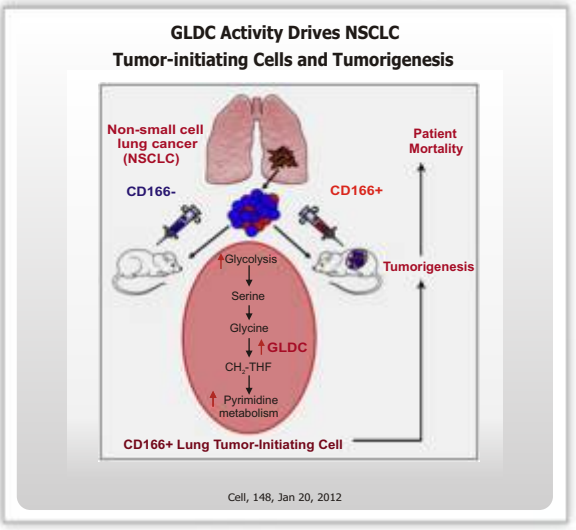
SMARTONCOLOGY
THE ONCOLOGY E-NEWSLETTER FROM SMARTANALYST
www.smartoncology.com
Volume 5, Issue 3 | Monthly Oncology E-newsletter | 2012
INTELLIGENT INSIGHTS. SMART RESULTS

# In the Spotlight:

## Glycine Decarboxylase Activity Drives NSCLC Tumor-initiating Cells and Tumorigenesis

Despite advances in our knowledge of cancer, the ability to develop clinically effective therapies based on this understanding has had limited success. Current therapies can control tumor growth initially, but most patients ultimately relapse. One prominent example is lung cancer, the leading cause of cancer-related mortality. Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancers.




Read more

## Tumor of the Month - Prostate Cancer

Prostate cancer is the second most frequently diagnosed cancer and the second leading cause of death in men in the US.[1] Introduction of the PSA (prostate-specific antigen) test as a screening strategy to identify men with prostate cancer increased the lifetime risk of being diagnosed from 9% in 1985 to 16% in 2007. Although the National Cancer Institute estimates that there will be 241,740 new cases and 28,170 deaths from prostate cancer in 2012,[2] and the 10-year risk of death from prostate cancer ranges from 8% to 26%; 60% of men will die of competing factors during the same time frame.[1] Side effects from aggressive treatment include urinary, bowel, and sexual dysfunction. Considering these facts, there is an urgent need for diagnostics that can more accurately identify which cancers will progress.

A man's risk for prostate cancer increases with advancing age as well as a positive family history of prostate cancer. African Americans have the greatest risk of being diagnosed with prostate cancer, and they tend to be diagnosed at an advanced stage.[1]

Read more

## Business News

Threshold and Merck KGaA to Co-develop and Commercialize TH-302

*Read More...*

## Research Highlights

IKKα Activation of NOTCH Links Tumorigenesis via FOXA2 Suppression

*Read More...*

## Clinical Development

ALSYMPCA Study: Positive Impact of Alpharadin on SRE Associated with Bone Metastases from CRPC

*Read More...*

## Biomarkers

Regulation of KLF4 Turnover Reveals an Unexpected Tissue-specific Role of pVHL in Tumorigenesis

*Read More...*

## Regulatory

FDA Approves Axitinib for Patients with Previously Treated Advanced RCC

*Read More...*

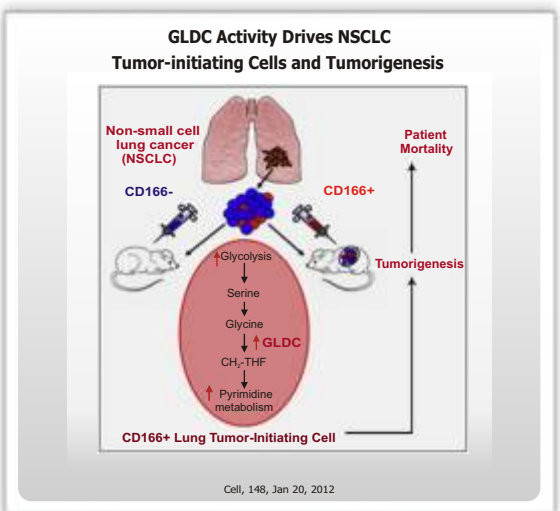


**The E-newsletter team**: Dr. Shirish Kumar, Sarika Manchanda, Dr. Vinamrata Bhatia, Kimberly Tully, Courtenay Veenis, Monica Tuli.

