

## Biotechnology — Initiation of Coverage

# ImmunoCellular Therapeutics (IMUC)

July 28, 2011

### Initiation of Coverage

Recommendation: BUY

Price Target: \$8.00

Carol Werther

617-532-6418

[carolw@ssrp.com](mailto:carolw@ssrp.com)



Source: StockCharts.com

### Stock Data – (OTC: IMUC)

Price: \$2.17  
52-week high: \$2.55  
52-week low: \$0.84  
Shares out: 29M  
Shares short: N/A  
Average volume (10-day): 59K

### Valuation Metrics

Market cap: \$62.8M  
Enterprise value: \$53.9M

### Financial Highlights (March:11)

Cash/equivalents: \$11.3M  
Debt: \$0  
Book value: \$4.93M  
Burn 2011: \$4.8M

	2010A	Q1:11A	2011E	2012E
Revs	\$0	\$0	\$0	\$0
Prior	--	--	--	--
EPS	\$(0.43)	\$(0.11)	\$(0.35)	\$(0.45)
Prior	--	--	--	--
P/E	--	--	--	--

### Company Description

ImmunoCellular Therapeutics, Ltd. is a clinical-stage biotechnology company focused on developing new immune-based products to treat and diagnose brain and other cancers.

- **We are initiating coverage of ImmunoCellular with a BUY rating and \$8 YE:11 price target.** IMUC is developing immunotherapies that target tumor cells and cancer stem cells. Using active immunotherapy, the company has discovered two cancer vaccines. IMUC uses its passive immunotherapy proprietary discovery technology to identify and develop monoclonal antibodies that may be used to treat and diagnose a wide range of cancers.
- **IMUC's lead product is ICT-107, a vaccine in pivotal phase II trials for patients with newly diagnosed glioblastoma multiforme (GBM).** ICT-107 is a personalized vaccine derived from the patient's tumor that uses a mixture of six antigens. The patient's dendritic cells (DCs) are then stimulated to attack the patient's cancer stem cells (CSCs), thereby stopping tumor cell growth.
- **The ICT-107 phase I trial demonstrated an overall survival rate (OS) of 100% at one year and 80% at two years.** This open-label trial enrolled 16 newly diagnosed patients who received three doses of ICT-107 in addition to the standard of care (SOC) of surgery, radiation, and chemotherapy. The results are favorable, with historical compares of 61.1% one-year and 26.5% two-year survival.
- **The ICT-107 phase II trial will enroll 200 newly diagnosed GBM patients at 25 qualified sites.** IMUC believes it will take through May 2012 to enroll the patients. The primary endpoint is OS. There is an interim analysis planned that may occur by YE:12. If the FDA accepts an endpoint other than OS and/or if the PFS is ~13 months and the median OS is 22 months, the BLA may be filed prior to 2015.
- **IMUC plans to file an IND for its second therapeutic cancer vaccine, ICT-121, this year.** ICT-121 is an "off-the-shelf" vaccine targeting recurrent GBM initially, but may address other cancers also. ICT-121 is a peptide that can produce an immune response in HLA-A\*0201 serotype patients that targets CD133 positive CSCs.
- **We forecast ICT-107 sales of \$34MM in 2016, rising to \$576MM in 2021.** Approximately 10,000 new GBM patients are diagnosed annually. About 80% undergo surgery and 70% of patients have the HLA A1 and A2 status required for the vaccine to work. This leaves ~6,000 available patients to be treated annually.
- **IMUC is significantly undervalued.** IMUC's enterprise value is less than \$100MM; on average, late-stage companies have a market cap of \$690MM and an enterprise value of over \$500MM. Although some of the disparity may be due to the pivotal result read-out four years away, given the recent approval of two immune-based cancer treatments we would expect significant appreciation as the pivotal trial approaches the interim analysis in late 2012.

Important Disclosures and Disclaimers can be Viewed at <http://www.ssrp.com> and on Page 26 of this Report

---

## INVESTMENT SUMMARY

We are initiating coverage of ImmunoCellular Therapeutics with a BUY rating and \$8 YE:11 price target. IMUC is developing immunotherapies that target tumor cells and cancer stem cells. Using active immunotherapy, the company has discovered two cancer vaccines. IMUC uses its passive immunotherapy proprietary discovery technology to identify and develop monoclonal antibodies that may be used to treat and diagnose a wide range of cancers. The company's lead product is ICT-107, a vaccine in a pivotal phase II trial for patients with newly diagnosed glioblastoma multiforme (GBM). ICT-107 is a personalized vaccine derived from the patient's tumor. This trial will enroll 200 patients at 25 qualified sites. IMUC believes it will take through May 2012 to enroll the patients. The primary endpoint is overall survival (OS). The ICT-107 phase I trial demonstrated an overall survival rate of 100% at one year and 80% at two years. We forecast ICT-107 sales of \$34MM in 2016, rising to \$576MM in 2021. Approximately 10,000 new GBM patients are diagnosed annually. About 80% undergo surgery and 70% of patients have the HLA A1 and A2 status required for the vaccine to work. This leaves ~6,000 available patients to be treated annually. IMUC is significantly undervalued when compared to other late-stage companies. Our YE:11 \$8 price target is based on 30x \$2.22 EPS in 2018, discounted back at 35%.

## VALUATION

IMUC is undervalued, based on its stage of development with an enterprise value under \$100MM. On average, late-stage companies have a market cap of \$690MM and an enterprise value of over \$500MM. Although some of the disparity may be due to the pivotal result read-out four years away, given the recent approval of two immune based cancer treatments we would expect significant appreciation as the pivotal trial approaches the interim analysis in late 2012.

Figure 1. Valuation Compares

Ticker	Company	Share Price	YTD	Shares (MM)	Market Cap (\$MM)	Debt	Cash	52-Week		Revenue - Consensus			EPS - Consensus			Enterprise Value
								High	Low	2010	2011	2012	2010	2011	2012	
AFFY	Affymax Inc.	\$6.77	3.91%	35.38	\$239.55	\$0.00	\$97.09	\$8.58	\$4.90	\$112.52	\$43.30	\$121.52	(\$0.57)	(\$2.33)	(\$0.34)	\$142.46
AEGR	Aegerion Pharmaceuticals Inc.	\$15.76	10.23%	20.92	\$329.62	\$0.00	\$44.10	\$25.92	\$9.00	\$0.00	\$0.00	\$161.65	(\$5.07)	(\$1.63)	\$1.01	\$285.52
AEZS	AEterna Zentaris Inc.	\$2.00	26.16%	95.19	\$190.37	\$0.00	\$33.93	\$2.68	\$0.93	\$27.88	\$25.64	\$27.65	(\$0.31)	(\$0.35)	(\$0.28)	\$156.44
ANTH	Anthera Pharmaceuticals Inc.	\$7.55	58.81%	40.64	\$306.84	\$0.00	\$63.38	\$9.08	\$2.82	\$0.00	\$0.00	\$32.50	(\$1.76)	(\$2.11)	(\$0.97)	\$243.46
ARIA	Ariad Pharmaceuticals Inc.	\$11.89	149.80%	131.99	\$1,569.41	\$9.76	\$103.63	\$13.50	\$3.07	\$178.98	\$24.48	\$48.33	\$0.74	(\$0.59)	(\$0.38)	\$1,475.54
ARNA	Arena Pharmaceuticals Inc.	\$1.60	-7.27%	145.89	\$233.43	\$124.91	\$150.67	\$8.00	\$1.21	\$16.61	\$13.48	\$11.28	(\$1.14)	(\$0.74)	(\$0.52)	\$207.67
BIOD	Biodol Inc.	\$1.79	3.28%	38.57	\$69.04	\$0.00	\$29.07	\$6.08	\$1.49	\$0.00	\$0.00	\$0.00	(\$1.58)	(\$0.79)	(\$0.82)	\$39.97
CHTP	Chelsea Therapeutics International	\$5.15	-28.53%	61.85	\$318.51	\$0.00	\$47.59	\$8.20	\$2.78	\$0.00	\$0.00	\$26.13	(\$0.91)	(\$1.05)	(\$0.90)	\$270.92
CRIS	Curis Inc.	\$3.71	97.47%	76.35	\$283.26	\$0.00	\$40.60	\$4.42	\$1.21	\$16.00	\$10.17	\$22.40	(\$0.06)	(\$0.21)	(\$0.07)	\$242.66
EXEL	Exelixis Inc.	\$7.60	-3.90%	127.84	\$971.55	\$208.46	\$162.66	\$12.82	\$2.86	\$185.05	\$153.34	\$138.24	(\$0.85)	(\$0.56)	(\$0.60)	\$1,017.34
GTXI	GTx Inc.	\$4.30	68.30%	61.72	\$265.39	\$0.00	\$58.63	\$6.86	\$2.27	\$60.61	\$13.71	\$14.36	\$0.39	(\$0.65)	(\$0.77)	\$206.76
IMMU	Immunomedics Inc.	\$4.00	17.32%	75.42	\$301.67	\$0.00	\$30.49	\$4.47	\$2.81	\$60.93	\$7.47	\$7.21	\$0.49	(\$0.28)	(\$0.33)	\$271.18
INCY	Incyte Corp.	\$17.44	10.51%	124.59	\$2,172.78	\$293.43	\$443.15	\$21.15	\$11.71	\$169.88	\$83.42	\$242.64	(\$0.26)	(\$1.50)	(\$0.69)	\$2,023.06
ISIS	Isis Pharmaceuticals Inc.	\$8.50	-14.72%	99.59	\$846.55	\$144.26	\$472.35	\$10.63	\$7.59	\$108.47	\$114.11	\$136.55	(\$0.62)	(\$0.66)	(\$0.63)	\$518.46
IMGN	Immunogen Inc.	\$13.33	50.97%	75.12	\$1,001.36	\$0.00	\$110.87	\$16.20	\$4.96	\$13.94	\$17.14	\$26.55	(\$0.87)	(\$0.85)	(\$0.76)	\$890.49
INFI	Infinity Pharmaceuticals Inc.	\$8.58	49.75%	26.60	\$228.23	\$0.00	\$100.22	\$10.42	\$4.42	\$71.33	\$93.14	\$112.00	(\$1.86)	(\$1.31)	(\$1.23)	\$128.01
KERX	Keryx Biopharmaceuticals Inc.	\$4.42	-2.18%	69.08	\$305.33	\$0.00	\$28.51	\$5.91	\$3.48	\$0.00	\$5.01	\$17.23	(\$0.34)	(\$0.35)	(\$0.42)	\$276.82
FOLD	Amicus Therapeutics Inc.	\$6.74	44.04%	34.52	\$232.64	\$2.34	\$107.45	\$8.12	\$2.36	\$0.92	\$24.10	\$39.04	(\$1.98)	(\$1.37)	(\$0.72)	\$127.53
MNKD	MannKind Corp.	\$3.31	-57.32%	130.69	\$432.57	\$444.65	\$70.43	\$10.05	\$3.27	\$0.09	\$1.64	\$0.00	(\$1.50)	(\$1.22)	(\$1.03)	\$806.79
MDVN	Medivation Inc.	\$20.69	38.83%	34.90	\$722.10	\$0.00	\$207.76	\$25.50	\$9.04	\$62.51	\$63.20	\$70.15	(\$0.99)	(\$1.20)	(\$1.01)	\$514.35
MITI	Micromet Inc.	\$5.66	-27.09%	91.53	\$518.06	\$0.77	\$221.97	\$8.63	\$4.75	\$28.74	\$25.29	\$28.95	(\$0.56)	(\$0.75)	(\$0.85)	\$296.86
NBIX	Neurocrine Biosciences Inc.	\$7.78	4.45%	55.20	\$429.46	\$0.00	\$126.87	\$9.30	\$5.28	\$33.50	\$78.64	\$54.04	(\$0.15)	\$0.64	\$0.06	\$302.60
OGXI	OncoGenex Pharmaceuticals Inc.	\$14.30	-12.33%	9.72	\$138.97	\$8.01	\$85.61	\$20.00	\$11.83	\$13.62	\$8.60	\$14.92	(\$1.79)	(\$2.05)	(\$2.16)	\$61.37
ONCY	Oncolytics Biotech Inc.	\$4.55	-30.30%	71.21	\$324.02	\$0.00	\$43.18	\$6.95	\$2.73	\$0.00	\$0.00	\$2.34	(\$0.32)	(\$0.35)	(\$0.35)	\$280.84
OREX	Orexigen Therapeutics Inc.	\$1.61	-79.70%	48.09	\$77.42	\$2.42	\$92.37	\$11.15	\$1.50	\$1.23	\$4.48	\$3.86	(\$1.10)	(\$0.78)	(\$0.80)	(\$12.53)
OSIR	Osiris Therapeutics Inc.	\$7.21	-5.39%	32.82	\$236.62	\$0.00	\$67.61	\$8.58	\$5.97	\$43.02	\$44.48	\$27.79	\$0.40	\$0.48	(\$0.27)	\$169.02
PATH	NuPathe Inc.	\$6.86	-21.74%	14.57	\$99.92	\$5.22	\$38.92	\$10.22	\$5.06	\$0.65	\$0.00	\$19.56	(\$4.39)	(\$1.92)	(\$2.30)	\$66.21
PCYC	Pharmacyclics Inc.	\$12.00	103.29%	60.77	\$729.22	\$0.00	\$74.15	\$13.09	\$4.75	\$9.31	\$9.69	\$27.24	(\$0.21)	(\$0.52)	(\$0.43)	\$655.07
PLX	Protalix BioTherapeutics Inc.	\$6.36	-34.37%	85.58	\$544.29	\$0.00	\$36.13	\$10.60	\$5.74	\$13.41	\$22.10	\$62.13	(\$0.35)	(\$0.20)	\$0.03	\$508.16
RIGL	Rigel Pharmaceuticals Inc.	\$8.77	22.44%	68.58	\$601.44	\$0.80	\$177.30	\$10.21	\$6.42	\$125.00	\$0.00	\$22.86	\$0.72	(\$1.51)	(\$1.21)	\$424.94
SGEN	Seattle Genetics Inc.	\$16.72	15.79%	113.78	\$1,902.33	\$0.00	\$281.81	\$21.41	\$11.35	\$107.47	\$52.83	\$166.15	(\$0.66)	(\$1.65)	(\$0.98)	\$1,620.53
THRX	Theravance Inc.	\$21.77	-8.10%	74.69	\$1,626.09	\$172.78	\$309.63	\$28.95	\$11.98	\$24.22	\$30.82	\$37.86	(\$1.16)	(\$1.22)	(\$1.42)	\$1,489.23
TSRX	Trius Therapeutics Inc.	\$8.15	109.97%	28.51	\$232.32	\$0.00	\$45.34	\$8.85	\$2.93	\$8.03	\$11.72	\$18.40	(\$2.36)	(\$1.58)	(\$1.27)	\$186.98
VRUS	Pharmasset Inc.	\$123.93	195.80%	37.18	\$4,608.21	\$11.64	\$127.08	\$137.81	\$24.02	\$1.02	\$3.34	\$2.74	(\$2.13)	(\$2.48)	(\$3.01)	\$4,492.77
VTUS	Ventrus Biosciences Inc.	\$11.99	82.02%	11.73	\$140.63	\$2.49	\$14.57	\$21.00	\$5.75	\$0.00	\$0.00	\$0.00	(\$17.16)	(\$2.32)	(\$1.59)	\$128.55
VVUS	VIVUS Inc.	\$8.05	-12.49%	81.89	\$659.20	\$0.00	\$139.19	\$11.48	\$5.00	\$0.00	\$0.00	\$24.57	(\$0.82)	(\$0.45)	(\$0.33)	\$520.01
ZIOP	ZIOPHARM Oncology Inc.	\$5.56	22.96%	68.19	\$379.16	\$0.00	\$60.39	\$7.85	\$3.45	\$0.00	\$0.93	\$0.90	(\$0.71)	(\$1.27)	(\$0.82)	\$318.77
AVG					\$655.88											\$577.16
High					\$4,608.21											\$4,492.77
Low					\$69.04											(\$12.53)

