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# Current Trends In Cancer Therapeutic Development

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Forty years ago this month, Richard Nixon signed a declaration of war on cancer under the National Cancer Act with a view to eradicate cancer as a leading cause of death in the United States. Since then, each decade has brought new therapies and new paradigms in cancer treatment including advances in radiation therapy, monoclonal antibodies and kinase targeting such as Rituxan from Biogen-Idec ([BIIB](#)), Herceptin from Roche ([RHHBY.PK](#)), and Gleevec from Novartis AG ([NVS](#)) among others. In the last five years recent developments in cancer stem cell technology has newly excited the oncology field as evidenced by an increased academic as well as commercial interest.

Cancer stem cells are considered the new frontier with respect to new drug targets as emerging evidence is showing they are actually one of the major underlying causes of tumor recurrence in addition to metastasis. These two events plague traditional chemotherapeutic treatment plans and even small changes in this area can have a large impact on patient outcome after treatment. This is because traditional chemotherapeutics and bio-therapeutics act on specific targets on or within the majority of tumor cells; however a key factor in the length of the clinical responses is that the cells develop a resistance to treatment over time. Thus, new and existing data are pointing to a reason for this acquired resistance, with the trail leading to the presence of a small minority of cells in the tumor called cancer stem cells (CSCs). These CSCs are often highly resistant to existing cancer therapies including targeted drugs, chemo- and radiation therapy and end up repopulating the cells lost within the tumor after treatment. The benefit of drugs specifically targeting CSCs is to provide a truly effective treatment that can create a lasting clinical response and in order to do this, it is now apparent that it is important to develop drugs that can target and kill CSCs. A major factor that has prevented the discovery of drugs targeting CSCs is that isolated CSCs rapidly differentiate in culture, yielding the non-CSCs that represent the majority of cells in tumors. This has now been recognized and being pursued by key innovators in the field.

Currently there are three therapeutic approaches to target cancer stem cells which are being pioneered by three separate companies. These three approaches are small molecule inhibitors of cell signaling pathways, monoclonal antibodies against these cancer stem cells and lastly cancer stem cell vaccines.

**Small Molecule Inhibitor:** *Verastem, Inc.* is expected to [announce](#) an IPO ([VSTM](#)) later this week with a price/filing range of \$9.00 -\$11.00, underwritten by UBS and Leerink Swann LLC. If successful, this should bring the market capitalization close to \$250

million post IPO, see: *Verastem* is a biopharmaceutical company which is focused on the discovery of small molecule drugs that selectively target cancer stem cells with principal efforts focused on breast cancer. Company recently filed S-1 and is planning to be listed on the public markets soon. Verastem employs its proprietary technology, linking the epithelial-to-mesenchymal transition, or EMT, to the emergence of CSCs, to create a stable population of cancer stem cells to screen for and identify small molecule compounds that are targeted to these cells specifically. Verastem believes that both its technology and approach provide an opportunity to develop future oncology therapeutics addressing many types of cancers by affecting the EMT leading to the emergence of CSCs. The most advanced small molecule product candidates are VS-507, VS-4718 and VS-5095 which is in preclinical studies as a potential therapeutic for breast and potentially other cancers. Verastem believe that these compounds may be especially beneficial as therapeutics in aggressive cancers with a high percentage of CSCs, such as triple negative breast cancer. This is a type of cancer in which a high percentage of CSCs correlates with a poorer prognosis and a lower overall survival rate than other types of breast cancer. The company expects to file an investigational new drug application, or IND, with the U.S. Food and Drug Administration, or FDA, in late 2012 to initiate a Phase 1 clinical trial on VS-507.

**Monoclonal Antibody:** *OncoMed Pharmaceuticals, Inc.*, a private biotechnology company, engages in the discovery and development of monoclonal antibody therapeutics that target specific markers on cancer stem cells. OncoMed's lead candidate OMP-21M18 is currently completing Phase I safety studies with preliminary indications in colorectal, pancreatic and other cancers. Preclinical studies show OMP-21M18 has demonstrated inhibition of tumor growth by reducing cancer stem cell frequency while promoting apoptosis in tumor cells when administered alone or in combination with chemotherapy in human colorectal cancer tumors with or without KRAS mutations. For example, up to 40% of colorectal cancers contain mutated KRAS genes, which have proven to be insensitive to treatment with monoclonal antibodies, such as Imclone's (Now Lilly) ([LLY](#)) Cetuximab (Erbix<sup>®</sup>) or Amgen's ([AMGN](#)) panitumumab (Vectibix<sup>™</sup>), that target the epidermal growth factor receptor. OMP-21M18 blocks Delta-like 4 ligand (DLL4), an activator of Notch signaling, a pathway known to be important in stem cells and cancer. Blocking DLL4 results in broad-base anti-tumor activity via multiple mechanisms, including inhibiting cancer stem cell growth, promoting cell differentiation and disrupting angiogenesis. Blocking DLL4 may make the drug effective in a variety of tumor types.

**Cancer Stem Cell Vaccine:** *ImmunoCellular Therapeutics Ltd.* ImmunoCellular ([IMUC.OB](#)) is focused on developing new immune-based products to treat and diagnose cancer and employs a cancer stem cell vaccine technology but also has patented mAB technology. The aim of the therapy is to harness the immune system, targeting not only regular tumor cells, but also the cancer stem cells believed to cause cancer growth and recurrence. The company's lead candidate is ICT-107, a unique personalized, dendritic cell-based vaccine for the treatment of glioblastoma multiforme (GBM) which is the most common and most aggressive malignant primary brain tumor in humans with some of the poorest survival statistics. Although the first indication being sought is GBM, the

technology has potential applications in many cancers with high unmet medical need, including pancreatic, ovarian, colon, small-cell lung, and multiple myeloma. Currently, ICT-107 is in a Phase II study following strong results in a Phase I study in which the drug significantly prolonged survival with minimal side effects. GBM median survival time based on standard of care is approximately 14-15 months (see the real time [statistics](#) of GBM treatment at UCLA with well over 600 patients treated thus far). In the completed phase I trial, ICT-107 demonstrated a median survival of 38.4 months which is two years longer than the current standard of care. Out of 16 patients treated with ICT-107, 8 patients have been alive for longer than 3 years after treatment with 6/8 patients having no disease whatsoever. The current ongoing phase II trial is a randomized, double blind, placebo control clinical trial in 20 plus centers in US looking at efficacy and this should complete in the next two years. According to the most recent company disclosure, 115 patients have already been enrolled in this trial so far. If the drug behaves similar to the preclinical studies and the previous human trial, the drug has a solid chance to become the standard of care in GBM. In addition, the company is in the process of filing another IND for ICT-121, which is a CD-133 targeting vaccine, for recurrent GBM. CD-133 is a ubiquitous marker identified in all solid tumor cancer stem cells including GBM and this vaccine could be the first universal cancer vaccine if it shows efficacy in its trials.

**Disclosure:** I have no positions in any stocks mentioned, and no plans to initiate any positions within the next 72 hours. The author has received no compensation to write about any specific stock, sector or theme. The author is long on IMUC.