# Spotlight Report

## Glycine Decarboxylase Activity Drives NSCLC Tumor-initiating Cells and Tumorigenesis

Despite advances in our knowledge of cancer, the ability to develop clinically effective therapies based on this understanding has had limited success. Current therapies can control tumor growth initially, but most patients ultimately relapse. One prominent example is lung cancer, the leading cause of cancer-related mortality. Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancers. Although NSCLC patients with epidermal growth factor receptor (EGFR) mutations respond to EGFR inhibitors initially, most patients experience a relapse within 1 year. These findings underscore the urgent need for both combination therapies and new approaches to treat cancerous cells.




Identification of factors critical to the tumor-initiating cell (TIC) state might open new avenues in cancer therapy. A recent study published in *Cell* by Zhang *et al.* sheds new light on the nature of the TIC state and the role of metabolic reprogramming in tumorigenesis. The results demonstrate that multiple components in the glycine/serine pathway are also oncogenes. In addition to embryonic lung factors, lung TICs also express high levels of GLDC, GCAT, SHMT1/2, PSPH, and PSAT1, suggesting that TICs rely on glycine/serine metabolism for tumorigenesis. Researchers have reported that the metabolic enzyme glycine decarboxylase (GLDC) is critical for TICs in NSCLC. TICs from primary NSCLC tumors express high levels of the oncogenic stem cell factor LIN28B and GLDC, which are required for both TIC growth and tumorigenesis. Overexpression of GLDC and other glycine/serine enzymes, but not catalytically inactive GLDC, promotes cellular transformation and tumorigenesis. GLDC has been implicated to induce dramatic changes in glycolysis and glycine/serine metabolism, leading to changes in pyrimidine metabolism to regulate cancer cell proliferation. Clinically, aberrant activation of GLDC correlates with poorer survival in lung cancer patients and aberrant expression of GLDC is observed in multiple cancer types.

This study links a glycine metabolism enzyme to lung cancer and tumorigenesis and shows that characterizing the unique molecular basis that defines cancer cells with tumorigenic capacity could provide novel drug targets for advancing cancer therapy.

*Source: Cell. 2012;148(1-2):259–272*

# Tumor of the Month - Prostate Cancer

Prostate cancer is the second most frequently diagnosed cancer and the second leading cause of death in men in the US.[1] Introduction of the PSA (prostate-specific antigen) test as a screening strategy to identify men with prostate cancer increased the lifetime risk of being diagnosed from 9% in 1985 to 16% in 2007. Although the National Cancer Institute estimates that there will be 241,740 new cases and 28,170 deaths from prostate cancer in 2012,[2] and the 10-year risk of death from prostate cancer ranges from 8% to 26%; 60% of men will die of competing factors during the same time frame.[1] Side effects from aggressive treatment include urinary, bowel, and sexual dysfunction. Considering these facts, there is an urgent need for diagnostics that can more accurately identify which cancers will progress.

A man's risk for prostate cancer increases with advancing age as well as a positive family history of prostate cancer. African Americans have the greatest risk of being diagnosed with prostate cancer, and they tend to be diagnosed at an advanced stage.[1]

Prostate cancers arise in the prostate gland, which is responsible for the production of a fluid that protects the sperm. The majority of prostate cancers are adenocarcinomas, which start in gland cells. In rare cases, prostate cancers may be sarcomas, small cell carcinomas, or transitional cell carcinomas.[3]

As stated earlier, PSA is used to screen for prostate cancers. However, PSA levels may also be increased by non-cancerous conditions such as enlarged prostate.[4] Furthermore, some men with prostate

Back to top of Spotlight Section | Back to top of Tumor of the Month Section | Back to Top of Document