## RISKS

- IMUC will need to raise additional capital prior to profitability in 2017
- IP 1 patent has been issued, several are pending
- CEO and CSO do not have contracts
- IMUC shares trade on the OTC Bulletin Board, which makes trading difficult
- Manufacturing of biologics on a commercial scale is complex, expensive, and may require new facilities
- Competition includes several vaccine companies and institutions with personalized vaccine therapy, off-the-shelf vaccine, and potential chemotherapy
- The reimbursement environment is increasingly difficult for high-priced therapies

## COMPANY BACKGROUND

IMUC completed a merger on January 31, 2006, where Spectral Molecular Imaging, Inc. became a wholly owned subsidiary. This merger was essentially a reverse merger, where the management and board took over. In May 2006, IMUC suspended its research and development activities on Spectral Molecular Imaging's spectral imaging technology, which was sold on September 11, 2006 to a co-founder of Spectral Molecular Imaging and inventor of its technology.

IMUC is a Los Angeles-based company, founded in May 2006. It is a virtual company with three full-time employees, including the president/CEO and the vice president over product development and manufacturing. The chairman of the board and CFO are part-time employees. The company utilizes a number of consulting agreements for clinical development, regulatory affairs, investor relations, and business development.

Dr. John Yu, IMUC's chairman of the board, is the director of surgical neuro-oncology at the Maxine Dunitz Neurosurgical Institute at Cedars-Sinai. He was able to identify the CSCs in GBM. Dr. Yu and his team have identified several peptides that can elicit an immune response targeting CD133, a common marker present on most GBM CSCs. These peptides are specific to certain HLA markers in humans. IMUC is developing product candidates to target CSCs that are believed to be responsible for the initiation and maintenance of GBM.

IMUC acquired an exclusive, worldwide license from Cedars-Sinai Medical Center in November 2006 for this cellular-based therapy technology, including dendritic cell-based vaccines for neurological disorders that include brain tumors, neurodegenerative disorders, and other cancers. This technology is covered by a number of pending US and foreign patent applications. In June 2008, IMUC licensed an additional technology from Cedars-Sinai to target CSCs that may be applicable for brain tumors as well as several other cancer indications. In September 2010, IMUC entered into a sponsored research agreement with Cedars-Sinai under which Cedars-Sinai will provide services in developing standard operating procedures for dendritic cell vaccine preparations. For IMUC to keep the rights to the Cedar-Sinai technology, the company must meet certain development and funding milestones. IMUC will pay certain milestones, as well as royalties on product sales.

IMUC purchased monoclonal antibody (mAB) technology in February 2008 and began an agreement with Molecular Discoveries LLC, a New York company, covering the acquisition of certain mAB-related technology owned by Molecular Discoveries. The technology acquired includes: 1) a platform technology referred to by Molecular Discoveries as DIAAD for the potentially rapid discovery of targets (antigens) and mABs for diagnosis and treatment of diverse human diseases, and (2) certain mAB candidates for the potential detection and treatment of multiple myeloma, small cell lung, pancreatic, and ovarian cancers. The mAB are covered by issued patents and pending patent applications that cover multiple myeloma, small cell lung, and ovarian cancers.

## PRODUCT CANDIDATES

IMUC's product candidate portfolio includes cellular immunotherapies targeting cancer and cancer stem cell antigens, peptide-based immunotherapies targeting CSCs, and mABs to diagnose and treat cancer. CSCs are considered a subset of cancerous cells, which are responsible for the growth and re-growth of the primary and metastatic tumors. To completely remove the tumor, the CSCs need to be eliminated since these cells are resistant to standard chemotherapy and radiation therapy. There are peptide markers on the surface of CSCs that can be used to target these cells. A vaccine can be created by using these peptides with an adjuvant that can generate an immune response by triggering T cells to identify and destroy these CSCs by targeting CD133 cells that have been identified in gliomas, colon cancer, and pancreatic cancer.

**ICT-107** is a therapeutic vaccine comprised of mature DCs targeting antigens from the patient's own tumor that attack the patient's CSCs. ICT-107 is given through intradermal injections (vaccinations) of autologous DCs, which have been harvested from peripheral blood precursors that have been co-cultured (pulsed) with tumor-associated antigens in patients with GBM. In June 2010, ICT-107 was granted orphan drug status by the FDA.

**ICT-121** is an "off-the-shelf" vaccine targeting recurrent GBM initially, but may address other cancers also. ICT-121 is a peptide that can produce an immune response in HLA-A\*0201 serotype patients; it targets CD133 positive CSCs. HLA is the molecule that foreign proteins present to the immune system by antigen-presenting cells. HLA-A2 represents the most prevalent HLA Class I type in North America. Preclinical studies are ongoing and an IND is on track to be filed this year. The trial will likely be a multi-center clinical trial in newly diagnosed and recurrent GBM patients. The endpoints will be clinical and immunological response. The trial may enroll 15-20 patients.

**ICT-109** is currently in pre-clinical studies in collaboration with George Mason University. ICT-109 can differentiate cancerous and non-cancerous samples in small lung cancer and pancreatic cancer. This mAB targets glycosylation sites that are only present on tumor cells. These sites are carcinoembryonic antigens, which play a role in tumorigenesis and cell adhesion. In collaboration with Antitope, Ltd, IMUC was able to humanize this mAB in August 2009. IMUC is searching for partners and licenses to combine ICT-109 with other cancer-killing technologies to continue development.

**ICT-69** is in pre-clinical studies targeting ovarian cancer cells and multiple myeloma. IMUC initiated a research and option license agreement with **Roche (RHHBY-\$44.72-NR)** in September 2009; however, RHHBY elected not to exercise in September 2010.

**Figure 2. ImmunoCellular's Pipeline**

Immunotherapies	Preclinical	Phase I	Phase II	Phase III	Market
<i>ICT-107</i> Glioblastoma					
<i>ICT-121</i> Glioblastoma					
<b>mAB</b>					
<i>ICT-109</i> Lung and Pancreatic Therapeutic					
<i>ICT-037</i> Colon & Ovarian Cancer, Multiple Myeloma					
<i>ICT-169</i> Ovarian Cancer & Multiple Myeloma					
<i>ICT Diagnostic fo SCLC</i> SCLC & Pancreatic Cancer					

Source: Company Reports

**Figure 3. ImmunoCellular Catalysts**

Milestones	Timing
Publication of the Phase I ICT-107 Trial in GBM	Q3:11
Announce listing of IMUC on the AMEX exchange	Q3:11
File IND for ICT-121 for recurrent GBM	2011
Complete enrollment of the ICT 107 Phase II trials	May '12
Interim analys of the ICT-107 GBM trial	Q4:12-Q1:13
Begin additional trials with ICT-107 in recurrent and pediatric GBM	2013
Competitive Milestones	Timing
Agenus's HSPPC-96 enters pivotal trials for newly diag GMB	H2:11
CENTRIC Phase III results in new GBM with cilengitide (Impretreve)	H1:12

## FINANCIAL MODEL

- We expect ICT-107 to launch in 2016 with a price of \$250,000 for a full course of treatment, consisting of 14 treatments over four years. We expect cost of goods sold to be between 10-12%, which includes a mid-single-digit royalty to Cedars-Sinai for the cellular-based therapy technology.
- IMUC entered into a license agreement with Cedars-Sinai in November 2006 and paid an upfront licensing fee of \$62,000; IMUC issued Cedars-Sinai 694,000 shares of common stock. IMUC must also pay additional specified milestones when the first product, ICT-107, begins the first phase III clinical trial, as well as when it is approved by the FDA. Those two milestones would total \$1,250,000. In addition, IMUC must meet certain development and funding milestones to keep the rights to the Cedars-Sinai licensed technology. In September 2010, IMUC entered into a sponsored research agreement for a cost of up \$446,000 for which Cedars-Sinai will provide services to develop standard operating procedures for DC vaccine preparations.
- IMUC entered an agreement with Socius Capital in December 2009, where Socius Capital has agreed to purchase up to \$10MM of IMUC's preferred stock. In May 2010, IMUC sold \$4MM of these shares to Socius Capital. There is still \$6MM that IMUC could drawdown. Socius has a 27% discount with no additional warrant coverage. IMUC must satisfy certain conditions to access this line of credit.
- As of March 31, 2011, directors and executive officers beneficially own ~25% of IMUC's outstanding common stock.
- There are 11.3MM options outstanding with an average exercise price of \$0.92, as well as 9.16MM warrants:

<b>Date Issued</b>	3/26/10	5/17/10	5/2/10	5/2/10	2/22/11
<b>Shares</b>	696,000	1,245,455	2,700,000	1,350,000	2,818,875
<b>Strike price</b>	\$ 1.15	\$ 1.50	\$ 2.00	\$ 2.50	\$ 2.25
<b>Term (months)</b>	26	36	60	60	60
<b>Date expired</b>	5/26/2012	5/17/2013	5/2/2015	5/2/2015	2/22/2016

Plus, 50K at \$1.60 with a two-year term expires December 2012; 100K at \$1.00 with a three-year term expires September 2013; 100K at \$2.00 with a three-year term expires September 2013; and 100K at \$2.00 with a three-year term expires April 2013.

- We expect the company to raise funds prior to ICT-107's approval — we estimate 2013 and 2015.
- ICT-107 has an orphan drug designation that provides for extra meetings with the FDA and an expedited six-month review, rather than the standard 10 months, plus market exclusivity for seven years.
- As of March 31, 2011 IMUC had a net operating loss of \$25.7MM.

### Upside to our model:

- IMUC may sign a partnership either for overseas or for worldwide rights. We have US sales only in our model.
- The phase II pivotal trial may end early, at the time of the interim analysis that is on track for YE:12. Either the FDA may accept an endpoint other than OS, and/or the PFS is ~13 months and the median OS is 22 months.

