VACCINES

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Director, Neuro-Oncology Program,

OUTSMARTING BRAIN TUMORS
September 6, 2014
Progression in 40 years with survival improvement

- **CT era**
  - Neurosurgery technology gains
  - Neuroanesthesia advancement

- **Response criteria**
  - Drug combinations

- **Chemical carcinogenesis**
  - FDA approved BCNU/CCNU
  - Understanding BBB

- **MRI era**
  - Tumor cell lines
  - Animal models
  - BTSG Trials begin

- **PTK/PDGF/EGFR inhibitors in clinical trials**

- **Quality of life gains momentum**
  - Tumor-specific survival gains
  - Gene & molecular biology gains

- **Temodar approved in 99 and become a standard care 2005 : MGMT**

- **Targeted Therapy**
  - Bevacizumab

- **Vaccine**
  - PD-1
  - PD-L1
  - CTLA-4

Timeline:
- 1964
- 1970
- 1976
- 1982
- 1988
- 1994
- 2000
- 2009
- 2013/14
What Have We Learned About the Role of the Immune System in Oncology?

- **1890s**
  - Coley reports cases of tumor regression following inoculation with erysipelas infection.  
  - Paul Ehrlich proposed a role for the immune system against cancer.

- **1909**
  - Burnet and Thomas: The theory of immunosurveillance: The immune system patrols the body to detect and destroy nascent tumor cells.

- **Late 1950s**
  - Beginning in the 1980s, immunosuppressed HIV patients were shown to be at increased risk of certain cancers.

- **1980s**
  - Reports of tumor regression in patients administered LAK with IL-2.
  - Tumors are found to express antigens that can elicit a T cell–mediated immune response.

- **1985**
  - Regulators of T-cell activity, spurring research into the role of immune checkpoints in cancer are elucidated.

- **1990s**
  - The immune response remains an active focus of cancer research.
  - Increased tumorigenesis in immunodeficient mice lacking T-, B- and NKT cells.

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HIV = human immunodeficiency virus; LAK = lymphokine-activated killer; IL-2 = interleukin-2; NKT = natural killer T.

What are vaccines?

• Vaccines are medicines that boost the immune system's natural ability to protect the body against “foreign invaders,” mainly infectious agents, that may cause disease.

• The immune system is a complex network of organs, tissues, and specialized cells that act collectively to defend the body. When an infectious microbe invades the body, the immune system recognizes it as foreign, destroys it, and “remembers” it to prevent another infection should the microbe invade the body again in the future.

• Traditional vaccines usually contain harmless versions of microbes—killed or weakened microbes, or parts of microbes—that do not cause disease but are able to stimulate an immune response against the microbes. When the immune system encounters these substances through vaccination, it responds to them, eliminates them from the body, and develops a memory of them. This vaccine-induced memory enables the immune system to act quickly to protect the body if it becomes infected by the same microbes in the future.

• The immune system’s role in defending against disease-causing microbes has long been recognized. Scientists have also discovered that the immune system can protect the body against threats posed by certain damaged, diseased, or abnormal cells, including cancer cells.
Cells of the Immune System

• APCs
  o Antigen-presenting cells – these ingest and degrade disease agents (cancer proteins) and display them like a medal to T cells!

• B cells
  o B lymphocytes

• T cells
  o T lymphocytes – these seek out and destroy cancer after seeing tumor proteins displayed by APCs; vaccine turbo charges T cells to destroy cancer!
Breakthrough of the Year 2013

CANCER IMMUNOTHERAPY
**Vaccines**

**Flu Vaccine**

A flu virus contains eight gene segments. The goal is to combine the desired HA and NA genes from flu strain 1 with the six other genes from flu strain 2, which grows well in eggs and is harmless in humans.

1. After removing the dangerous part of the HA gene, scientists splice the HA and NA genes from flu strain 1 into circular pieces of DNA called plasmids.

2. Additional plasmids are created using the remaining six genes found in flu strain 2.

3. Scientists insert the HA and NA plasmids from flu strain 1 and the six plasmids carrying genes from flu strain 2 into animal cells growing in the laboratory.