## Tumor of the Month
(Cont'd)

cancer do not show an increase in PSA level. A recent review summarized metabolomic studies that have looked for prostate cancer biomarkers, and while the field has potential, none of the metabolites have been validated for use in clinical practice.[5]

The side effects of therapy, combined with the inability to accurately determine which patients will progress, has caused the medical community to encourage men diagnosed with prostate cancer to take an active role in deciding the best course of treatment.[1] For early-stage prostate cancer, many patients opt for surgery; radiation therapy and "watchful waiting" are also viable options.[6] Hormonal therapy (sometimes called chemical castration) is used in debilitated older patients or for advanced disease. Prostate cancer frequently becomes resistant to hormonal therapy, resulting in difficult-to-treat CRPC (castration-resistant prostate cancer). Taxotere (docetaxel injection) with prednisone is used to treat CRPC, but resistance is a common problem. Jetvana (cabazitaxel injection), a taxane less affected by the multidrug resistance P-glycoprotein efflux pump, can be used with prednisone in patients resistant to docetaxel.[7,8] In 2011, the FDA approved Zytiga (abiraterone), a CYP17 inhibitor, which inhibits testosterone production, and Provenge (sipuleucel-T), an immunotherapeutic for the treatment of prostate cancer.[9]

At the 2012 Genitourinary Cancer Symposium in San Francisco, Medivation and Astellas announced positive results of the Phase III AFFIRM trial for patients previously treated with a docetaxel regimen.[10] Patients were randomly assigned in a 2:1 fashion to 160 mg/day MDV3100 vs. placebo. Both PFS and OS were prolonged by ~5 months (PFS was 8.3 months for MDV3100 vs. 2.9 months for placebo; median OS was 18.4 months for MDV3100 vs. 13.6 months for placebo). The drug inhibits androgen receptor (AR) signaling by three mechanisms: inhibits binding of AR to DNA, competitively inhibits the interaction between androgen and AR, and prevents nuclear translocation of AR.[11] MDV3100 is also being tested in the Phase III PREVAIL trial in therapy-naïve, advanced prostate cancer patients.[12]

Furthermore, at the 2012 Genitourinary Cancer Symposium, Bayer presented positive data for its Phase III trial of Alpharadin (radium-223).[9] As with MDV3100, Alpharadin controls bone metastases. The alpha particle emitter targets changes in the bone such as those caused by metastatic lesions. Median OS increased from 11.2 months in placebo-treated patients to 14 months for patients treated with Alpharadin. Patients receiving Alpharadin also had a longer median time without bone-related events compared with patients receiving placebo (13.6 vs. 8.4 months, respectively).

The FDA stopped three clinical trials of GTx's prostate cancer drug, Capesaris (GTx-758), due to the increased threat of clots.[13] The drug was being tested as a first-line therapy for androgen-dependent advanced prostate cancer and as a second-line hormonal treatment therapy. Capesaris is a selective estrogen receptor (ER) alpha agonist, which suppresses luteinizing hormone and ultimately prevents androgen production by the testes.[14]

Celgene is testing lenalidomide in the Phase III MAINSAIL study, which will evaluate the safety and efficacy of docetaxel and prednisone with or without lenolidomide in patients with CRPC.[15] Both arms will receive 75 mg/m$^2$ docetaxel IV on day 1, and 5 mg prednisone orally twice each day (BID) on each day of the treatment cycle. The experimental arm will receive oral lenalidomide (10 mg, 15 mg, 20 mg, or 25 mg) once each day for days 1–14, while the control arm will receive an oral placebo on those days. The primary outcome is OS, with secondary outcomes of PFS and ORR.

Aflibercept (AVE0005, VEGF Trap), protein fusing the extracellular domains of VEGFR1 and VEGFR2 to the constant region of human IgG1, is also being tested in combination with docetaxel and prednisone in mCRPC.[16]

Patients with metastatic prostate cancer are being enrolled in a clinical trial testing the bisphosphonate – zoledronic acid – for metastatic prostate cancer, metastatic breast cancer, and multiple myeloma with bone involvement. The primary objective is to compare the proportion of patients with ≥1 skeletal-related event during 2 years of treatment with zoledronic acid administered every 12 weeks vs. every 4 weeks.[17]