Figure 4. IMUC Revenue Model

US Market	2015E	2016E	2017E	2018E	2019E	2020E	2021E
Newly Diagnosed GBM	10,824	11,041	11,262	11,487	11,717	11,951	12,190
Resectable Eligible	8,659	8,833	9,009	9,189	9,373	9,561	9,752
Applicable Patients	6,062	6,183	6,307	6,433	6,561	6,693	6,826
<i>% Penetration</i>	<i>0.0%</i>	<i>5.0%</i>	<i>15.0%</i>	<i>20.0%</i>	<i>25.0%</i>	<i>30.0%</i>	<i>30.0%</i>
New Patients on ICT-107	0	309	946	1,287	1,640	2,008	2,048
Patients Still on ICT-107 Yr 2	0	0	247	757	1,029	1,312	1,606
Patients Still on ICT-107 Yr 3	0	0	0	136	416	566	722
Patients Still on ICT-107 Yr 4	0	0	0	0	20	62	85
Total Patients on ICT-107	0	309	1,193	2,043	2,670	3,320	3,654
WSP - ICT-107 (1st Year)	\$ -	\$ 142,857	\$ 145,714	\$ 148,629	\$ 151,601	\$ 154,633	\$ 157,726
WSP - ICT-107 (2nd Year)	\$ -	\$ -	\$ 35,714	\$ 36,429	\$ 37,157	\$ 37,900	\$ 38,658
WSP - ICT-107 (3rd Year)	\$ -	\$ -	\$ -	\$ 35,714	\$ 36,429	\$ 37,157	\$ 37,900
WSP - ICT-107 (4th Year)	\$ -	\$ -	\$ -	\$ -	\$ 35,714	\$ 36,429	\$ 37,157
WSP Change Per Year			2%	2%	2%	2%	2%
ICT-107 Revenue	\$ -	\$ 44,163,232	\$ 146,674,927	\$ 303,694,112	\$ 404,706,147	\$ 513,384,278	\$ 576,348,324

Source: SSRP research

Each of 14 doses over 4 yrs =	\$ 17,857
1st year cost of 8 doses=	\$ 142,857
2nd year cost of 4 doses=	\$ 35,714
3rd year cost of 3 doses=	\$ 35,714
4th year cost of 1 doses=	\$ 35,714
cummulative 4 yr cost	\$ 250,000

**REVENUE MODEL ASSUMPTIONS**

Patients must have HLA A1 and A2. Of Caucasians, 50% have HLA-A2 and 30% A1; ~55% of Asians and ~70% of African Americans have the correct HLA status. In total, ~80% of the US population has the correct HLA status. Each patient would receive 14 doses over four years — eight doses in the first year and each year after. Assuming a cumulative price of \$250K, each dose would be \$17.9K.

IMUC believes it has better economics than the personalized prostate vaccine Provenge, by Dendreon (**DNDN-\$37.31-NR**), which produces separate batch for each dose. Provenge is priced at \$93K annually, indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. Medicare is reimbursing Provenge. Bristol Myers’ (**BMY-\$28.61-NR**) Ipilimumab, which was approved in March 2011, is a human mAB specific for human cytotoxic T lymphocyte-associate antigen 4 (CTLA-4) for the treatment of unresectable or metastatic melanoma. Blockage of CTLA-4 has been show to augment T-cell activation and proliferation. Ipilimumab (Yervoy) is priced at \$30K/dose, and most patients are to receive four doses of this off-the-shelf vaccine. BMY has said it will cap the price at \$80K/course of therapy.

Figure 5. IMUC Income Statement

IMUC Quarterly Earnings Model, 2001-2016E (\$ millions)																			
Income Statement	2007	2008	2009	2010	Q1	Q2E	Q3E	Q4E	2011E	2012E	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E
ICT-107 (US)	-	-	-	-	-	-	-	-	-	-	-	-	-	44,163	146,675	303,694	404,706	513,384	576,348
ICT-121 (US)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	*	*	*	*
Total revenues	-	-	-	-	-	-	-	-	-	-	-	-	-	44,163	146,675	303,694	404,706	513,384	576,348
COGS	-	-	-	-	-	-	-	-	-	-	-	-	-	4,858	16,134	33,406	44,518	56,472	63,398
SG&A	946	1,366	1,677	2,036	554	600	650	700	2,504	3,000	3,800	4,370	7,648	21,031	26,288	31,546	37,855	45,426	52,240
R&D	78	1,297	963	2,293	917	1,000	1,500	1,700	5,117	8,450	10,000	11,500	13,225	14,548	16,002	17,602	19,363	21,299	23,429
Depreciation and Amortization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other operating costs, net	1,297	513	308	808	242	200	200	200	842	1,000	1,000	1,000	1,000	1,000	1,001	1,002	1,003	1,004	1,005
Total operating expenses	2,321	3,176	2,948	5,136	1,713	1,800	2,350	2,600	8,463	12,450	14,800	16,870	21,873	36,578	43,292	50,150	58,221	67,729	76,674
Operating income	(2,321)	(3,176)	(2,948)	(5,136)	(1,713)	(1,800)	(2,350)	(2,600)	(8,463)	(12,450)	(14,800)	(16,870)	(21,873)	2,727	87,249	220,137	301,968	389,183	436,276
Interest expense, net	162	117	22	4	2	2	2	2	8	7	6	5	5	4	5	8	10	12	15
Other non-operating income	(1,456)	-	-	(1,018)	(1,047)	-	-	-	(1,047)	(1,000)	(1,000)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)	(1,500)
Income before taxes	(3,615)	(3,060)	(2,926)	(6,150)	(2,758)	(1,798)	(2,348)	(2,598)	(9,502)	(13,443)	(15,794)	(18,365)	(23,368)	1,231	85,754	218,645	300,478	387,695	434,791
Provision for income taxes	-	-	-	-	-	-	-	-	-	-	-	-	-	419	29,156	74,339	102,162	131,816	147,829
Reported net income, net	(3,615)	(3,060)	(2,926)	(6,150)	(2,758)	(1,798)	(2,348)	(2,598)	(9,502)	(13,443)	(15,794)	(18,365)	(23,368)	813	56,598	144,306	198,315	255,879	286,962
Special charges	-	-	-	(2,093)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GAAP net income	(3,615)	(3,060)	(2,926)	(8,243)	(2,758)	(1,798)	(2,348)	(2,598)	(9,502)	(13,443)	(15,794)	(18,365)	(23,368)	813	56,598	144,306	198,315	255,879	286,962
EPS Reported	(\$0.33)	(\$0.24)	(\$0.21)	(\$0.43)	(\$0.11)	(\$0.06)	(\$0.08)	(\$0.09)	(\$0.35)	(\$0.45)	(\$0.42)	(\$0.48)	(\$0.49)	\$0.02	\$1.08	\$2.69	\$3.62	\$4.58	\$5.04
EPS GAAP	(\$0.33)	(\$0.24)	(\$0.21)	(\$0.43)	(\$0.11)	(\$0.06)	(\$0.08)	(\$0.09)	(\$0.35)	(\$0.45)	(\$0.42)	(\$0.48)	(\$0.49)	\$0.01	\$0.89	\$2.22	\$3.00	\$3.81	\$4.21
Basicshares (millions)	10,853	12,540	13,720	19,189	24,314	28,959	29,016	29,074	27,841	29,756	37,231	37,975	47,785	51,559	52,590	53,642	54,715	55,809	56,926
Fully diluted shares (millions)					35,614	40,259	40,316	40,374	39,141	41,056	48,531	49,275	59,085	62,859	63,890	64,942	66,015	67,109	68,226

## ICT-107 FOR NEWLY DIAGNOSED GBM

The capacity to generate large numbers of DCs in vitro from a patient's monocytes or myeloid bone marrow precursor cells has led to the ex-vivo loading of DCs with tumor antigens and injection of DC vaccines as a prominent strategy for induction of anti-tumor immunity in cancer patients. Preclinical studies have shown DCs to be the most potent activators of B- and T-cell responses, and therefore DC vaccines are regarded as one of the most promising strategies for successful tumor immunotherapy. The dendritic strategy to induce immunological responses against proprietary antigen combinations was the basis for ICT-107, an immunotherapy incorporating six antigens. ICT-107 was characterized by consultants as an approach more likely to result in a response from GBM that has a highly diverse tumor cell population.

ICT-107 is a personalized vaccine comprised of mature DCs-targeting antigens from the patient's own tumor that attack the patient's GBM CSCs. To receive ICT-107, patients must be newly diagnosed with GBM and have not yet received radiation and chemotherapy. Some of the patient's white blood cells (WBCs) are removed during outpatient aphaeresis and cultured in a laboratory with six different synthetic purified antigens (Figure 6). Upon maturation, these DCs are trained to stimulate T-cell immune responses to the presence of these antigens in the body. The mature DCs are then aliquoted, frozen, and shipped back to the patient site for vaccination. The manufacturing process has been developed to create 20 doses, and cryopreservation technology will keep the vaccine for several years. The DCs are then injected into the patient as a vaccine over several months. The goal is for the ICT-107 vaccine to stimulate the patient's immune response to kill the remaining GBM tumor cells after surgery and chemotherapy.

**Figure 6. Antigens Pulsed with Dendritic Cells to Create ICT-107**

Antigens	Tumor Expression	Cancer Stem Cell Expression
gp100	Melanoma, Brain Cancer	
Trp-2	Melanoma, Brain Cancer	High
Her-2/neu	Breast, Ovarian Cancer	Medium
MAGE-1	Melanoma, Brain Cancer	
AIM	Breast, Ovarian, Colon, Brain	High
IL-13aR2	Brain Cancer	

*Company Presentation*

In January 2010, IMUC reported the results of a study in which it was shown that certain specific antigens are highly expressed on CSCs. Thus, ICT-107, which targets those antigens, may effectively target not only the cells that make up the bulk of certain cancerous tumors, but also the CSCs that are widely believed to give rise to them and cause their recurrence.

**Figure 7. Antigens' (HER-2, gp100, MAGE-1) Presence in Glioblastoma CSCs**

GBM cell line	HER-2	gp100	MAGE-1
U-87MG	+	+	+
U-118MG	+	-	+
U-373MG	-	-	+
U-138MG	-	+	+
IR-801	+	+	+
IR-802	+	-	+
IR-803	+	+	+
Normal brain tissue ( $n = 6$ )	66.7% <sup>b</sup>	50% <sup>b</sup>	0% <sup>b</sup>
Primary tumor cell lines ( $n = 43$ )	81.4% <sup>b</sup>	46.5% <sup>b</sup>	39.5% <sup>b</sup>

<sup>a</sup> GBM, glioblastoma multiforme; RT-PCR, reverse transcription-PCR.  
<sup>b</sup> Data indicate the percentage of samples that had positive expression.

*Liu, G., et al., Cancer Research 2004*

The FDA approved the first cancer treatment vaccine in April 2010. DNDN manufactures this personalized vaccine, called Provenge (sipuleucel-T), which is approved for use in some men with metastatic prostate cancer. It is designed to stimulate an immune response to prostatic acid phosphatase (PAP), an antigen that is found on most prostate cancer cells. In two trials Provenge increased survival by ~four months. The vaccine is created by isolating immune system cells, called antigen-presenting cells (APCs), from the patient's blood using aphaeresis. The APCs are sent to DNDN, where they are cultured with a protein called PAP-GM-CSF. This protein consists of PAP linked to another protein called granulocyte-macrophage colony-stimulating factor (GM-CSF). The latter protein stimulates the immune system and enhances antigen presentation. APC cells cultured with PAP-GM-CSF constitute the active component of sipuleucel-T. Each patient's cells are returned to the patient's treating physician and infused into the patient. Patients receive three treatments, usually two weeks apart, with each round of treatment requiring the same manufacturing process. Although the precise mechanism of action of sipuleucel-T is not known, it appears that the APCs that have taken up PAP-GM-CSF stimulate T cells of the immune system to kill tumor cells that express PAP.

Cancer vaccines appear to have safety profiles comparable to those of traditional vaccines, even though the side effects of cancer vaccines can vary among vaccine formulations and from one person to another. The most commonly reported side effect of cancer vaccines is inflammation at the site of injection, including redness, pain, swelling, warming of the skin, itchiness, and occasionally a rash. People sometimes experience flu-like symptoms after receiving a cancer vaccine, including fever, chills, weakness, dizziness, nausea or vomiting, muscle ache, fatigue, headache, and occasional breathing difficulties. Blood pressure may also be affected.

### **ICT-107 CLINICAL TRIALS/EFFICACY**

***ICT-107 demonstrated a survival benefit in an open-label phase I clinical trial.*** The phase I trial evaluated 16 newly diagnosed and three recurrent GBM patients with HLA A1 and A2 status. Patients underwent tumor resection, magnetic resonance imaging (MRI), and tumor assessment prior to enrollment into the study. Post-surgical treatment consisted of six weeks of chemotherapy (temozolomide, or TMZ) and radiation followed by a washout period. After screening and informed consent, patients had aphaeresis at the study site for collection of peripheral blood mononuclear cells (PBMCs). The aphaeresis product was then sent to a central site where the monocytes were purified and cultured into DCs. The DCs were pulsed with synthetic peptides that correspond to immunogenic epitopes of tumor antigens. The pulsed DCs were then aliquoted and frozen before shipping back to the site. The control group received unpulsed autologous DCs. All patients were then intradermally reinfused with their autologous DCs. All patients expressed at least three antigens, and 75% expressed all six. Increased PFS was observed with increased expression of MAGE-A1, AIM2, gp100, and HER2. Expression of CD133 in subsequent surgical samples was decreased or negative.

The trial began in May 2007 and the results were reported at ASCO in June 2010 (Figure 8). The phase I clinical study of ICT-107 in newly diagnosed GBM patients who received three doses of ICT-107 in addition to the SOC of surgery, radiation, and chemotherapy reported a median PFS of 16.9 months, a one-year OS of 100%, and a two-year OS of 80%. This compares favorably with historical 61.1% one-year and 26.5% two-year survival based on the patients with SOC and 38% in GBM patients whose tumor is completely resected (Strupp et al, NEJM 2005).