4. The genes in the plasmids instruct the animal cells to make the desired new flu strain.

**Brain Tumor Vaccine**

A diagram illustrating the process of creating a brain tumor vaccine. The vaccine is created by combining tumor antigens with dendritic cells (DCs). The process involves:

- crunchy-antigen
- tumor + DCs
- blood

DC vaccine

**Brain Tumor Vaccine**

A diagram illustrating the process of creating a brain tumor vaccine. The vaccine is created by combining tumor antigens with dendritic cells (DCs). The process involves:

- crunchy-antigen
- tumor + DCs
- blood

DC vaccine
Cancer Vaccines: Personalized Therapy

• Cancer vaccines are medicines that belong to a class of substances known as biological response modifiers. Biological response modifiers work by stimulating or restoring the immune system’s ability to fight infections and disease. There are two broad types of cancer vaccines:

- **Preventive (or prophylactic) vaccines**, which are intended to prevent cancer from developing in healthy people: Hepatitis B/Liver cancer, HPV/Cervical Cancer

- **Treatment (or therapeutic) vaccines**, which are intended to treat an existing cancer by strengthening the body’s natural defenses against the cancer: Provenge/Metastatic Prostate cancer
Cancer Vaccines: Personalized Therapy

• What advantages do cancer vaccines have?

• High specificity, Low toxicity
  – The tumor is specifically targeted, normal cells that look or act similarly (dividing cells, normal brain cells, etc.) are not.

• Long-term persistence & memory
  – Vaccination jump-starts an ongoing physiological process in the body that doesn’t go away when treatment ends.
  – Vaccines train the body's immune system to recognize a disease agent as foreign, destroy it, and "remember" how to do this better the next time. This is critical for brain tumors, which can frequently recur.

• High diversity, adaptability
  – As tumors grow, they mutate and change, acquiring treatment resistance; ongoing immune responses are borne from equally changeable genetic events, and can potentially keep up with changing tumors.
How are cancer treatment vaccines designed to work?

• Cancer treatment vaccines are designed to treat cancers that have already developed. They are intended to delay or stop cancer cell growth; to cause tumor shrinkage; to prevent cancer from coming back; or to eliminate cancer cells that have not been killed by other forms of treatment.

• Developing effective cancer treatment vaccines requires a detailed understanding of how immune system cells and cancer cells interact. The immune system often does not “see” cancer cells as dangerous as it generally does with microbes. Therefore, the immune system does not mount a strong attack against the cancer cells.

• Several factors may make it difficult for the immune system to target growing cancers for destruction. Most important, cancer cells carry normal self antigens in addition to specific cancer-associated antigens. Furthermore, cancer cells sometimes undergo genetic changes that may lead to the loss of cancer-associated antigens. Finally, cancer cells can produce chemical messages that suppress anticancer immune responses by killer T cells. As a result, even when the immune system recognizes a growing cancer as a threat, the cancer may still escape a strong attack by the immune system.
Table 1. Selected trials of immunotherapy in GBM

<table>
<thead>
<tr>
<th>Reference or NCCT identifier</th>
<th>Design</th>
<th>No. of Subjects</th>
<th>Phase</th>
<th>Results/endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(41)</td>
<td>PEPvIII-KLH was administered 2 weeks after surgery and once per month thereafter until radiographic progression.</td>
<td>18</td>
<td>II</td>
<td>PFS: 14.2 Months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MS: 26 Months</td>
</tr>
<tr>
<td>(36)</td>
<td>21 patients (17 newly diagnosed, 3 recurrent, and 1 brainstem glioma) underwent leukapheresis; DCs were isolated and pulsed with tumor-associated antigen peptides administered at 3-week intervals.</td>
<td>21</td>
<td>I</td>
<td>PFS 16.9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MS: 38.4 months</td>
</tr>
<tr>
<td>(48)</td>
<td>Glioma lysate-pulsed DCs and imiquimod or poly-ICLC adjuvant were administered every 3 months until tumor progression.</td>
<td>23</td>
<td>I</td>
<td>PFS: 15.9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MS: 31.4 months</td>
</tr>
<tr>
<td>(44)</td>
<td>CDX-110 was administered in three biweekly intradermal injections followed by monthly injections until radiographic tumor progression; patients then received temozolomide.</td>
<td>65</td>
<td>II</td>
<td>MS: 21.3 months</td>
</tr>
</tbody>
</table>
Phase I trial of a multi-epitope-pulsed dendritic cell vaccine for patients with newly diagnosed glioblastoma

