Daniela A. Bota[18], Paul Duic[19], Jai Grewal[59], Heinrich Elinzano[20], Steven A. Toms[20], Kevin O. Lillehei[21], Tom Mikkelsen[22], Tobias Walbert[22], Steven R. Abram[23], Andrew J. Brenner[24], Steven Brem[25], Matthew G. Ewend[26], Simon Khagi[26], Jana Portnow[27], Lyndon J. Kim[28], William G. Loudon[29], Reid C. Thompson[30], David E. Avigan[31], Karen L. Fink[32], Francois J. Geoffroy[33], Scott Lindhorst[34], Jose Lutzky[35], Andrew E. Sloan[36], Gabriele Schackert[37], Dietmar Krex[37], Hans-Jorg Meisel[38], Julian Wu[39], Raphael P. Davis[40], Christopher Duma[41], Arnold B. Etame[42], David Mathieu[43], Santosh Kesari[44], David Piccioni[44], Manfred Westphal[45], David S. Baskin[46], Pamela Z. New[46], Michel Lacroix[47], Sven-Axel May[48], Timothy J. Pluard[49], Victor Tse[50], Richard M. Green[51], John L. Villano[52], Michael Pearlman[53], Kevin Petrecca[54], Michael Schulder[55], Lynne P. Taylor[56], Anthony E. Maida[58], Robert M. Prins[1], Timothy F. Cloughesy[1], Paul Mulholland[57] and Marnix L. Bosch[58*]

Updated (2018) blinded interim data presented in plenary session at Society for Neuro-Oncology in November 2018

Survival of Whole ITT Population, From Surgery

(interim data: 2018)



Population	n	Median OS since surgery	Survival at 1 year	Survival at 2 years	Survival at 3 years
ITT	331	23.1 months	89.3%	46.4%	28.2%

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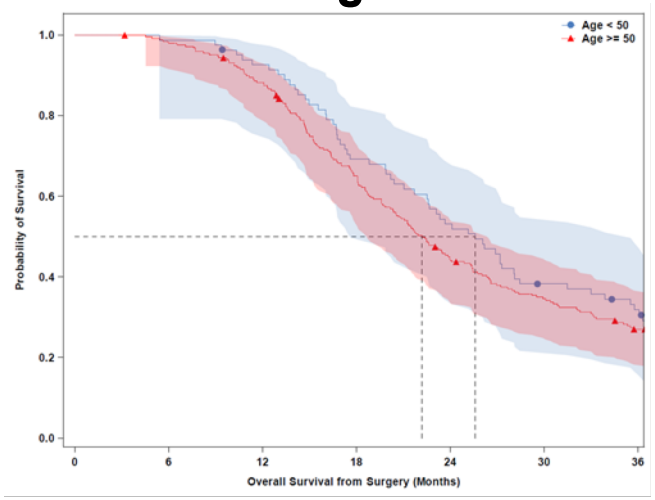
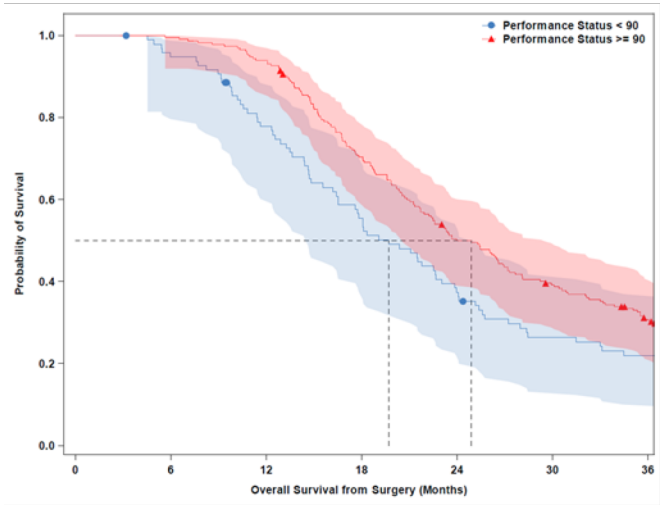
Survival By Prognostic Factors, From Surgery

(interim data: 2018)