**Figure 9. Phase I Results Compared to Historical SOC**

		ICT-107 + SOC		Historical SOC <sup>^*</sup>	
N		52		287	
<b>PFS (%)</b>	<b>Months</b>	<b>range</b>		<b>range</b>	
	6	100	63.2-99.1	53.9	48.1-59.6
	12	62.5	34.8-81.1	26.9	21.8-32.1
	18	43.8	23.5-70.6	18.4	13.9-22.9
	<b>24</b>	<b>43.8</b>	<b>23.5-70.6</b>	<b>10.7</b>	<b>7.0-14.3</b>
<b>Median (mons)</b>		16.9	11.1-39.3	6.9	5.8-8.2
<b>OS (%)</b>	<b>Months</b>				
	6	100		86.3	82.3-90.3
	12	100		61.1	55.4-66.7
	18	93.8	63.2-99.1	39.4	33.8-45.1
	<b>24</b>	<b>80.2</b>	<b>52.4-93.5</b>	<b>26.5</b>	<b>21.2-31.7</b>
<b>Median mons</b>		NR >30		14.6	13.2-16.8

<sup>^</sup>XRT + TMZ

\*Source: company reports, NEJM 2005

**The randomized, double-blind, placebo-controlled phase IIb trial began in January 2011.** Patients are randomized by age in a 2:1 ratio to ICT-107 or placebo (unloaded DCs, as in the phase I). Patients will receive at least 4 intradermal injections of the ICT-107 vaccine and additional vaccine injections every 3-6 months during a maintenance phase. The trial will enroll 200 patients with newly diagnosed GBM following surgery and chemo radiation (SOC). All patients will have their WBCs removed via aphaeresis. Patients in the ICT-107 arm will have their WBCs cultured in a laboratory with purified antigens similar to the ones on GBM cells. The main difference between the phase IIb and the phase I is the first trial did not have a maintenance phase.

**The primary endpoint is a composite of OS and PFS.** Secondary endpoints include rates of OS and PFS at six months after surgery, then assessed every three months until the end of the study. The company anticipates the study may take 2-3 years. Additional secondary endpoints include: 1) immune response to ICT-107, 2) number of grade 3 and 4 toxicities, 3) number of serious adverse events (SAEs), 4) number of treatment emergent adverse events (AEs); 5) treatment-related toxicities, and 6) predictors of response. The company estimates that the trial will be complete in Q4:14. The trial has 80% power to demonstrate a six-month improvement in OS.

**IMUC believes it will take through May 2012 to enroll the trial.** IMUC has qualified 25 sites so far and has submitted the trial to 16 prospective sites' Institutional Review Boards (IRB) for approval. Of these 16 sites, nine have received IRB approval. The goal is to have 20+ centers up and running. So far there are only 4-5 up and running.

**There is an interim analysis planned at 17 months that could occur in late in 2012.** Thirty-three events are needed to trigger the interim analysis. It is rather difficult to predict when the interim analysis will occur until more centers are up and running; however, right now it may be available Q4:12-Q1:13. If the interim analysis shows a six-month OS, it is unlikely that will be sufficient for an early approval. For the trial to end early, an OS rate of 26 months or longer may be necessary. IMUC does not plan on that happening.

**Our consultants found the 80% two-year OS rate to be "quite impressive."** The ease of patient enrollment was noted by our consultants as a critical issue, because other vaccine trials have had difficulty, ie. **Celldex Therapeutics' (CLDX-\$3.57-NR) CDX-110 ACT III trial.** Our consultants felt the promising phase I data and well designed phase II treatment protocol would be applicable to ~70% of their first-line GBM patients with HLA A1 and A2 status and makes ICT-107 a highly interesting mid-stage therapeutic.

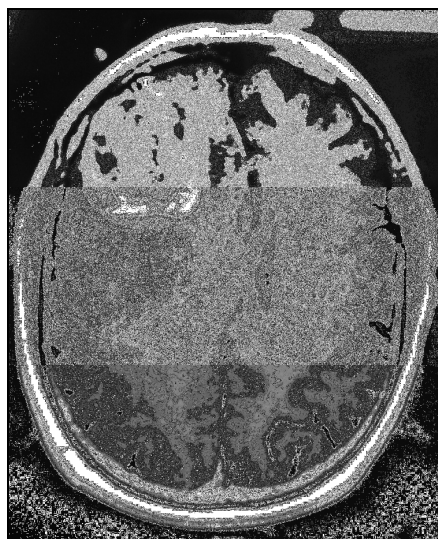
**ICT-107 has designated orphan drug designation that provides for extra meetings with the FDA and an expedited six-month review, rather than the standard 10 months, plus market exclusivity for seven years.**

## BACKGROUND ON BRAIN TUMORS AND GLIOBLASTOMA (GBM)

Each year approximately 14K new cases of malignant glioma are diagnosed in the US. Of those, 60-70% are malignant glioma, 7-15% are anaplastic astrocytomas, 10% are anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas, with rarer tumors, account for the rest. The WHO has classified the tumors, based on histology, into four prognostic grades. Grades 3 and 4 are considered malignant. GBM is the deadliest brain tumor, with only approximately one third of patients surviving for one year, and less than 5% living beyond five years. The five-year survival rate for anaplastic astrocytoma is 27%.

Malignant gliomas are invasive tumors and typically contain both neoplastic and stromal tissues, which contribute to their histologic heterogeneity and variable outcomes. In addition to the tumor itself, inflammation and edema cause significant neurological deficits, as the pressure on normal brain tissue increases as the tumor grows. The aggressive nature of the tumor and the uncompromising intracranial space contribute to the lethal reputation of GBM. MRI does not necessarily distinguish between tumor, edema, and radiation necrosis.

**Figure 10. Characteristic GBM Appearance on MRI Scan**



## TREATMENT FOR NEWLY DIAGNOSED GBM

It is very difficult to treat GBM, due to several complicating factors: 1) tumor cells are very resistant to conventional therapies; 2) the brain is susceptible to damage due to conventional therapy; 3) the brain has a very limited capacity to repair itself; and 4) many drugs cannot cross the blood-brain barrier to act on the tumor. Supportive treatment focuses on relieving symptoms and improving the patient's neurologic function. The primary supportive agents are anticonvulsants and corticosteroids. Corticosteroids, usually dexamethasone, given 4-10 mg every 4-6 hours, can reduce brain edema through rearrangement of the blood-brain barrier. The result is reducing the intracranial pressure and decreasing headaches or drowsiness.

### ***Palliative treatment usually improves the patient's quality of life (QoL) and may extend survival time.***

Treatment includes surgery, radiation therapy, and chemotherapy. A maximally feasible resection with maximal tumor-free margins is usually performed along with external beam radiation and chemotherapy. For patients eligible for surgery, the goal is total resection of the tumor, which usually results in a better prognosis. Removal of 98% or more of the tumor has been associated with a significantly longer, healthier time than if less is removed. The chances of near-complete initial removal of the tumor can be greatly increased if the surgery is guided by a fluorescent dye known as 5-aminolevulinic acid. GBM cells are widely infiltrative through the brain at diagnosis, and so despite a "total resection" of all obvious tumors, most people with GBM later develop recurrent tumors, often near the original site. Approximately 20% of patients are not eligible for surgery.

***Next, radiation is used to further slow recurrent disease.*** A pivotal clinical trial from the early 1970s showed that among 303 GBM patients randomized to radiation or non-radiation therapy, those who received radiation after surgery had a median survival of 8.75 months vs. 3.5 months. Whole brain radiotherapy is not better than the more precise and targeted three-dimensional conformal radiotherapy. A total radiation dose of 60-65 Gy has been found to be optimal.

**Figure 11. GBM Treatment Options**

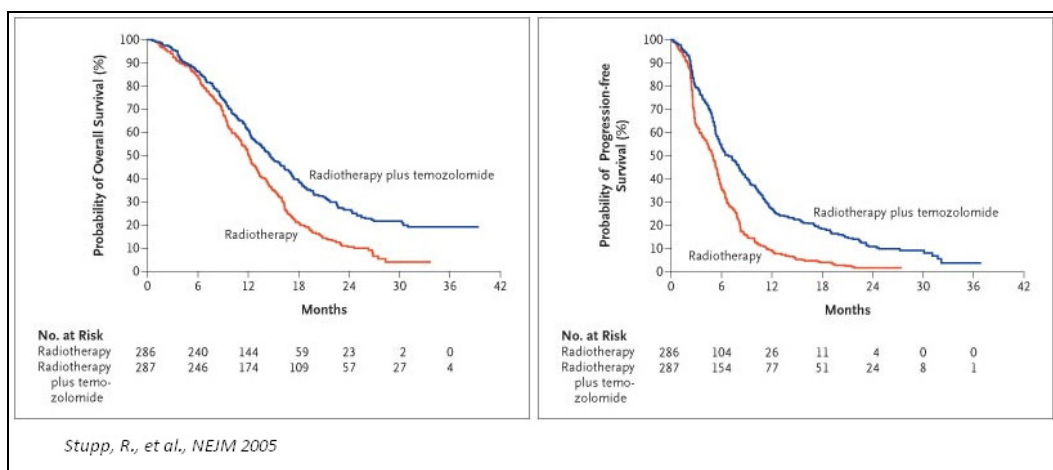
Condition	WHO Grade	Treatment
<b>Newly diagnosed tumors</b>		
Glioblastomas	grade IV	Maximal surgical resection, plus radiotherapy, plus concomitant and adjuvant TMZ or carmustine wafers (Gliadel)
anaplastic astrocytomas	grade III	Maximal surgical resection, with these post surgery options (NO SOC): radiotherapy, plus concomitant and adjuvant TMZ, or adjuvant TMZ alone
Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas	grade III	Maximal surgical resection, with these post surgery options (no SOC): radiotherapy alone, TMZ or PCV with or without radiotherapy afterward, radiotherapy plus concomitant and adjuvant TMZ, or radiotherapy plus and adjuvant TMZ
<b>Recurrent tumors</b>		Reoperation in selected patients, carmustine wafers (Gliadel), conventional chemotherapy (e.g. lomustine, carmustine, PCV, carboplatin, irinotecan, etoposide), Avastin + irinotecan, experimental therapies.

Source: NEJM 2005

**Standard therapy for newly diagnosed malignant gliomas involves surgical resection, when feasible, radiotherapy, and chemotherapy.** Unfortunately malignant gliomas cannot be completely eliminated surgically because of their infiltrative nature. The value of surgery in prolonging survival is controversial, but patients who undergo extensive resection probably have a modest survival advantage. The addition of radiotherapy to surgery increases survival among patients with GBM from a range of 3-4 months to 7-12 months. Unfortunately, 90% of tumors will recur at the original site. In other cancers where radiation can prolong survival or even cure tumors, the addition of chemotherapy to radiation improves survival. However, with GBM the majority of studies with chemotherapy showed no benefit.

**The current SOC for treating newly diagnosed GBM since 2005 is the use of TMZ given concurrently with and following radiotherapy.** Early trials with chemotherapy failed to show a benefit. Merck's (MRK-~~xx.xx~~-NR) Temodar (TMZ) has been the exception when a trial was conducted that randomized patients to standard radiation versus radiation plus TMZ. The 575-patient trial showed the group receiving TMZ survived a median of 14.6 months as opposed to 12.1 months for the group receiving radiation alone. The median survival for patients treated with radiotherapy was 12.1 months, while radiation plus TMZ was 14.6 months. The median PFS was 6.9 months for patients treated with radiotherapy and TMZ and five months for patients treated just with radiotherapy alone (Figure 12). The two-year OS rate was only 10.4% in those treated with radiotherapy alone compared with 26.5% in those who received radiotherapy plus TMZ. The combined-modality regimen was well tolerated and associated with minimal additional toxicity. TMZ seems to work by sensitizing the tumor cells to radiation. Follow up to this trial indicates that TMZ with radiation continued to have superior survival throughout the five-year period ( $p < 0.0001$ ).

**Figure 12. Current Standard of Care for Treatment of Glioblastomas**



TMZ is an oral alkylating agent that minimizes the levels of O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT). MGMT is an important repair enzyme that contributes to resistance to TMZ. A randomized trial published by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) clinical trials group (Strupp, *The Lancet Oncology*, 2009) showed that addition of TMZ to radiotherapy in the treatment of

patients with newly diagnosed GBM significantly improved survival. An exploratory subanalysis of the EORTC/NCIC data was done in 573 GBM adult patients to confirm or identify new prognostic factors for survival. Epigenetic silencing of the MGMT gene by promoter methylation reduces expression of the DNA repair enzyme and confers greater sensitivity to alkylating agents, including TMZ. MGMT promoter methylation (45% of the total) that was treated with TMZ had a median survival of 21.7 months and a two-year survival rate of 46%. In contrast, patients without MGMT promoter methylation who were treated with TMZ had a significantly shorter median survival of only 12.7 months and a two-year survival rate of 13.8%. Currently, TMZ is used in the GBM treatment regardless of MGMT promoter methylation status. The MGMT promoter methylation rate in newly diagnosed GBM in the more recent RTOG 0525 phase III trial reported at ASCO 2011 was ~one-third (33.4%), a rate that is somewhat lower than prior reports. Many studies now stratify by MGMT promoter methylation status in GBM trials that use alkylating chemotherapy such as TMZ.

## OTHER CELL AND IMMUNOTHERAPIES IN DEVELOPMENT FOR NEWLY DIAGNOSED GBM

### Immunotherapies

Despite the belief that effective immune responses against central nervous system (CNS) tumors would be prevented by the “immunoprivileged” status of the brain, studies have demonstrated that immune effector cells and antibodies can gain access to the CNS and induce powerful immunological mechanisms against recognized target cells within the brain. Clearly, normal immune mechanisms are insufficient in battling CNS malignancies on their own, as tumors such as GBM evade the immune system and grow unchecked in patients. Therefore, the immune system is either incapable of mounting a meaningful anti-tumor response, or by the time malignant tumor growth reaches detection and diagnosis it has escaped the pressure of what may have initially been an effective physiologic anti-tumor immune response. Most experts believe the potential clearly exists to develop ways to coax the body into producing an effective immunologic response, and immunotherapies represent a very real future avenue for the treatment of CNS tumors, including GBM. The microenvironment of the CNS is entirely capable of supporting the full spectrum of cellular and humoral immune responses, and the challenge lies with coupling the best anti-tumor antigens with the mechanism that produces the most effective immunological response. Currently, peptide vaccines and DC therapies are generating the most interest.