Surasak Phuphanich · Christopher J. Wheeler · Jeremy D. Rudnick · Mia Mazer · HongQian Wang · Miriam A. Nuño · Jaime E. Richardson · Xuemo Fan · Jianfei Ji · Ray M. Chu · James G. Bender · Elma S. Hawkins · Chirag G. Patil · Keith L. Black · John S. Yu

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Abstract

Background This study evaluated the safety and immune responses to an autologous dendritic cell vaccine pulsed with class I peptides from tumor-associated antigens (TAA) expressed on gliomas and overexpressed in their cancer stem cell population (ICT-107).

into dendritic cells, pulsed with TAA peptides, and administered intradermally three times at two-week intervals.

Results Twenty-one patients were enrolled with 17 newly diagnosed (ND-GBM) and three recurrent GBM patients and one brainstem glioma. Immune response data on 15 newly diagnosed patients showed 33 % responders. TAA
LONG TERM REMISSION OVER 5 YEARS IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA (GBM) TREATED WITH ICT-107 VACCINE: A FOLLOW UP STUDY

Surasak Phuphanich, Christopher Jay Wheeler, Jeremy Rudnick, Mia Mazer, Hong Qiang Wang, Miriam Nuno, Jaime Richardson, Xuemo Fan, Jianfei Ji, Ray M Chu, James Bender, Elma S. Hawkins, Chirag Patil, Keith L. Black, John Yu;

Neuro-Oncology Program, Cedars-Sinai Medical Center, Los Angeles, CA ImmunoCellular Therapeutics Ltd., Woodland Hills, CA
OBJECTIVES

Primary
• To identify patients who survived longer than 5 years and benefit from ICT-107 vaccine in patients with newly diagnosed GBM.
• To identify patients with disease free more than 5 years after ICT-107 vaccine in patients with newly diagnosed GBM

Secondary
• Monitor survival and time to tumor progression of these patients vaccinated with antigen-pulsed dendritic cells.
• Monitor the cellular immune responses of the patients vaccinated with antigen-pulsed dendritic cells
**ICT-107 peptides target Cancer Stem Cells & GBM tumor antigens**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Epitope</th>
<th>HLA restriction</th>
<th>Sequence</th>
<th>Tumor Expression</th>
<th>CSC Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>gp100</td>
<td>209 (210M)</td>
<td>A2</td>
<td>IMDQVPFSV</td>
<td>Melanoma, brain cancer</td>
<td></td>
</tr>
<tr>
<td>Trp-2</td>
<td>180</td>
<td>A2</td>
<td>SVYDFFVWL</td>
<td>Melanoma and brain cancer</td>
<td>High</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>773</td>
<td>A2</td>
<td>VMAGVGSPYV</td>
<td>Breast, ovarian cancer</td>
<td>High</td>
</tr>
<tr>
<td>IL-13αR2</td>
<td>345</td>
<td>A2</td>
<td>WLPFGFILI</td>
<td>Brain cancer</td>
<td>High</td>
</tr>
<tr>
<td>MAGE-1</td>
<td>161</td>
<td>A1</td>
<td>EADPTGHSY</td>
<td>Melanoma, brain cancer</td>
<td></td>
</tr>
<tr>
<td>AIM-2</td>
<td>14</td>
<td>A1</td>
<td>RSDSGQQARY</td>
<td>Breast, ovarian, colon, brain</td>
<td>High</td>
</tr>
</tbody>
</table>
ICT-107’s Mechanism of Action

1. Injection of activated dendritic cell vaccine, ICT-107

2. ICT-107 migrates to lymphoid organs

3. ICT-107 activates key T-cells

4. T-cells relocate to glioblastoma & initiate immune response

5. Immune response destroys both tumor cells and CSCs

- Antigens Targeting Tumor Cells
- Antigens Targeting Cancer Stem Cells

Tumor Cells
Cancer Stem Cell (CSC)
T-cell killing tumor cell
lymph node
ELIGIBILITY

• No age or gender limit, though minimal weight limitations for leukapheresis is about 15-20 Kg.

• **Patients must be HLA-A1 or HLA-A2 positive.**
  • Patients must demonstrate the presence of at least one of the antigens by immunohistochemistry or other method.

• Adults and children with glioblastoma multiforme.

• Patients may be maintained on glucocorticoid therapy at no more than Decadron 2mg BID.