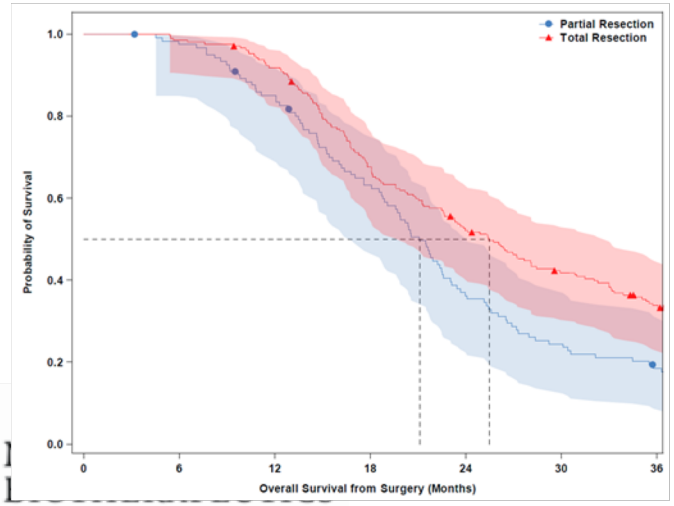
Age



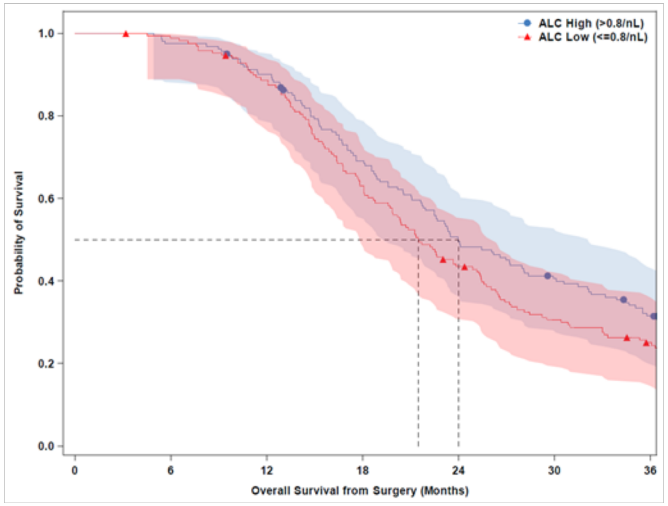
Performance Status



Extent of Surgery

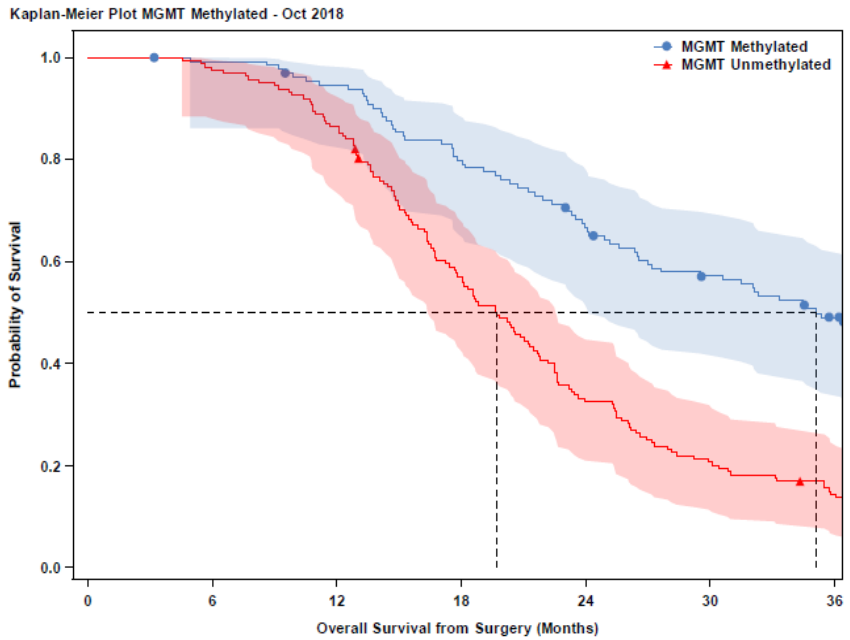


Lymphocyte Count



Survival By MGMT Methylation Status, From Surgery

(interim data: 2018)



Data set	n	Median OS since surgery	Survival at 1 year	Survival at 2 years	Survival at 3 years
MGMT Methylated	131	35.1 months	94.6%	66.6%	49.1%
MGMT Unmethylated	162	19.8 months	86.4%	32.6%	14.3%

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Survival of Top 100 Patients, From Surgery

(interim data: 2017 & 2018)

	n	KM- derived mOS	95% CI
Top 30% (2017)	100	40.4 mos	35.5-46.5
Top 30% (2018)	100	58.4 mos	45.9-94.5

Extended survival not fully explained by known prognostic factors

Top 100 Patients: Demographics

Prognostic Factor	Top 100	ITT
Age <50 + methylated MGMT + Complete resection	8%	6%
Median age and range	56 (21, 70)	55 (19, 73)
Age >65 years	16%	17%
Age <50 years	28%	25%
KPS median (range)	90 (50, 100)	90 (40, 100)
KPS ≥80	95%	82%
Methylated MGMT	66%	39%
Complete resection (CR)	75%	63%
ALC ≥800	70%	60%

Survival Findings: Key Points

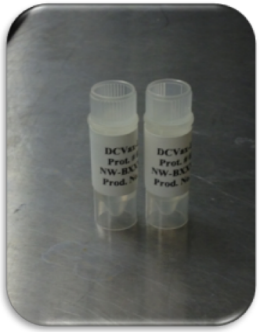
- Overall survival in the ITT population is longer than observed in historical and contemporary controls

- **This extended survival is observed both in patients with favorable prognostic factors and in patients with unfavorable prognostic factors**
  - Age ≥50 years and Age <50
  - Karnofsky performance status ≥90 and <90
  - Complete surgical resection and incomplete resection
  - Lymphocyte count high and lymphocyte count low
  - MGMT methylated and MGMT unmethylated

The DCVax®-L Approach is Practical for Commercialization And Amenable To Automation

DCVax®-L: Operationally Practical for Commercialization

- Only 1 manufacturing run per patient
- Frozen product ("off the shelf" doses); frozen shelf life validated
- Amenable to automation
- Simple administration to patient: intra-dermal injection
- Compatible with Standard of Care and diverse experimental treatments



- Excellent safety profile – no inpatient or ICU stays and no added drugs to manage side effects

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