In November 2011, Bavarian Nordic initiated a Phase III trial of its novel vaccine – Prostvac.[18] The vaccine, a combination of recombinant poxviruses (specifically, vaccinia and fowl pox) engineered to express PSA, is designed to increase the immunogenicity of prostate tumors. Unlike the recently approved Provenge, the vaccine does not need to be individualized to each patient. The trial will test Prostvac in patients with asymptomatic or minimally symptomatic mCRPC. The trial will enroll 1,200 patients in three arms (see figure), and its primary endpoint is OS. A positive result will require that one or both arms must be superior to placebo. A secondary endpoint will measure the proportion of patients receiving PROSTVAC with or without GM-CSF who remain event-free (radiological progression, pain progression, initiation of chemotherapy, or death) at 6 months compared with placebo.

In a Phase III, double-blind, randomized, placebo-controlled study, published in the January 7 issue of *Lancet*, researchers reported that denosumab increases bone metastasis-free survival (BMFS) in men with CRPC.[19]

Back to top of Tumor of the Month Section | Back to Top of Document

## Tumor of the Month
(Cont'd)

Prostate cancer metastasizes almost exclusively to bone, causing painful lesions, which result in fractures and spinal cord compression. Prostate tumors induce the activation of osteoclasts by stimulating the expression of RANKL by the stroma and osteoblasts. Pre-clinical models of prostate cancer show that inhibition of osteoclasts prevents bone metastasis. Denosumab, a fully human monoclonal antibody, binds and inactivates RANKL. In a trial of 1,432 patients (716 for each arm: denosumab vs. placebo), men were treated with subcutaneous injection of denosumab (120 mg) or placebo every 4 weeks until the target number of study events was attained. Denosumab prolonged BMFS by 4.2 months compared with placebo (median BMFS was 29.5 months [95% CI: 25.4–33.3 months] for denosumab vs. 25.2 [22.2–29.5] months for placebo). Denosumab treatment was associated with increased time to both first bone metastasis and symptomatic bone metastasis. Median time to overall progression was 22.3 (denosumab) vs. 21.9 (placebo) months, and OS was not different (median OS of 43.9 months [95% CI: 40.1–not estimable] for denosumab vs. 44.8 months [40.1–not estimable] for placebo). Researchers noted that improvement in BMFS and time to first bone metastasis with denosumab treatment in the study showed that a bone-targeted agent could delay time to bone metastasis in men with prostate cancer. The findings also provide the first direct clinical evidence for the important role of the bone microenvironment and RANKL signaling in the development of bone metastases in men with prostate cancer.

**A Randomized, Double-blind, Phase III Efficacy Trial of PROSTVAC-V/F +/- GM-CSF in Men with Asymptomatic or Minimally Symptomatic Metastatic Castrate-resistant Prostate Cancer**

| Arm 1 | Arm 2 | Arm 3 |
|---|---|---|
| **Biological:** PROSTVAC-V/F-TRICOM + GM-CSF PROSTVAC-V/F consists of 2 different vaccines: | **Biological:** PROSTVAC-V/F-TRICOM + GM-CSF PROSTVAC-V/F consists of 2 different vaccines: | **Vector placebo:** (Placebo vector is the same for both viruses) Weeks 1, 3, 5, 9, 13, 17, and 21 |
| **PROSTVAC-V-TRICOM:** Week 1; $2x10^8$ inf. units by sc injection | **PROSTVAC-V-TRICOM:** Week 1; $2x10^8$ inf. units by sc injection | **GM-CSF placebo:** Weeks 1,3,5,9,13,17, and 21 on days 1 to 4 |
| **PROSTVAC-F-TRICOM:** Weeks 3,5, 9, 13, 17, and 21 at $1x10^9$ inf. units by sc injection | **PROSTVAC-F-TRICOM:** Weeks 3,5, 9, 13, 17, and 21 at $1x10^9$ inf. units by sc injection | |
| **GM-CSF:** Weeks 1,3,5,9,13,17, and 21 at 100 mcg by sc injection on days 1 to 4 of each week | **GM-CSF placebo:** Weeks 1,3,5,9,13,17, and 21 at 100 mcg by sc injection on days 1 to 4 of each week | |

# Business News

### Threshold and Merck KGaA to Co-develop and Commercialize TH-302

Threshold Pharmaceuticals announced that a global agreement was signed with Merck KGaA to co-develop and commercialize TH-302, Threshold's small molecule, hypoxia-targeted drug. TH-302 is currently being investigated in a global Phase III clinical trial in patients with soft tissue sarcoma; a randomized, Phase II trial in patients with advanced pancreatic cancer from which topline results are expected in February 2012; and additional clinical studies in other solid tumors and hematological malignancies.