• 3 months must have elapsed after radiation.
  • > 4 weeks since completion of non-nitrosourea
  • > 6 weeks since completion of nitrosourea
  • > 1 week from non-cytotoxic drugs including tamoxifen, thalidomide, cis-retinoic acid.

• Adequate hematologic (Hb >9.9 gm/dl ANC<1,000, PLT>60,000) renal (BUN <30 mg/dl/Cr <2 mg/dl) and liver functions (TB<1.5, transaminases < 2 times normal upper limit)

• Karnofsky performance status (KPS) >60%.
TREATMENT PROTOCOL

Newly Diagnosed GBM patients

Surgery

Radiation-TMZ

Treatment q 2 weeks x 3

TMZ chemo-monthly cycles
# Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male, n (%)</th>
<th>12 (75.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>Mean (SD)</td>
<td>55.3 (10.7)</td>
</tr>
<tr>
<td>Median</td>
<td>54.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>34-79</td>
<td></td>
</tr>
<tr>
<td>Karnofsky status</td>
<td>Mean (SD)</td>
<td>87 (10.1)</td>
</tr>
<tr>
<td>Median</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>60-100</td>
<td></td>
</tr>
<tr>
<td>HLA status, N (%)</td>
<td>A1+</td>
<td>5</td>
</tr>
<tr>
<td>A2+</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>A1+/A2+</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prior therapy, n</td>
<td>Surgery</td>
<td>16</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Temozolomide</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliadel</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Extent of surgery, N (%)</td>
<td>Sub-total resection</td>
<td>4</td>
</tr>
<tr>
<td>Complete resection</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>First Surgery to Vaccine (mon)</td>
<td>Mean (SD)</td>
<td>5.49 (2.52)</td>
</tr>
<tr>
<td>Median</td>
<td>4.52</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2.96-12.39</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid therapy (%)</td>
<td>18.7</td>
<td></td>
</tr>
</tbody>
</table>

§ Score collected at screening.
RESULT AS OF NOVEMBER 2013

• We identified 8 of 16 newly diagnosed GBM patients, who survived more than 5 years and 6 patients of this group with disease free (PFS) over 5 years (Phuphanich S, et al Cancer Immunol Immunother. Jan:62(1):125-35, 2013).

• For Survival: 7 of 8 patients are still alive at 60.7, 65.1, 67.5, 67.4, 69.4, 77.9 and 82.7 months.
  - 3 patients, who developed tumor progression, received salvage therapy (Bevacizumab, CPT-11, Vorinostat, Dose dense TMZ)

• For Progressive Free Survival: There are total of 4 of 6 are still disease free at 65.1, 67.4, 77.9 and 82.7 months
  - One died of leukemia at 61 months and no evidence of GBM
  - Another patient recently developed tumor progression at 62 months and under surgery and active treatment with TMZ
Case #4 and #6 Detail History for PFS/OS at 89 and 95 m
Update on 09/05/2014

#4: Male/53 years old, Biopsy 4/11/07, New onset of seizure
Gross total resection (GTR) of left Frontal 5/2/07 without expressive aphasia
GBM with MGMT-, XRT/TMZ then ICT-107 vaccine 9/6/2007 x 3 doses
and 24 cycles of Temozolomide with last dose in January, 2010.
Working full time as Fashion Designer clothes for prom dress
Business man and Active Runner: clinical remission over 7.5 years

#6 Female/62 years old, Headache and speech difficulty
GTR of left Temporal lobe 10/24/2006, GBM with MGMT+
XRT/TMZ and 6 cycles of Dose Dense TMZ
(7-day on & off) with Levitra
Home maker: Clinical remission almost 8 years
Healthy Living

Vaccine may give brain cancer patients time

Monday, February 14, 2011

LOS ANGELES (KABC) -- Each year, 22,000 Americans are diagnosed with brain cancer. Glioblastomas are the most deadly types of brain tumors, but now local researchers are trying to perfect a new type of treatment that may give the patient precious additional time.
Case #4: Axial MRI with contrast and Flair-Left Frontal GBM before and after surgery in May, 2007
Case #4 Follow up contrast/Flair MRI in October, 2013
It's a Miracle: Three Women's Stories of Survival

Mary Wong Lee

“They Said I’d Likely Be Gone in 15 Months.”
Mary survived an aggressive brain tumor.