**CLDX’s CDX-110.** Rindopepimut (CDX-110) is a vaccine consisting of 13 amino acids unique to EGFRvIII, a functional variant of the epidermal growth factor receptor (EGFR). EGFR is validated as a target for cancer therapy, with several drugs approved – RHHBY’s oral erlotinib (Tarceva), **AstraZeneca’s (AZN-\$48.81-NR)** gefitinib (Iressa), and IV mAbs like **Bristol Myers’ (BMY-\$28.61-NR)** cetuximab (Erbix) and **YM Bioscience’s (YMI-\$2.38-NR)** nimotuzumab. Only Tarceva and Erbitux are approved in the US. Iressa and nimotuzumab are approved overseas. Unlike EGFR, EGFRvIII is not present in normal tissues, which should reduce its toxicity profile. EGFRvIII is a transforming oncogene that can directly contribute to cancer cell growth. EGFR is estimated to be over-expressed in 40-50% of GBM patients; EGFRvIII is only over-expressed in 25-30% of those EGFR-positive GBM patients. This limits the number that could benefit from this off-the-shelf (not personalized or autologous) vaccine. Patients with EGFRvIII-expressing glioblastoma have a median survival only one month shorter than the total GBM population as a whole, but less than 10% of patients are alive beyond two years. In September 2010, ex-partner **Pfizer (PFE-\$19.30-NR)** returned all rights to CLDX. The companies have conducted three phase II clinical trials – ACTIVATE, ACT II, and ACT III – in newly diagnosed GBM.

The ACTIVATE trial included 21 patients with newly-diagnosed GBM that expressed EGFRvIII. Patients had undergone gross-total resection followed by conformal radiation therapy and concurrent TMZ (5 mg/m<sup>2</sup>/day) with no disease progression. Sixteen patients received three doses of CDX-110 mixed with SQ GM-CSF (142 mcg) every two weeks, and five patients received three saline placebo doses in a blinded fashion. All patients then received monthly CDX-110 plus GM-CSF until disease progression. Median OS was 24.6 months (95% CI: 21.6, infinity), median TTP was 14.2 months. Median OS in a historical matched cohort was 15.2 months (95% CI: 13.9, 20.5) (p=0.0001) and median TTP in the historical matched control was 7.13 months (p=0.0001). There were no significant adverse events reported.

The ACT II study included 23 patients and was a similar trial to ACTIVATE. The early saline placebo phase in the ACTIVATE study was omitted, and two doses of maintenance TMZ were evaluated (13 patients received 200 mg/m<sup>2</sup> daily times five every 28 days, while 10 received 100 mg/m<sup>2</sup> daily times 21 days every 28 days for a maximum of 12 cycles). Monthly CDX-110 vaccination mixed with GM-CSF was given on day 21 of each cycle until tumor progression. Median OS is 24.4 months, and OS has not yet been reached but is estimated to be 33.1 months, based on preliminary results. The survival of a matched historical control group was 14.3 months (95% CI: 13.0, 16.2) and 15.2 months for a subgroup treated with TMZ (95% CI: 13.9, 20.5 p=0.0078). TTP was 16.6 months for patients in the ACT II study compared with 6.4 months for the historical control group (95% CI: 5.0, 14.1). Local injection site reaction was the primary reported toxicity.

ACT III was a multicenter, randomized, open-label phase IIb/III study conducted at 20 centers in North America (ACTIVATE and ACT II were conducted at MD Anderson and Duke). Patients with gross total resection of newly

diagnosed EGFRvIII+ GBM and successful completion of standard radiotherapy with concurrent TMZ were eligible for enrollment. At initial screening, 27% (166/624) met the criteria using ICH, 199/624 (31%) were positive for vIII expression with PCR. CDX-110 was administered every other week  $\times 3$  before starting maintenance TMZ and monthly thereafter on day 21 of each TMZ cycle, until disease progression. Eighty-one patients were enrolled (65 receiving the vaccine). The trial was amended to a single-arm design when 14/16 patients randomized to the SOC control arm declined further participation after notification of treatment assignment. The final PFS for the 65 (evaluable) patients was 5.5 post vaccinations. In addition 43 of 65 patients were alive with progression at 5.5 months. This is a 66% PFR at 5.5 months. It is important to note the PFR of 5.5 months from vaccination in the ACT III study is an equivalent time point to the PFR of 8.5 months since diagnosis or surgery, which was used in the ACTIVATE and ACT II trials. Usually, the median time elapsed from diagnosis to vaccination was three months. Local injection-site reactions were the most common treatment-related AEs reported in the majority of patients. Reversible hypersensitivity reactions (all grades) occurred in 5% of patients with one reaction being reported as serious and requiring discontinuation of CDX-110. A PFR of 66% at 5.5 months is similar to that reported from the previous Duke/MD Anderson Cancer Center trial.

CLDX plans to initiate a 300-patient pivotal trial in H2:11 and expects to involve 100 sites internationally. The company expects a PFS survival primary endpoint with OS and QoL as secondary endpoints. However, this plan is subject to change post an FDA meeting.

Consultants were not thrilled with the study, noting that the requirement of gross total resection and uncommon EGFR (+) status left the majority of patients ineligible for the vaccine. The heterogeneous nature of EGFR amplification and mutation makes a vaccine based on a single antigen highly problematic. The therapy will progress into further testing, but consultants were concerned about the prospect of enrolling control patients given the difficulties ACT III encountered.

**Figure 13. Phase I Results Compared to IMC-107**

<b>Trial</b>	<b>N</b>	<b>Median PFS mons</b>	<b>Median OS mons</b>	<b>OS @ 24 mons</b>
ACT III	65	12.3	24.3*	50%*
ACT II	22	15.3	24.4	50%
ACTIVATE	18	14.2	24.6	50%
Matched hx control <sup>^</sup>	17	6.4	15.2	6%
SOC rad/TMZ (Stupp 2005)	287	6.9	14.6	27%
IMC-107 Phase I	16	16.9	not reached	80%

\* estimated

<sup>^</sup>Sampson, et al. JCO 2010 Nov 1st

Source: company reports, SSRP research

**Agenus' (AGEN-\$0.77-NR) Prophage Series G-100 personalized vaccine is in a phase II trial that began at UCSF.** UCSF is in charge of the recurrent GBM trials. It also initiated a phase II clinical trial in newly diagnosed glioma, testing Prophage Series vaccine G-100 in combination SOC with a target of 50 patients. As of April 2011, approximately 20 patients had been treated. Based on promising early signals, the trial is being extended beyond UCSF to 10 prominent US brain tumor research centers. Patients receive the Prophage series G-100 intradermally four weeks consecutively, then monthly until progression or vaccine runs out. Results are expected in Q1:14. Prophage is approved in Russia as Oncophage for the adjuvant treatment of kidney cancer patients at intermediate risk for disease recurrence.

**Northwest Biotherapeutics' (NWBO-\$0.62-NR) DCVax-Brain uses a patient's own DCs to develop the vaccine.** The DCs are extracted from the body, loaded with tumor biomarkers or "antigens," creating a personalized therapeutic vaccine. The patient is then injected with the vaccine, which begins an immune response against cancer cells, resulting in delayed TTP and prolonged survival. Phase I results were published in *Clinical Cancer Research* in March 2011. The phase I trial enrolled 23 GBM patients that were either newly diagnosed or had recurred. It was a dose escalation study that tested three biweekly injections of glioma lysate-pulsed DCs followed by booster vaccinations with either imiquimod or poly-ICLC adjuvant every three months until tumor progression. The median OS from the time of initial surgical diagnosis of GBM was 31.4 months, with one-, two-, and three-year survival rates of 91%, 55%, and 47%, respectively. The side effects were minimal, limited mostly to flu-like symptoms and rashes near the vaccine injection site. There was no dose limiting toxicity. Patients whose tumors had mesenchymal gene expression signatures exhibited increased survival following DC vaccination compared with historic controls of the same genetic subtype. Mesenchymal GBM accounts for approximately 1/3 of patients. Tumor samples with a mesenchymal gene expression signature had a

higher number of CD3+ and CD8+ tumor-infiltrating lymphocytes compared with glioblastomas of other gene expression signatures ( $p=0.006$ ). In addition, according to the long-term follow-up data as of July 2010, 33% of the patients had reached or exceeded four-year survival, 27% had reached or exceeded six-year survival, and the longest surviving patient to date had exceeded 10 years.

DCVax-Brain is in a DBPC randomized phase II trial with 240 newly diagnosed GBM patients. It has been designed and powered as a pivotal trial. Patients will receive SOC surgery, radiation, and TMZ, and two of three patients will also use DCVax. As of last January, 13 US clinical sites with 33 patients enrolled. These patients have continued to be treated with the DCVax regimen and follow-up during the last two years.

***Other personalized vaccines produced at universities are in clinical trials for newly diagnosed GBM.*** Several universities have the manufacturing capacity to run their own DC vaccine trials. These include the University of California, Los Angeles, Duke University, and the University of Pittsburgh. In addition, the NCI also has trials ongoing.

## **ANGIOGENESIS/GROWTH FACTOR INHIBITORS**

Angiogenesis, the process of blood vessel formation, is critical for the growth of many solid tumors. GBM is one of the most angiogenic tumors, and cells heavily produce various proangiogenic factors, including VEGF, basic fibroblast growth factor (bFGF), PDGF, and HGF, which contribute to peritumor edema and inflammation as well as growth of the primary tumor. Integrins also play a role in angiogenesis regulation.

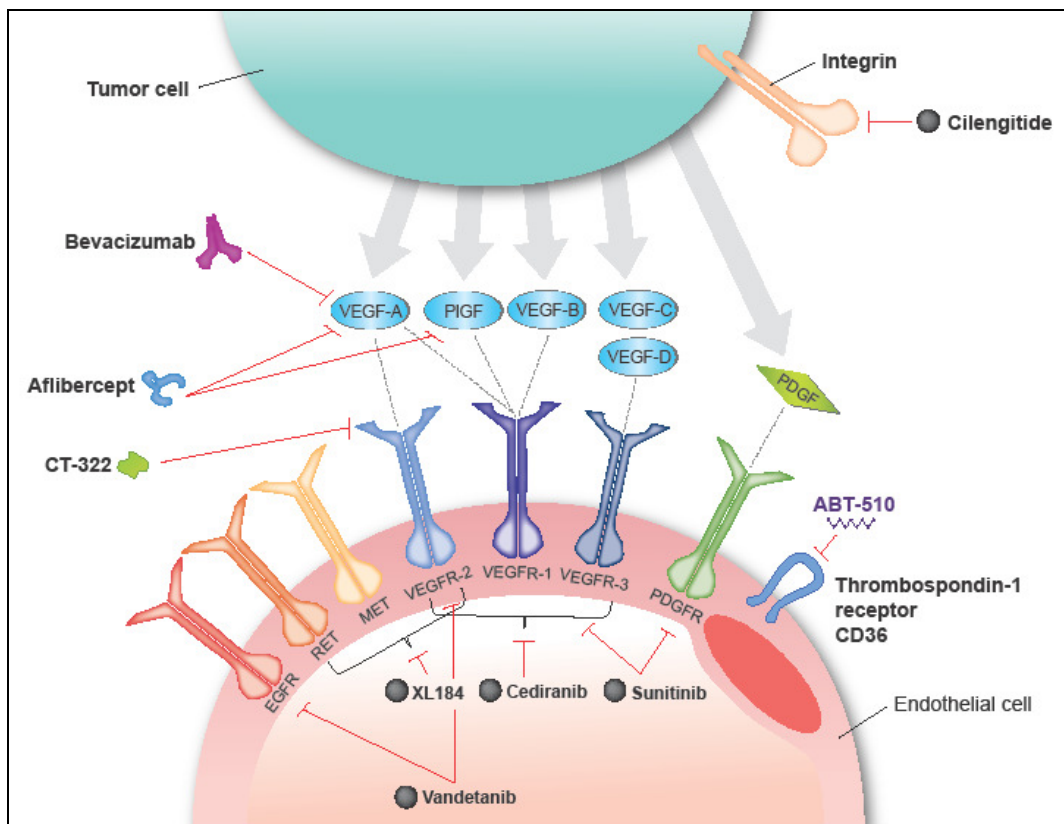
***RHHBY/Genentech's Avastin.*** Avastin is a mAB that inhibits angiogenesis, meaning it cuts off the independent blood supply that a tumor develops to feed and oxygenate itself. A molecularly targeted therapy, Avastin neutralizes vascular endothelial growth factor (VEGF), a chemical signal that stimulates the growth of new blood vessels, or angiogenesis. Single-agent Avastin received accelerated approval by the FDA on May 5, 2009, for the treatment of recurrent GBM based on two phase II trials. Avastin is not approved for GBM in the EU. In addition to recurrent GBM, Avastin has been approved for use in metastatic colorectal cancer (mCRC), breast cancer (BC), and kidney cancer, as well as non-small cell lung (NSCL) cancer.