Under the terms of the agreement, Merck will receive co-development rights and exclusive global commercialization rights and will provide Threshold an option to co-commercialize the therapeutic in the US. In exchange, Threshold will receive an upfront payment of $25 M and could receive up to $35 M in additional development milestones during 2012. Threshold is also eligible to receive a $20 M milestone payment on the basis of positive results from its randomized Phase II trial in pancreatic cancer. Total potential milestone payments are $525 M consisting of $280 M in regulatory and development milestones and $245 M in sales-based milestones.

*Source: Threshold Pharmaceuticals*

### Arno Therapeutics to Collaborate with Invivis Pharmaceuticals to Develop Cancer Drug

Arno Therapeutics announced that it has signed an exclusive, worldwide licensing agreement with Invivis Pharmaceuticals to develop the investigational drug, onapristone, an anti-progestin hormone blocker that has been shown to have considerable anti-tumor activity in breast cancer.

Back to top of Tumor of the Month Section | Back to top of Business Section | Back to Top of Document

## Business News
(Cont'd)

Arno also plans to develop a companion diagnostic to identify patients who are positive for the biomarker and may benefit from treatment with onapristone. Pursuant to the terms of the license agreement, Arno will pay Invivis certain research, clinical, and regulatory milestone payments as well as royalties on net sales of licensed products. In addition to the license agreement, Arno will receive certain clinical development support services from Invivis pursuant to a separate agreement.

*Source: Arno Therapeutics*

### EUSA Pharma Acquires Development and Commercialization Rights to Asparec from Alizé Pharma

EUSA Pharma announced that it has acquired the exclusive worldwide development and commercialization rights to Asparec for the treatment of acute lymphoblastic leukemia (ALL) from Alizé Pharma. Under the terms of the agreement, EUSA will pay Alizé Pharma an upfront fee, regulatory milestone payments, and royalties on future product sales. Asparec is a recombinant, pegylated Erwinia chrysanthemi–derived L-asparaginase. It is currently in Phase I development for the treatment of ALL in patients with hypersensitivity to standard of care E. coli–derived asparaginase therapy and has been granted orphan status by the US and European regulatory authorities.