“My doctor’s side of the conversation got quiet, and then he left the room. When he came back he had tears in his eyes.”

For two weeks in the fall of 2006, Mary Wong Lee of San Dimas, California, had been plagued by on-and-off headaches, but when words began escaping her the 55-year-old office manager got worried. “I’d be writing letters or reports and I just wanted to say ‘appreciate’ or ‘opportunity,’ but couldn’t think how to spell them,” she says. She told her longtime general practitioner, who sent her for an MRI. About a week later Lee stopped by his office to say she'd gotten the test. “Let me call and see if they have the results yet,” he said. “His side of the conversation got quiet and then he left the room,” Lee says. “When he came back he had tears in his eyes.”

Lee had glioblastoma multiforme, one of the most aggressively malignant types of brain cancer. “It's a formidable enemy,” says Keith L. Black, MD, director of the Maxine Dunitz Neurosurgical Institute at Cedars-Sinai Medical Center in Los Angeles, where Lee was referred. “Most of the time we lose the battle.” Even with standard treatment she’d likely be
Case # 6: Axial and Coronal MRI with contrast – Lt Temporal GBM before surgery in Oct, 2006
Case 6: A follow up contrasted MRI in October, 2013:
Progression Free and Overall Survival in months for Newly Diagnosed Glioblastoma Patients.

<table>
<thead>
<tr>
<th>Time in months</th>
<th>% Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival</strong></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>62.5 (34.9, 81.1)</td>
</tr>
<tr>
<td>24</td>
<td>43.8 (19.8, 66.0)</td>
</tr>
<tr>
<td>60</td>
<td>37.5 (15.4, 59.8)</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>16.9 (8.9, 49.8)</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>18</td>
<td>93.7 (63.2, 99.1)</td>
</tr>
<tr>
<td>24</td>
<td>80.3 (58.6, 96.7)</td>
</tr>
<tr>
<td>60</td>
<td>50.0 (24.5, 71.0)</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>38.4 (25.9, 40.7)</td>
</tr>
</tbody>
</table>

CI: Confidence Interval
A randomized, double-blind, placebo-controlled phase 2 trial of dendritic cell (DC) vaccination with ICT-107 in newly diagnosed glioblastoma (GBM) patients

Patrick Y. Wen, David A. Reardon, Buresak Phuphanich, Terri Armstrong, Robert Aiken, Joseph C. Landolfi, William T. Curry, Jay-Jiguang Zhu, Michael J. Glantz, David M. Peerboom, James Markert, Renato V. LaRocca, Donald O'Rourke, Karen L. Ank, Lyndon J. Kim, Michael L. Gruber, Glenn Jay Lesser, Edward Pan, Santosh Kesari, Elma B. Hawkins, John Yu

June 1, 2014
Vaccine offers hope for cancer patients

A new vaccine offers patients diagnosed with a common and aggressive type of brain cancer some hope.

Added Aug 13, 2012
OBJECTIVES

• Primary
  o To compare overall survival (OS) in patients when treated with ICT-107 versus Control

• Secondary
  o To compare progression-free survival (PFS) in patients when treated with ICT-107 versus Control
  o To determine the safety and tolerability of ICT-107
  o To describe the immune response in patients treated with ICT-107
  o To determine predictors of response
KEY ELIGIBILITY CRITERIA

• INCLUSION
  - Confirmed, initial diagnosis of GBM
  - ≥ 18 years of age
  - Human leukocyte antigen (HLA) A1 or HLA-A2 positive
  - Karnofsky Performance Score of ≥ 70%
  - Adequate baseline hematologic and chemistry profiles
  - Negative serum pregnancy test and contraception
  - Written informed consent
ICT-107 Ph II Trial Design

Consent → Apheresis → Surgery → Screen and Enroll → SOC Chemoradiation → Randomize → Eligibility Confirmation → Vaccine Induction Phase

- Patient-Specific Vaccination
- ICT-107 or Control
- 1/wk for 4 wks

Maintenance Phase
- Week 1: SOC Maintenance TMZ
- Week 2: Rest Week
- Week 3: Clinical Assessments + maintenance vaccine (ICT-107 or Control) + tumor assessments
- Week 4: Rest Week

Maintenance includes vaccination on a 1, 3, 6, 6... monthly schedule as long as the patient does not recur
Patient Disposition
October 2013 and April 2014 Data Analysis