***An Avastin phase II trial with 70 newly diagnosed GBM patients was published in the Journal of Clinical Oncology (JCO) last year.*** Patients received standard radiation therapy within 3-6 weeks after surgery with daily TMZ and biweekly Avastin. After completion of radiation therapy, patients took TMZ for five days every four weeks and continued biweekly Avastin. MGMT promoter methylation was assessed on patient tumor tissues. A University of California, Los Angeles/Kaiser Permanente Los Angeles (KPLA) control cohort of newly diagnosed patients treated with first-line RT and TMZ who had mostly received BV at recurrence was derived for comparison.

***The OS and PFS were 19.6 and 13.6 months, respectively.*** This compared favorably to 21.1 and 7.6 months in the University of California, Los Angeles/KPLA control cohort, and 14.6 and 6.9 months in the EORTC and NCCI control cohort. The PFS was statistically significant, and the OS showed a trend. There was a correlation of the MGMT promoter methylation, and improved OS and PFS. Comparative subset analysis showed that poor prognosis patients (recursive partitioning analysis class V/VI) may derive an early benefit from the use of first-line Avastin. The addition of Avastin to radiation/TMZ first-line therapy was tolerable without unanticipated toxicities. In general, non-hematologic toxicities were similar compared to Avastin use at recurrence, with the exception of potentially greater incidence of arterial and venous thromboembolism.

***RHHBY plans to file for Avastin approval in newly diagnosed GBM in 2013.*** Avastin is currently being studied in two large front-line phase III trials, one with a gliosarcoma cohort and one pure GBM trial. RTOG-0825 is a DBPC phase III trial of conventional concurrent chemoradiation and adjuvant TMZ plus Avastin versus conventional concurrent chemoradiation and adjuvant TMZ in patients with newly diagnosed GBM. This trial will enroll 942 patients with histopathologically confirmed GBM. The AVAGLIO (NCT00943826) study is an international, multicenter, randomized, double-blind study including over 920 patients with newly diagnosed histologically confirmed GBM, investigating the efficacy and safety of Avastin combined with SOC, TMZ chemotherapy, and radiotherapy following surgery. The primary endpoints of the AVAGLIO trial are PFS (defined as the duration for which patient remains alive without the disease worsening) and OS. Secondary endpoints that will be explored include one- and two-year OS rates, safety, and health related QoL. Results are expected in 2013. These studies will answer the question of whether Avastin is more effective upfront or upon recurrence. Additionally, the phenomenon of "rebound" after cessation of Avastin, where tumors exhibit a far more aggressive phenotype, was of potentially significant concern, and the front-line trial will be highly scrutinized for overall risk/benefit.

Figure 14. Angiogenic Signaling in Brain Tumors



Source: <http://www.ro-journal.com/content/6/1/2> (Radiation Oncology 2011, 6:2)

**Merck KGaA's (MRK-€74.76-NR) cilengitide is an  $\alpha(v)\beta(3)$  and  $\alpha(v)\beta(5)$  integrin antagonist with antiangiogenic properties that is in two trials, CENTRIC and CORE.** CENTRIC completed enrollment in June 2011 with 504 newly diagnosed GBM patients who are evaluating twice weekly 2,000 mg IV cilengitide plus standard radiation and TMZ vs. standard therapy alone. The endpoints are OS, PFS, PK, QoL, and safety. The patients all have MGMT gene in the tumor tissue. CORE is a phase II clinical trial in newly diagnosed GBM in 264 patients with an unmethylated promoter of the gene in the tumor tissue. Results are expected in Q1:13.

In a phase I/IIa trial of cilengitide for newly diagnosed GBM with a median follow-up of 34 months, 43 patients (83%) progressed and 34 patients (65%) died. The six-month PFS rate (primary end point) was 69%, median PFS was 8.0 months (95% CI, 6-10.7 months), median OS was 16.1 months, and one- and two-year OS rates were 68% and 35%, respectively. PFS and OS were longer in patients with tumors with the MGMT promoter methylation (13.4 and 23.2 months) versus those without MGMT promoter methylation (3.4 and 13.1 months). The combination of cilengitide with TMZ and radiotherapy was well tolerated, with no additional toxicity. It is not clear how the OS in this study truly compares with radiation and TMZ alone, because information on second-line and salvage therapies was not included in the JCO publication.

The editorial in JCO was rather critical of the cilengitide trial; the author disliked PFS as primary endpoint and it was unclear if an OS of 16.1 months vs. 14.6 months (historical) is much benefit. He noted that several similarly designed phase II trials have reported comparable improvements in median OS (18 to 21 months) in newly diagnosed GBM, though the benefit was more likely due to better SOC. His criticism of the MGMT gene analysis was that the median OS of 23.2 months was similar to the original radiation/TMZ study. Other experts were cautiously optimistic about the prospects of cilengitide, as single-agent use may not be enough to make a meaningful impact in the highly aggressive GBM, but neuro-oncologists are holding out hope for non-VEGF targeted anti-angiogenic therapies, which may be combined with other agents to yield synergistic effects.

***YMI's anti-EGF mAB nimotuzumab was the subject of a European phase II/III study.*** Data from the 2008 EORTC meeting reported a median OS for the GBM patient cohort treated with nimotuzumab plus radiation of 8.4 months, with the placebo arm showing a median OS of 7.9 months. Since this trial did not incorporate TMZ into the design, it is difficult to compare to the current SOC for front-line GBM. The ongoing phase III, which has enrolled ~150 patients to date, incorporates nimotuzumab into the SOC of radiation and TMZ following resection in newly diagnosed patients. Due to the variability of the proportion of patients with EGFR amplification and mutations, the impact of EGFR inhibitors — including nimotuzumab — is unclear. With only ~50% of GBM patients showing EGFR amplification, and tumors themselves showing very inconsistent expression (1/10-1/15 of all GBM tumor cells showing amplification/mutation in patients who are EGFR (+)), the impact of EGFR inhibition in the larger GBM population remains to be proven.

***AGEN's Prophage Series G-200 vaccine (HSPPC-96; vitespen), formerly Antigenics' Oncophage, is a patient-specific therapeutic cancer vaccine candidate that contains the heat shock protein, gp96, and peptides that are purified from the patients' own tumor tissue.*** It is administered as a simple weekly or biweekly intradermal injection. At this year's American Society of Clinical Oncology (ASCO) meeting, phase II results were presented of the Prophage G-200 trial that included 33 recurrent GBM patients. The primary endpoint was OS at 26 weeks, which represents the average survival time for patients experiencing recurrence of their GBM. Results from this trial showed that 93% of the patients were alive at 26 weeks after surgery, and median OS was 11 months (47.6 weeks). Results from pre-defined exploratory analyses of disease progression showed a median PFS of ~5 months (20 weeks). Importantly, measures of immune response post vaccination with Prophage Series G-200 demonstrated a significant tumor-specific CD8+ T-cell response as well as innate immune responses as marked by a significant increase in levels of circulating NK cells. Adverse events considered related to Prophage Series G-200 were grade 1 or 2 in nature and mainly associated with the injection, including skin reactions and stinging at the site of injection as well as fatigue. No related grade 3 or 4 adverse events were reported in this trial. The lead investigator is Dr. Andrew Parsa, who is at the University of California at San Francisco (UCSF). The company is planning a randomized phase II trial of the vaccine that could begin later this year.

## CHEMOTHERAPY AGENTS

***Cell Therapeutics' (CTIC-\$1.30-NR) OPAXIO (paclitaxel poliglumex, PPX) was the subject of interim results presented at ASCO 2011.*** More than 50% of patients were still alive at the median of 22 months in a phase II clinical study of OPAXIO combined with TMZ and radiotherapy in patients with newly diagnosed high-grade malignant brain tumors (astrocytomas and glioblastomas). Although not a randomized trial, treatment with OPAXIO, TMZ, and RT resulted in a median PFS of 13.5 months; median OS has not yet been reached with a median follow-up of 22 months. OPAXIO is a potent radiosensitizer. In this study, 25 patients were enrolled with confirmed high-grade glioma, of which 17 patients (68%) had GBM and eight patients (32%) had AA. The main toxicity reported was grade 4 thrombocytopenia and neutropenia (six patients/24%). These toxicities were thought to be due to a potential drug interaction between OPAXIO and TMZ and/or and other concomitant medications. Among the 22 evaluable patients, the ORR was 45% (10 of 22) with 27% (6 of 22) of patients achieving a CR. With a median follow-up of 22 months, 76% of patients remained PF at six months with an overall median PFS of 14.9 months (13.5 months for patients with GBM).

Figure 15. Selected Phase II/III Clinical Trials in Newly Diagnosed GBM

Drug	Company	Trial Name	Phase	# of Pts	St. Date	End Date	Primary Outcome
Activated T Lymphoc	Innocell Corporation	Clinical Trial to Assess the Efficacy and Safety of 'INNOCELL Immuncell-LC' With Temozolomide in Newly Diagnosed Glioblastoma of Korea	III	180	Dec-08	Apr-13	MRI
Bevacizumab	Genentech/Roche	Temozolomide and Radiation Therapy With or Without Bevacizumab in Treating Patients With Newly Diagnosed Glioblastoma	III	942	Apr-09	Apr-10	OS
		A Study of Avastin (Bevacizumab) in Combination With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Glioblastoma	III	920	Jun-09	Sep-13	OS, PFS
Cediranib	AstraZeneca	Temozolomide and Radiation Therapy With or Without Cediranib Maleate in Treating Patients With Newly Diagnosed Glioblastoma	II	177	Feb-10	Oct-10	6-mo PFS
Cilengitide	Merck KGaA	Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status (CENTRIC)	III	504	Sep-08	Jun-16	OS
BSI-201 (PARP-1)	Sanofi/BiPar	The study of PARP-1 inhibitor-1 in newly diag. GBM	1/II	100	May 2008	H2:11	
Enzastaurin	Eli Lilly & Co	Enzastaurin Versus Lomustine in Glioblastoma	III	397	Mar-06	Apr-12	Time to Progressive Disease
		Enzastaurin Before and Concomitant With Radiation, Followed by Enzastaurin in Patients With Newly Diagnosed Glioblastoma	II	60	Oct-07	Jul-11	6-mo PFS
		Trial of Enzastaurin and Bevacizumab in Adults With Recurrent Malignant Gliomas	II	120	Nov-07	Jan-12	Time to Progressive Disease
Imatinib	Novartis	Study of Imatinib Mesylate in Combination With Hydroxyurea Versus Hydroxyurea Alone as an Oral Therapy in Patients With Temozolomide Resistant Progressive Glioblastoma	III	240	Oct-04	Aug-08	PFS - Should have results!
Nimotuzumab	Oncoscience AG	Nimotuzumab in Adults With Glioblastoma Multiforme	III	150	Aug-07	Aug-10	MRI
NovoTTF-100A device	NovoCure Ltd.	Effect of NovoTTF-100A Together With Temozolomide in Newly Diagnosed Glioblastoma Multiforme (GBM)	III	283	Jun-09	Oct-12	PFS
CDX110 Vaccine	CellDex	Pts must have documented EGFRvIII expression in tissue. Phase III to begin in 2011	III				
APG101	Apogenix GmbH	APG101 in Glioblastoma	II	83	Dec-09	Aug-11	Progression-Free Survival
Bortezomib (Velcade)	Takeda/Millennium Pharma	Bortezomib, Temozolomide, and Regional Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma Multiforme or Gliosarcoma	II	70	Feb-12	Oct-12	OS
CCI-779 (Temozolomide)	Pfizer/Wyeth	Radiation Therapy and Temozolomide or Temozolomide in Treating Patients With Newly Diagnosed Glioblastoma	II	108	Oct-09	Oct-12	1-yr OS
Cetuximab	ImClone LLC Bristol-Myers Squibb Merck KGaA	Effect of Radiation Therapy Plus Temozolomide Combined With Cilengitide or Cetuximab on the 1-year Overall Survival of Patients With Newly Diagnosed MGMT-promoter Unmethylated Glioblastoma	II	108	Sep-09	Sep-11	1-yr OS
Gliadel	Genentech Eisai	Gliadel, XRT, Temodar, Avastin Followed by Avastin, Temodar for Newly Diagnosed Glioblastoma Multiforme (GBM)	II	72	Mar-11	Oct-12	OS
HSPPC-96 vaccine	Agenus (Antigenics)	HSPPC-96 Vaccine With Temozolomide in Patients With Newly Diagnosed GBM (HeatShock)	II	55	Jun-09	H1:14	OS
LY2157299	Eli Lilly & Co	A Study Combining LY2157299 With Temozolomide-based Radiochemotherapy in Patients With Newly Diagnosed Malignant Glioma	I/II	62	Apr-11	Feb-14	Dosing
Panobinostat	Novartis	A Panobinostat Presurgery (CLBH589C)	II	24	Apr-10	Apr-12	PFS
RAD001 (Everolimus)	Genentech/Roche Novartis	RT, Temozolomide, and Bevacizumab Followed by Bevacizumab/Everolimus in First-line Treatment of GBM	II	60	Jan-09	Dec-11	PFS
AdV-tk Vaccine	Avantagene	Phase 2a Study of AdV-tk with Standard Radiation Therapy for GBM	II	52	Mar-07	Dec-11	Safety
Trivax Vaccine	Trimed Biotech GmbH	Dendritic Cell Cancer Vaccine for High-grade Glioma (GBM-Vax)	II	56	Mar-10	Dec-12	12 mo PFS
Valproic Acid		Valproic Acid With Temozolomide and Radiation Therapy to Treat Brain Tumors	II	41	Mar-06	Mar-11	PFS / OS
TVI-Brain-1	TVAX Biomedical	Study of a DCVax-Brain to treat Newly diagnosed GBM					
Azixa (Verubilin)	Myrexis, Inc.	Verubilin, Radiation Therapy, and Temozolomide to Treat Patients With Newly Diagnosed Glioblastoma Multiforme	II	128	Dec-10	Oct-13	9-mo PFS
SSRP Research							

## ICT-121 FOR RECURRENT GBM

Recurrent GBM is fatal and has no clear SOC — surgery, chemotherapy, and radiotherapy are all used. Recommended chemotherapy for recurrent GBM includes TMZ, nitrosourea, cyclophosphamide, platinum-based combination regimens, and procarbazine, lomustine, and vincristine combination therapy. For example, TMZ only produces a 5.4% ORR and a 21% six-months PFS rate. In the past 20 years, the neuro-oncology academic community has done many well-designed, well-conducted trials using various systemic agents. The use of similar designs and centralized reviews have results in ORR of <10%, six-month PFS of  $\leq 20\%$  and OS ranging from 6-7 months. More recent trials of single-agent TMZ or irinotecan, also known as CPT-11, have demonstrated only slight increases in six-month PFS, the highest rate being 26%.