*Source: EUSA Pharma*

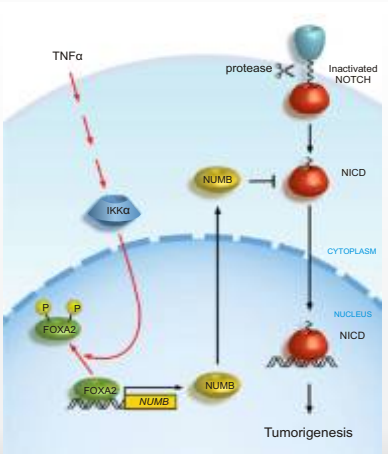
# Research Highlights

### IKKα Activation of NOTCH Links Tumorigenesis via FOXA2 Suppression

The proinflammatory cytokine TNFα plays critical roles in promoting malignant cell proliferation, angiogenesis, and tumor metastasis in many cancers. However, the mechanism of TNFα-mediated tumor development remains unclear. Recently, many non-IκB targets of IKKα and IKKβ have been identified. It is known that IKKα can regulate several target genes involved in cell transformation, tumor progression, and angiogenesis. Moreover, upon activation by TNFα stimulation, IKKα regulates transcription of target genes. However, how IKKα regulates distinct pathways independent of the traditional IKKα/IKKβ complex has not yet been clearly identified. FOXA proteins have been shown to play important roles in regulating a wide spectrum of biological processes. Although dysregulation of FOXA2 has been directly linked to the progression of certain cancers, the role of FOXA2 in tumor progression is not clear. NOTCH proteins play fundamental roles in cell fate decisions. Once released from the extracellular part of the molecule, the NOTCH intracellular domain (NICD) translocates into the nucleus to activate transcription of target genes. Aberrant expression of the dominant active cytoplasmic domain of NOTCH receptors through chromosomal translocations or mutations in hematopoietic cells leads to cell autonomous oncogenic activation of NOTCH. NUMB is an important determinant of asymmetric cell division in mammalian development. Recent studies have demonstrated that NUMB acts as a tumor suppressor by inhibiting NOTCH signaling and that a loss of NUMB leads to increased NOTCH activity and confers a NOTCH-dependent proliferative advantage in several cancers.

In a recent study published in *Molecular Cell*, Liu *et al.* demonstrated a relationship between two well-defined cancer-associated pathways – NOTCH and TNFα signaling – and identified an axis in the TNFα pathway that activates NOTCH1 signaling. They report a TNFα/IKKα/FOXA2/NUMB/NOTCH1 pathway that is critical for inflammation-mediated tumorigenesis. The study showed that IKKα, an important downstream kinase of TNFα, interacts with and phosphorylates FOXA2 at S107/S111, thereby suppressing FOXA2 transactivation activity and leading to decreased NUMB expression, and further activates the downstream NOTCH pathway and promotes cell proliferation and tumorigenesis. Moreover, they found that levels of IKKα, pFOXA2 (S107/ 111), and activated NOTCH1 were significantly

**Proposed Model of FOXA2 Phosphorylation by IKKα**




Molecular Cell, 45, Jan 20, 2012

## Research Highlights (Cont'd)

higher in hepatocellular carcinoma tumors than in normal liver tissues and that pFOXA2 (S107/111) expression was positively correlated with IKKα and activated NOTCH1 expression in tumor tissues. Therefore, dysregulation of NUMB-mediated suppression of NOTCH1 by TNFα/IKKα-associated FOXA2 inhibition likely contributes to inflammation-mediated cancer pathogenesis.

In summary, the identification of FOXA2 as a downstream substrate of IKKα links the TNFα and NOTCH1 signaling pathways and provides an important new starting point for uncovering the molecular basis of TNFα-mediated human tumor growth and identifying potential targets for cancer therapy. Inhibition of FOXA2 phosphorylation or activation of NUMB could have important clinical implications for the treatment or prevention of cancer.

*Source: Molecular Cell. 2011; 45(2):171–184.*

### Identification of a Mutation in the Extracellular Domain of EGFR Conferring Cetuximab Resistance in Colorectal Cancer

Patients with colorectal cancer benefit from therapies targeting the EGFR. *KRAS* mutation status predicts an individual's innate resistance to these antibodies – cetuximab and panitumumab – and because of this, individuals with KRAS-mutant colorectal cancer are excluded from treatment with these antibodies. However, subjects with colorectal cancer who respond to antibodies to EGFR ultimately acquire resistance to these agents.

To identify the mechanisms of acquired cetuximab resistance, Montagut *et al.*, in a study published in *Nature Medicine*, established cetuximab-resistant cells from a highly sensitive human metastatic colorectal cancer cell line and identified a clinically relevant point mutation within the EGFR extracellular domain that arises during cetuximab therapy and confers resistance to this agent. DNA sequencing of the *EGFR* coding region (NM_005228.1) revealed a C→A substitution at nucleotide 1,476 in cetuximab-resistant cells. This acquired EGFR ectodomain mutation (S492R) prevented cetuximab binding and conferred resistance to the antibody. *In vitro* biochemical binding studies confirmed that the S492R mutant was selectively defective in binding cetuximab but not panitumumab. Cetuximab is a chimeric mouse-human immunoglobulin G1 (IgG1), whereas panitumumab is a fully human IgG2. Clinically, these differences translate into distinct toxicity profiles for each antibody, although both antibodies show similar clinical activity and are generally considered to be equivalent therapies. However, the present study reveals an opposite pre-clinical and clinical response to the two antibodies in the presence of the acquired S492R EGFR mutation. The specificity of the S492R mutation is expected to facilitate reliable testing to guide the clinical use of panitumumab after cetuximab failure and justifies prospective independent validation of the S492R EGFR mutation. The characterization of a new mechanism of resistance to the EGFR-specific antibody cetuximab provides clues into how therapeutic strategies might be designed to overcome this specific resistance mechanism.