All patients enrolled
N = 278

All patients randomized
N = 124

ICT-107
N = 81

Control
N = 43

Patients off study
Oct: N = 67 (83%)
April: N = 69 (85%)

Reasons:
Progressive Disease
Oct: N = 48 (59%)
April: N = 50 (62%)

Other*
Oct: N = 19 (23%)
April: N = 19 (23%)

Patients on study
Oct: N = 14 (17%)
April: N = 12 (15%)

Reasons:
Progressive Disease
Oct: N = 29 (67%)
April: N = 30 (70%)

Other*
Oct: N = 7 (16%)
April: N = 8 (19%)

Note: *Other includes treatment completion, withdrawn consent, investigator withdrawn, etc.
PFS for the ITT and PP Populations
(Central Radiology Review)
Updated in April 2014

ITT Population (N=124)
ICT-107
N = 81 (61 events)
Median = 11.2 mo (8.22, 13.05)
HR = 0.57
Age, MGMT stratified P* = 0.011

Control
N = 43 (39 events)
Median = 9 mo (5.52, 10.29)

PP Population (N=117)
ICT-107
N = 75 (57)
Median = 11.4 mo (8.68, 13.05)
HR = 0.54
Age, MGMT stratified P* = 0.006

Control
N = 42 (38)
Median = 9.0 mo (5.00, 10.29)

* Two-sided log-rank p-value

Statistically significant treatment benefit
OS (From Randomization) for ITT and PP Populations
Updated in April 2014

ITT Population (N=124)
- ICT-107: N = 81 (51 events)
  - Median = 18.3 mo (14.89, 21.14)
  - HR = 0.87
  - Age, MGMT stratified P* = 0.643
- Control: N = 43 (28 events)
  - Median = 16.7 mo (12.33, 23.05)

PP Population (N=117)
- ICT-107: N = 75 (46 events)
  - Median = 18.6 mo (15.32, 23.47)
  - HR = 0.79
  - Age, MGMT stratified P* = 0.477
- Control: N = 42 (27 events)
  - Median = 16.7 mo (12.85, 23.05)

Numeric but not statistical treatment benefit
MGMT Status Creates Two Different Patient Populations From the Survival Perspective
Per-Protocol Population with April 2014 Survival Data

- **PP Population (N=117*)**
  - MGMT - Methylated (N=42)
    - ICT-107: N=25 (8 events)
      - Median: not yet defined
      - HR: 0.797
      - Age stratified P*: 0.683
    - Control: N=17 (6 events)
      - Median: not yet defined

- **MGMT - Unmethylated (68)**
  - ICT-107: N=44 (33 events)
    - Median: 15.4mo (11.93, 18.94)
    - HR: 0.765
    - Age stratified P*: 0.347
  - Control: N=24 (21 events)
    - Median: 14.2mo (10.22, 17.75)

*110 of 117 in PP population have MGMT defined
†Two-sided log-rank p-value

The MGMT methylated control has at least double the median survival of the unmethylated control
Conclusions for ICT-107 Ph II

- No significant difference in adverse events between ICT-107 and control
- The vaccine is biologically active in terms of producing an immune response
- PFS was statistically improved for the entire treated population
- ICT-107 activity is strongest in the HLA-A2 subgroup clinically, immunologically, and with regard to antigen expression. This activity is observed in both the MGMT methylated and unmethylated subgroups
- Extended PFS in the treated group appears to come with commensurate improved quality of life
  - Quality of Life, as measured by FACT-BR, is maintained equally until progression for ICT-107 and Control patients
  - ICT-107 patients retain greater performance capacity, as measured by KPS, than controls and tend to be placed on steroids later
- Vaccine potency as measured by HLA-DR expression and IL-12 secretion is predictive of OS
- Results support advancement to a phase III trial
Currently recruiting participants: Brain Cancer Vaccines