New agents are initially tested, often in single-arm studies, in the recurrent disease setting due to a lack of SOC. Promising therapies are then tested in randomized trials when combined with radiation/TMZ in the initial treatment setting. In May 2009, the FDA granted accelerated approval of single-agent Avastin for patients with GBM that has progressed following prior therapy based on two phase II trials. The National Comprehensive Cancer Network (NCCN) guidelines were amended to include a recommendation for the use of Avastin, with or without chemotherapy (i.e., irinotecan, bischloroethylnitrosourea (BCNU), or TMZ), for progressive GBM. The recommended dose for treating GBM is 10 mg/kg by IV every two weeks. Avastin costs ~\$4,500 a dose and patients are administered it twice a month. The annual cost would be \$118K. Despite this, enrollment in a clinical trial is considered standard practice at recurrence.

**Figure 16. NCCN Agents for Treatment of Recurrent GBM**

NCCN Listed Agents	# Patients	Median Age	Median PFS Weeks	Median OS Weeks	Supporting Trial(s)
Platinum Based Regimens <sup>1</sup> (AA, GBM)	30	40	11	32	Phase 2, single-arm
PCV <sup>2</sup> (Recurrent GBM)	63	46	13	33	Phase 2, single-arm
Cyclophosphamide <sup>3</sup> (Recurrent GBM)	40	51.5	8	16	Phase 2, single-arm
Temozolomide <sup>4-7</sup> (Recurrent GBM, multiple histology)	14-128	52-54	8.5-15	22-38	Phase 2, various (single-arm, historical control, randomized)
Carmustine wafer <sup>8</sup> (Recurrent GBM)	110	48 (mean)	Not Reported	31	Phase 3, randomized*
Bevacizumab (BV) <sup>9</sup> (Recurrent GBM)					
BV	85	54	17	37	Phase 2, randomized**
BV+CT-11	82	57	23.4	35	

<sup>1</sup>Yung WK, et al. J Clin Oncol 1991; <sup>2</sup>Kapelle AC, et al. Neurology 2001; <sup>3</sup>Chamberlain MC, Tsai-Wei DD. Cancer 2004; <sup>4</sup>Perry et al.

Cancer 2008; <sup>5</sup>Perry et al. J Clin Oncol 2010; <sup>6</sup>Brada et al., Ann Oncol 2001; <sup>7</sup>Yung et al. Br J Cancer 2000; <sup>8</sup>Brem et al. Lancet 1995;

<sup>9</sup>Friedman et al. J Clin Oncol 2009; \*FDA approved based on OS benefit; \*\*FDA approved based on response rates

Source: ASCO 2011 Poster

Avastin was approved based on the results of two studies that showed Avastin reduced tumor size in some GBM patients. In the one study, 28% of GBM patients had tumor shrinkage, 38% survived for at least one year, and 43% survived for at least six months without their disease progressing. Unlike the case for colon cancer, lung cancer and other cancers where bevacizumab acts by potentiating chemotherapy, the studies leading to approval showed that in GBM, the addition of chemotherapy to bevacizumab did not improve on results from bevacizumab alone. Bevacizumab reduces brain edema and consequent symptoms, and it may be that the benefit from this drug is due to its action against edema rather than any action against the tumor itself. Some patients with brain edema do not actually have any active tumor remaining, but rather develop the edema as a late effect of prior radiation treatment. This type of edema is difficult to distinguish from that due to tumor, and both may coexist. Both respond to bevacizumab.

A study by Kreisl, et al, published in the JCO in 2009, evaluated 48 patients with heavily pretreated GBM (median of two prior chemotherapy regimens) that received Avastin 10 mg/kg Q2W until disease progression. At the time of progression, patients received Avastin plus irinotecan. During the Avastin-only part of the study, the median PFS was 16 weeks (95% CI, 12-26 weeks), the six-month PFS rate was 29% (95% CI, 18-48%), and the ORR was 35% (with one complete response).

When WHO radiographic criteria and on stable or decreasing corticosteroid use was evaluated, the ORR was 19.6% (95% CI, 10.9-31.3%); the median OS was 31 weeks (95% CI, 21-54 weeks), and the six-month OS was 57% (95% CI, 44-75%). Single-agent Avastin was well tolerated. The most treatment-related AEs were grade 3 or 4 thromboembolic events (12.5%), grade 2 or 3 hypertension (12.5%), grade 2 or 3 hypophosphatemia (6%), and grade 2 or 3 thrombocytopenia (6%). Of the six patients (12.5%) who experienced a thromboembolic event, three had pulmonary emboli and one had a cerebral vascular event. There were thromboembolic events in five patients and one instance of bowel perforation in another; that of six patients (12.5%) being discontinued from the study. There were no intracranial hemorrhages reported.

A second study evaluating the safety and efficacy of single-agent Avastin in recurrent GBM was published in the JCO in 2009 (Freidmann, et al). The large, randomized, non-comparative phase II study (BRAIN) was in 167 patients with GBM after the first or second relapse who were randomized to Avastin monotherapy or in combination with irinotecan. All patients received prior radiotherapy (completed at least eight weeks prior to receiving Avastin) and TMZ. Patients received Avastin (10 mg/kg IV) alone or Avastin plus irinotecan every two weeks until disease progression or until unacceptable toxicity. Patients with active brain hemorrhage were excluded. The efficacy of Avastin was demonstrated using response assessment based on both WHO radiographic criteria, radiologic assessment was based on MRI imaging (using T1 and T2/FLAIR), and by stable or decreasing corticosteroid use. The primary endpoint was 6-month PFS and ORR, as determined by an independent radiology review. Secondary endpoints included safety and OS.

In the Avastin-only arm 28.2% (one complete response) of patients responded to the treatment, tumor shrinkage was 50%, or more, which is a significant increase from the historic 5% response rates, ( $p < 0.0001$ ). In the single Avastin arm of 85 patients, 42.6% (95% CI 29.6-55.5%) PFS at six-months compared to the historic 15-20% rates. Survival was 9.2 months, a slight increase of the typical 6-7 month survival time. Patients with first and second relapse had PFS at six months of 46.4% and 27.8%, respectively. The median PFS time was 4.2 months (95.0% CI, 2.9-5.8 months). Overall survival was 9.2 months.

In the Avastin + irinotecan arm, the six-month PFS rate was 50.3% (97.5% CI, 36.8-63.9%), also above the historical 15% rate for salvage chemotherapy and irinotecan alone ( $p = 0.0001$ ). For first and second relapse the six month PFS was 49% and 57.1%. Thirty-one patients (37.8%) had an ORR. The ORR for patients in first of second relapse was 39.4%, and 31.3% in the Avastin + irinotecan group. The median PFS time was 5.6 months (95.0% CI, 4.4-6.2 months). Overall survival was 8.7 months, a little less than the Avastin-only study.

In patients receiving Avastin alone or Avastin plus irinotecan ( $n = 163$ ), the incidence of Avastin-related adverse events (Grade 1-4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and RPLS (1%). The incidence of Grade 3-5 events in these 163 patients was bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

While some serious side effects were noted – brain hemorrhage, strokes, and heart attacks – they were seen in a very small number of patients. Avastin also appeared to reduce brain swelling, allowing patients to significantly lower the steroid dose and eliminating a number of debilitating side effects. When the swelling and steroids were reduced, some patients saw a marked improvement in function. A significant study finding was that Avastin was nearly as effective alone as it was when given with chemotherapy, but was much better tolerated.

In patients receiving Avastin alone ( $n = 84$ ), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%), and diarrhea (21%). Of these, the incidence of Grade  $\geq 3$  adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%), and diarrhea (1%). Two deaths on study were possibly related to Avastin – one retroperitoneal hemorrhage and one neutropenic infection.

***Novocure's NovoTTF-100A System was approved by the FDA in April 2011 for the treatment of adult GBM patients following tumor recurrence after receiving chemotherapy.*** We are not sure the product is launched yet and are unable to find a price. The NovoTTF-100A device, which weighs about six pounds (three kilograms), creates a low intensity, alternating electric field within the tumor that exerts physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death prior to division. The FDA approval was based on data from a randomized pivotal trial of 237 patients with GBM tumors that had recurred or progressed despite previous surgical, radiation, and chemotherapy treatments. Patients treated with the NovoTTF alone achieved a comparable OS time to patients treated with the physician's choice of the best chemotherapy. The rate of PFS at six months was 21% in the NovoTTF group compared to 15% in chemotherapy patients. Also, patients treated with the NovoTTF had a 14% tumor RR compared to 10% in chemotherapy-treated patients in the trial; three complete radiographic responses were in the NovoTTF group compared to zero in the control group. NovoTTF-treated patients

reported better QoL scores and fewer side effects. Specifically, QoL was superior in the following subscale domains: vomiting, nausea, pain, diarrhea, constipation, cognitive functioning, and emotional functioning, all of which are hallmarks of patient suffering while receiving chemotherapy. The most commonly reported side effect from NovoTTF treatment was a mild-to-moderate rash beneath the electrodes.

***AGEN's Prophage Series G-200 vaccine (HSPPC-96; vitespen), formerly Antigenics' Oncophage, is a patient-specific therapeutic cancer vaccine candidate that contains the heat shock protein, gp96, and peptides that are purified from the patients' own tumor tissue.*** It is administered as a simple weekly or biweekly intradermal injection. At this year's American Society of Clinical Oncology (ASCO) meeting, phase II results were presented of the Prophage G-200 trial that included 33 recurrent GBM patients. The primary endpoint was OS at 26 weeks, which represents the average survival time for patients experiencing recurrence of their GBM. Results from this trial showed that 93% of the patients were alive at 26 weeks after surgery, and median OS was 11 months (47.6 weeks). Results from pre-defined exploratory analyses of disease progression showed a median PFS of ~5 months (20 weeks). Importantly, measures of immune response post vaccination with Prophage Series G-200 demonstrated a significant tumor-specific CD8+ T-cell response as well as innate immune responses as marked by a significant increase in levels of circulating NK cells. Adverse events considered related to Prophage Series G-200 were grade 1 or 2 in nature and mainly associated with the injection, including skin reactions and stinging at the site of injection as well as fatigue. No related grade 3 or 4 adverse events were reported in this trial. The lead investigator is Dr. Andrew Parsa, who is at the University of California at San Francisco (UCSF). The company is planning a randomized phase II trial of the vaccine that could begin later this year.

***AZD2171 (cediranib) is an oral a VEGF receptor inhibitor that has demonstrated a high radiographic response rate.*** It was shown to normalize tumor vessels in recurrent GBM patients and is undergoing further study. Despite positive results in a previous study, cediranib missed its primary endpoint in a randomized, parallel-group multicenter phase III study in patients with recurrent GBM called REGAL. The REGAL study randomized 325 patients on a 2:2:1 ratio to three groups: 1) oral cediranib monotherapy 30 mg/day (n=131); 2) a combination of oral cediranib 20 mg/day plus oral lomustine 110 mg/m<sup>2</sup> once every six weeks (n=129); or 3) a control group of oral lomustine 110 mg/m<sup>2</sup> and an oral placebo (n = 65). The primary endpoint was PFS, determined by a centralized independent review by a radiologist who was blinded to treatment status. The study found no statistically significant advantage in the monotherapy (median, 92 days, p=.889) or combination therapy (median, 125 days, p=.162) groups over the control group (median, 82 days). Similarly, there was no statistical difference between groups for OS which ranged from 8-9.8 months. There was a statistically significant reduction in steroid use in the monotherapy (p=.006) and the combination groups (p=.012), compared with the control group. There was also a statistically significant prolongation of time to neurological decline in the combination group, compared with the control group (p=.009). However, cediranib failed on the proportion of patients alive and PFS at six months, with a rate of 16% in the monotherapy group, compared with 34.5% in the combination group and 24.5% in the control group. The profile of toxicity with cediranib is consistent with what has been previously reported, and includes fatigue (16.4%), hypertension (14.1%), and diarrhea (6.3%). In a previous study cediranib had a much higher rate of 25.8%. The investigator thought the dose may be too low since the earlier study used 45 mg compared with 30 mg. Adverse events occurred at a similar rate in all groups: 60.9% in the monotherapy group, 79.7% in the combination group, and 60.9% in the control group.