*Source: Nature Medicine. 2012;18(2):221–223.*

### Structure of HDAC3 Bound to Co-repressor and Inositol Tetraphosphate

Histone deacetylase enzymes (HDACs) participate in gene repression and are emerging cancer drug targets. They regulate gene expression by removing acetyl groups from lysine residues in histone tails, resulting in chromatin condensation. The enzymatic activity of most class I HDACs requires recruitment into multisubunit co-repressor complexes, which are in turn recruited to chromatin by repressive transcription factors.

A study by Watson *et al.* published in *Nature* reports the structure of a complex between an HDAC and a co-repressor, namely, human HDAC3 with the deacetylase activation domain (DAD) from the human SMRT co-repressor (also known as NCOR2). As well as allowing insight into the activation mechanism of the enzyme, the structure reveals two remarkable features. First, the SMRT–DAD undergoes a large structural rearrangement on forming the complex. Second, there is an essential inositol tetraphosphate molecule – D-myo-inositol-(1,4,5,6)-tetrakisphosphate (Ins(1,4,5,6)$P_4$) – acting as an "intermolecular glue" between the two proteins. Assembly of the complex is clearly dependent on Ins(1,4,5,6)$P_4$, which may act as a regulator – potentially explaining why inositol phosphates and their kinases have been found to act as transcriptional regulators. The requirement of Ins(1,4,5,6)$P_4$ for co-repressor–HDAC assembly presents novel opportunities for therapeutic intervention that may complement existing HDAC inhibitors. It may be possible to develop molecules that target the Ins(1,4,5,6)$P_4$ binding site itself, but it may also be possible to target the enzymes responsible for Ins(1,4,5,6)$P_4$ synthesis.

*Source: Nature. 2012;481(7381):335–340.*

Back to top of Research Highlights Section | Back to Top of Document

# Clinical Development

## ALSYMPCA Study: Positive Impact of Alpharadin on SRE Associated with Bone Metastases from CRPC

Additional data from the Phase III ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer patients) study of Alpharadin (radium-223 chloride) was presented at the 2012 Genitourinary Cancers Symposium, organized during February 2–4, 2012, in San Francisco, California.

The ALSYMPCA trial is an international, double-blind, randomized (2:1), placebo-controlled, Phase III clinical study evaluating Alpharadin plus best standard of care compared with placebo plus best standard of care in patients with CRPC and symptomatic (painful) bone metastases. The study recruited 921 patients, who were docetaxel ineligible or intolerant or had failed prior docetaxel therapy. The primary endpoint of the study was OS. Secondary endpoints included time to occurrence of skeletal related events (SREs), changes and time to progression in PSA and alkaline phosphatase (ALP), safety, and impact on quality-of-life measures. Detailed analysis of the SRE data indicated that Alpharadin treatment significantly improved three out of four SRE components, as well as being associated with a 64% improvement in median time to first SRE of 13.5 months vs. 8.4 months for placebo (HR = 0.610, P = 0.00046). The three components of the SRE measurement that were significantly improved by Alpharadin vs. placebo were time to spinal cord compression (P = 0.016), time to pathological bone fracture (P = 0.013), and time to external beam radiation (P = 0.0038).

Commenting on these results, Dr. Oliver Sartor, MD, medical director at Tulane Cancer Center said that although the effects on OS with Alpharadin have already been observed, the improvements in time to first SRE, particularly the significant reduction in time to spinal cord compression, are perhaps shown for the first time in CRPC patients. Alpharadin is an effective therapy with a well-tolerated safety profile and might provide a new standard of care for treatment of CRPC patients with bone metastases.