- Study of a Drug [DCVax®-L] to Treat Newly Diagnosed GBM Brain Cancer (DCVax®)
- Study To Test the Safety and Efficacy of TVI-Brain-1 As A Treatment for Recurrent Grade IV Glioma
- Imiquimod/Brain Tumor Initiating Cell (BTIC) Vaccine in Brain Glioma
- Surviving Vaccine Therapy for Patients With Malignant Gliomas
- Phase I Rindopepimut After Conventional Radiation in Children w/ Diffuse Intrinsic Pontine Gliomas
- Vaccine Immunotherapy for Recurrent Medulloblastoma and Primitive Neuroectodermal Tumor (PNET)
- HSPPC-96 Vaccine With Temozolomide in Patients With Newly Diagnosed GBM (HeatShock)
- A Pilot Study of Glioma Associated Antigen Vaccines in Conjunction With Poly-ICLC in Pediatric Gliomas
- Dendritic Cell Vaccine for Patients With Brain Tumors
- Autologous Dendritic Cells Pulsed With Autologous Apoptotic Tumor Cells Administered to Patients With Brain Tumors
- HLA-A2-Restricted Glioma Antigen-Peptides Vaccinations With Poly-ICLC for Recurrent WHO Grade II Gliomas
- Dendritic Cell Cancer Vaccine for High-grade Glioma (GBM-Vax)
- Vaccine Therapy in Treating Patients Undergoing Surgery for Recurrent Glioblastoma Multiforme
- Effects of Vaccinations With HLA-A2-Restricted Glioma Antigen-Peptides in Combination With Poly-ICLC for Adults With WHO Grade II Astrocytomas
- GP96 Heat Shock Protein-Peptide Complex Vaccine in Treating Patients With Recurrent or Progressive Glioma
- Study of Peptide Vaccination With Tumor Associated Antigens Mixed With Montanide in Patients With CNS Tumors
Active Clinical Protocols 2014: Immunotherapy Focus at Cedars

Protocol IRB Approved: Glioblastoma (GBM)

1. Immunological targeting of CD133 in recurrent glioblastoma: A translational and clinical study of an autologous CD-133 DC vaccine (1st Recurrence only with HLA-A2+, <1 cm3)

2. A phase I trial of vaccination with autologous dendritic cells pulsed with lysate derived from an allogeneic glioblastoma stem-like cell line for patients with newly diagnosed or recurrent glioblastoma (<3rd Recurrence and <1 cm3)

3. A Phase I Trial of Surgical Resection Followed by Vaccination with Dendritic Cells Pulsed with Tumor Lysate with Imiquimod for Patients with Malignant Glioma

4. A phase I/II of SL701, peptide vaccine for recurrent glioblastoma (1st Recurrence <4 cm3 and HLA-A2+)

5. Ipillimumab+ Nivolumab for 1st Recurrent GBM- BMY

Protocol priority New protocol concept: Vaccine + PD-1/PD-L1, CTL4 +PD-1 Antibody

a) ICT-107 +MK-3475 or Lambrolizumab (PD-1)- LOI Merck
b) RTOG: Ipillimumab + Nivolumab for Newly Diagnosed GBM
c) Pidilizumab (PD-1 Ab) for brainstem glioma and recurrent GBM-CureTech
d) Masitinib in combination with lomustine, or masitinib in combination with irinotecan in patients with glioblastoma multiforme and who relapsed after a first line chemotherapy with temozolomide
Rationale for combining PD-1/PD-L1 with Vaccine: ICT-107

• Adaptive immunotherapy regimen combining PD-1 checkpoint blockade with anti-tumor vaccination may significantly enhance anti-tumor activity than either agent alone

• Inhibition of PD-1 suppression of T-cell activation is expected to enhance tumor antigen-specific T cell responses

• Preliminary results of phase IIb randomized newly diagnosed GBM that enrolled 124 patients were reviewed after 67 events and demonstrated that ICT-107 was very well tolerated, and that PFS increased by 3 months in the ICT-107, per-protocol arm of the study (p=0.01, HR=0.53). A trend of improved OS was also noted on the ICT-107 arm

• Evaluation of pre-ICT-107 vaccine and post- vaccine samples demonstrated increase in PD-L1 expression in tumor in ¾ post vaccine samples and absence of PD-L1 expression in all pre-vaccine samples. There was also evidence of antigen specific cytotoxic T cells in post vaccine sample in a patient treated with ICT-107
DEATH OF A BRAIN TUMOR

The Meanie came out of nowhere and made himself at home in my brain.

He took all the space he felt like, crowding his surroundings, till one day was spotted by the body police - a few white cells. At first, they were unsure what to do about the ominous invader.

They called their friends and sent the Meanie packing... but he refused to go, so they decided to kill him.

And that is the end of Meanie the Tumor.