***Sanofi Aventis (SNY-38.22-NR)/REGN's aflibercept (VEGF Trap).*** Aflibercept is a fusion protein that binds to both VEGF and placental growth factor. A single-arm phase II study enrolled 42 recurrent GBM patients and 16 patients with anaplastic glioma who had received concurrent radiation and TMZ and adjuvant TMZ were enrolled at first relapse. Aflibercept 4 mg/kg was delivered via IV on day one of every two-week cycle. The six-month PFS rate was 7.7% for the GBM patients and 25% for patients with anaplastic glioma. Overall radiographic response rate was 24% (18% for GBM and 44% for anaplastic glioma). The median PFS was 24 weeks for patients with anaplastic glioma (95% CI, 5-31 weeks) and 12 weeks for patients with GBM (95% CI, 8-16 weeks). A total of 14 patients (25%) were removed from the study for toxicity, on average less than two months from treatment initiation. The main treatment-related grades 3 and 4 adverse events (38 in total) included fatigue, hypertension, and lymphopenia. Two grade 4 CNS ischemias and one grade 4 systemic hemorrhage were reported. Aflibercept rapidly decreases permeability on dynamic contrast enhanced MRI imaging, and molecular analysis of baseline tumor tissue identified tumor-associated markers of response and resistance. The authors concluded aflibercept monotherapy has moderate toxicity and minimal evidence of single-agent activity.

***MRK's Cilengitide is an investigational selective  $\alpha\beta 3/5$  integrin inhibitor that was tested in a phase IIa randomized, multicenter, open-label trial.*** Patients with recurrent GBM received cilengitide monotherapy: 500 mg (n=41) and 2,000 mg (n=40). Reardon, et al (JCO 2008), reported a median OS of 9.9 months (2,000 mg arm) and 6.5 months in the 500 mg arm. At ASCO 2010, the long-term follow-up was presented: mean treatment duration was 139 days (range 11-139). Median follow-up was 53.3 and 48.3 months for cilengitide 500 and 2,000 mg, respectively. OS rates were consistently greater with cilengitide 2,000 mg (37.3, 22.5, 15, 10, and 10% at 12, 24, 36, 48, and 54 months, respectively)

vs. cilengitide 500 mg (22, 12.2, 4.9, 2.4, and 0% at 12, 24, 36, 48, and 54 months, respectively); hazard ratio was 0.635 with 95% confidence interval (0.402-1.003). Fifteen patients received cilengitide treatment for >six months, six patients for >one year. Treatment-related AEs tended to occur within six months of receiving the first dose of cilengitide; the most common (>one subject) was fatigue (n=3), while the most common grade 3/4 serious AE was convulsion (n=2). No drug-related grade 3/4 AEs occurred >six months from the first cilengitide dose and only two patients reported serious AEs during that time.

**RHHBY's Tarceva was used in a randomized phase II trial, where patients with progressive GBM were given either Tarceva or cytotoxic chemotherapy with TMZ or carmustine.** Tarceva compared unfavorably, with PFS at six months of only 11% vs. 24% in the control group. EGFRvIII mutation did not correlate with efficacy.

**Lilly's enzataurin, a PKC-beta inhibitor, was the subject of a phase III trial that randomized patients to receive it or lomustine for progressive GBM.** The six-month PFS rate was 11% for enzastaurin, 19% for lomustine.

**Peregrine's (PPHM-\$1.70-NR) Cotara is a targeted MAb linked to a radioisotope (I-131) that is administered as a single-infusion therapy directly into the tumor, destroying the tumor from the inside out, with minimal exposure to healthy tissue.** PPHM's phase II, open-label, multicenter trial was designed to enroll 40 GBM patients at first relapse. The primary endpoint is safety and tolerability of the maximum tolerated dose, a single 25-hour interstitial infusion of 2.5 mCi/cc of Cotara. Secondary endpoints include OS, PFS, and proportion of patients alive at six months after treatment. The interim analysis showed a median OS of 8.8 months (38 weeks, 40 patients at first relapse). The company plans to meet with the FDA in Q4:11 to determine the optimal registration pathway.

## OTHER EXPERIMENTAL DRUG CANDIDATES

There are many other agents in development including inhibitors for the targets, such as EGFR, PDGFR, and the PI3K/Akt/mTOR pathway.

**Figure 17. Selected Phase II/III Clinical Trials in Recurrent GBM**

Drug	Company	Trial Name	Phase	# of Pts	St. Date	End Date	Primary Outcome	Target
AMG 102	Amgen	AMG 102 and Avastin for Recurrent Malignant Glioma	II	36	Aug-10	Dec-12	Radiological Response Rates	HGF/SF
Cediranib	AstraZeneca	Cediranib Maleate With or Without Gefitinib in Treating Patients With Recurrent or Progressive Glioblastoma	II	112	May-11	Nov-13	PFS	VEGFR-2
		Cediranib in Combination With Lomustine Chemotherapy in Recurrent Glioblastoma (REGAL)	III	300	Oct-08	Jun-12	Efficacy	VEGFR-2
CT-322	Bristol-Myers Squibb	CT-322 in Treating Patients With Recurrent Glioblastoma Multiforme and Combination Therapy With Irinotecan	II	72	Oct-07	Dec-11	6-mo PFS	VEGFR-2
Sorafenib	Bayer Onyx	Ph. 2 Sorafenib + Protracted Temozolomide in Recurrent GBM	II	32	Sep-07	Sep-10	6-mo PFS	VEGFR-2
Sunitinib	Pfizer	A Phase II Trial of Sutent (Sunitinib; SU011248) for Recurrent Anaplastic Astrocytoma and Glioblastoma	II	55	Mar-07	Jun-11	6-mo PFS	VEGFR-2
Cotara	Peregrine	Dose Confirmation Study of Cotara for the Treatment of Glioblastoma Multiforme at First Relapse	II	40	8-May	11-Jun	Safety & tolerability	131I-chTNT-1/B MAB
PX-866	Oncothyreon	A Study of PX-866 in Patients With Glioblastoma Multiforme at Time of First Relapse or Progression	II	30	Dec-10	Dec-12	Progression Rates	
Azixa (Verubilin)	Myrexis, Inc.	Phase 2 study MPC-6827 for Recurrent GBM	II	68	Apr -09	Sept 11	PFS	microtubule destabilizer and vascular disrupting agent
Tandutinib	Millenium Pharmaceuticals	Tandutinib Plus Bevacizumab to Treat Recurrent Brain Tumors	II	80	Apr-08	Aug-11	6-mo PFS	PDGFR-Beta
Vandetanib	AstraZeneca	A Randomized Phase II Trial of Vandetanib (ZD6474) in Combination With Carboplatin Versus Carboplatin Alone Followed by Vandetanib Alone in Adults With Recurrent High-Grade Gliomas	II	128	Sep-09	Jul-11	Anti-tumor activity	VEGFR-2
TVI-Brain-1	TVAX Biomedical	Study To Test the Safety and Efficacy of TVI-Brain-1 As A Treatment for Recurrent Grade IV Glioma	I/II	86	Jun-11	Q1:14	6-mo PFS	Autologous vaccine
IMC-3G3	Lilly/ImClone LLC	Ramucirumab or Anti-PDGFR Alpha Monoclonal Antibody IMC-3G3 in Treating Patients With Recurrent Glioblastoma Multiforme	II	80	Jul-10	Apr-11	6-mo PFS	

Source: company reports, SSRP research, Clinical Trials.gov

## PATENTS

Cedars-Sinai has filed applications regarding IMUC's cancer vaccine development. IMUC is responsible to enforce these patents. Last month, IMUC announced the issuance of a US patent relating to a technology for the treatment of cancer for which the company holds an exclusive, worldwide license. Patent No. 7,939,090, entitled "System and method for the treatment of cancer, including cancers of the central nervous system," covers the combination of a DCs-based vaccine combined either before or concurrently with chemotherapy at the recurrence of the disease. This patent has applicability to multiple types of cancer. There are six other patents pending. IMUC also acquired exclusive worldwide ownership rights to eight granted US and ten other patents for various European and Asian territories, as well as several US and foreign patent applications through the acquisition of the monoclonal antibody-related technology from Molecular Discoveries. The issued patents relate to monoclonal antibodies targeting various cancers, including human myeloma, ovarian cancer and small cell lung cancer, and have expiration dates ranging from 2019-2023.

## MANAGEMENT

### **John Yu, M.D.**, *Chairman of the Board*

Dr. Yu became chairman of the board following his service as chief scientific officer and as a director from November 2006 to January 2007. Dr. Yu is also a full-time faculty at Cedars-Sinai Medical Center in the department of neurosurgery with his clinical focus on the treatment of malignant and benign brain and spinal tumors.

### **Manish Singh, Ph.D.**, *President, Chief Executive Officer, and Director*

Dr. Singh has been in this position since February 2008. Before ImmunoCellular, Dr. Singh was the director at California Technology Ventures from June 2003 to December 2007. Dr. Singh also co-founded and served as acting CEO of Aliva Biopharmaceuticals from January 2006 to December 2007.

### **James Bender, Ph.D.**, *Vice President – Product Development and Manufacturing*

Dr. Bender has been vice president of product development and manufacturing since February 2010, following a term as vice president of clinical development on a part-time basis from September 2008 to February 2010. Dr. Bender has spent time with IDM Pharma, Nexell Therapeutics, and Baxter Healthcare Corporation.

### **C. Kirk Peacock, CPA**, *Treasurer and Chief Financial Officer*

Mr. Peacock has served as treasurer and CFO for ImmunoCellular on a part-time basis since January 2006. Mr. Peacock was also the interim president from November 2007 to February 2008. Before ImmunoCellular, Mr. Peacock was the CFO of CytRx Corporation from August 2003 to July 2004, as well as serving as CFO for several start-up companies, including DigitalMed, Inc., and Ants.com, Inc.

### Important Disclosures and Disclaimers – Third Quarter 2011

**Analyst Certification:** Each research analyst who authored the attached research report certifies the following: 1) All of the views expressed in this research report reflect my personal opinions about the subject company or any company mentioned in this research report; 2) I have not and will not receive compensation in exchange for the recommendation or views in this research report; and 3) Neither I nor the firm that employs me believes or have reason to believe that I have any material conflicts of interest with regard to the subject company or any company mentioned in this research report at the time of its publication.

**Analyst/Firm Financial Interest/Control:** Neither the analyst nor any members of his/her household has a financial interest in the covered company, or companies mentioned in this research report, including the ownership of shares, warrants, or options on the subject company's securities. In addition, neither the analyst nor any member of his/her family is an officer, director or advisory board member of the subject company. At the end of the month immediately preceding the publication of this research report, the firm and/or its affiliates did not beneficially own 1% or more of any class of common equity securities of the subject company, nor any company mentioned in this research report. Summer Street Research Partners ("SSRP" or "the Company") does not make markets in any securities, including those of the subject companies in this research report. The research analysts' compensation is not directly related to the specific recommendations or views expressed in this research report. Research Analyst(s) compensation is however based upon various factors including SSRP's total revenues, a portion of which may in the future be generated by investment-banking related activities.

**Investment Banking and Other Services:** SSRP has not provided investment-banking, advisory or other similar services to the subject companies described in this research report, nor are they clients of the SSRP. Further, the firm and its affiliates have not managed or co-managed a public/private offering of securities for the subject companies in this research report, and have not received compensation for investment-banking services from the subject companies in this research report. We expect to receive or intend to seek compensation from the subject companies for investment-banking related services in three months from the date of this research report. The firm has not received investment-banking revenues or participated in a public/private offering of securities as a manager or co-manager of the subject company's securities in the past 12 month from the date of this research report. Nor has the firm or its research analysts received compensation from the subject company or any company mentioned in this research report for products and services in the past 12 months. In addition, no research analyst, employee or affiliate of SSRP with the ability to influence the substance of this research report has received any compensation for products and service in the past 12 months.

**Definition of SSRP's Stock Rating System as used in this Research Report:** BUY – We believe the stock's total return will significantly outperform its peer group; NEUTRAL – We believe the stock's total return will not be significantly different than its peer group; SELL – We believe the stock's total return will significantly under perform its peer group.

**General Disclaimers:** The information contained herein is intended for distribution to institutional investors and is for informational purposes only. SSRP's research reports should be considered as only a single factor in making an investment decision. The information herein was obtained from various sources; we do not guarantee its accuracy or completeness and it should not be relied upon as such. Additional information is available by contacting SSRP. Neither the information nor any opinion expressed constitutes an offer, or an invitation to make an offer to buy or sell any securities. The data contained herein is intended for the sole and exclusive use of clients of SSRP. No reproduction, transmission or replication of any of the information or data contained within this document may be done without the expressed written consent of SSRP. Medical Consulting Research Inc. (MCRI) is a division of SSRP.

#### Investment Rating Distribution for the Period 4/1/11 through 6/30/11:

Rating	Count	Percentage
BUY	16	80%
NEUTRAL	2	10%
SELL	2	10%
<b>Companies under coverage at 6/30/11</b>	<b>20</b>	<b>100%</b>

We have assigned an investment rating for at least one year for the following subject companies mentioned in this report:

#### IMUC

##### Ratings History

Date	Rating	Share Price	Price Target
7/28/11	BUY	\$2.17	\$8.00

##### IMUC Investment Risks

- IMUC will need to raise additional capital prior to profitability in 2017
- IMUC shares trade on the OTC Bulletin Board
- Manufacturing of biologics on a commercial scale is complex, expensive, and may require new facilities
- Competition includes several vaccine companies and institutions with personalized vaccine therapy, off-the-shelf vaccine, and potential chemotherapy
- The reimbursement environment is increasingly difficult for high-priced therapies

**Valuation Method for Price Target:** Multiple of earnings discounted back



Source: StockCharts.com