*Source: Algeta*

## Masitinib Significantly Extends OS as Compared with Sutent in Gleevec-resistant GIST

AB Science SA announced encouraging results from a Phase II study with its investigational drug – masitinib – a tyrosine kinase inhibitor, in Gleevec-resistant gastrointestinal stromal tumors (GIST). Masitinib significantly improved OS in patients with Gleevec-resistant GIST compared with Sutent (sunitinib).

In this study, 44 patients with inoperable, locally advanced or metastatic GIST and showing disease progression while treated with Gleevec (imatinib) (400 to 800 mg/day) received either masitinib (23 patients) at 12 mg/kg/day or sunitinib (21 patients) until progression. After a median follow-up of 14 months, median OS was not reached for masitinib compared with 15 months for Sutent (P = 0.022). After 18 months, 79% of patients treated with masitinib were still alive vs. 20% for patients treated with sunitinib. After 2 years, 53% of patients treated with masitinib were still alive vs. 0% for the patients treated with sunitinib. The study also demonstrated that masitinib was significantly better tolerated than sunitinib. The safety profile of masitinib was better than that of sunitinib, with a significantly longer safety event-free survival (P = 0.002) and a lower occurrence of severe adverse events. In masitinib-treated patients, nausea, diarrhea, and asthenia were the most common adverse events. Complete data have been submitted to the American Society of Clinical Oncology (ASCO) for publication.

*Source: AB Science*

## Prolonged OS in a Phase II Study of AGS-003 in Patients with mRCC

Argos Therapeutics announced updated results from an open-label, Phase II study of its Arcelis immunotherapy – AGS-003 – in combination with sunitinib in patients with unfavorable risk, metastatic renal cell carcinoma (mRCC), according to which the compound prolonged survival. Based on these results, the company is planning to initiate the international Phase III ADAPT study. Data from the open-label Phase II study were presented in a poster and oral session at the 2012 ASCO Genitourinary Cancers Symposium in San Francisco.

The study enrolled 21 patients with newly diagnosed, metastatic clear cell RCC. Following nephrectomy or metastasectomy to harvest tumor mRNA, autologous monocytes were collected by leukapheresis to produce RNA-loaded dendritic cells specific to each patient's disease. Treatment consisted of 6-week cycles of sunitinib, 4 weeks on and 2 weeks off, plus AGS-003, which was administered as an intradermal injection every 3 weeks for five doses, and then every 12 weeks until progression in combination with sunitinib. Immune responses were evaluated at baseline and following five doses of AGS-003 using multiparametric flow cytometry to assess the induction of anti-tumor, CD28+ memory T-cell responses. Results indicate that multiple partial responses were observed with this combination regimen while 11 of 15 (73%) patients with serial immune assessments demonstrated increases in their CD28+ memory T cells. These immune responses correlated directly with prolonged survival in this study. Overall, the median PFS was 11.2 months and

Back to top of Clinical Development Section | Back to Top of Document

## Clinical Development
(Cont'd)

estimated Kaplan–Meier median OS was 29.3 months in this study, based on follow-up through January 2012. In addition, AGS-003 was well tolerated in combination with sunitinib, with no immunotherapy-related serious adverse events.

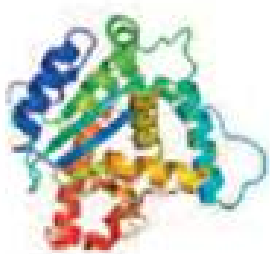
*Source: Argos Therapeutics*

### Positive Phase IIb Results of TH-302 in Patients with Pancreatic Cancer

Threshold Pharmaceuticals announced that its Phase IIb, randomized, controlled clinical trial (n = 214) evaluating the efficacy and safety of two doses of the investigational agent TH-302 – a hypoxia-targeted drug – in combination with gemcitabine compared with gemcitabine alone in patients with first-line advanced pancreatic cancer achieved its primary endpoint, with a 63% improvement in PFS and a safety profile consistent with earlier studies.

Study TH-CR-404 was a multicenter, randomized, controlled, dose-ranging, Phase IIb crossover clinical trial of TH-302 in combination with gemcitabine in patients with first-line advanced pancreatic cancer. The primary endpoint of the trial was PFS. The secondary endpoints were ORR, OS, change in CA19-9, as well as various other efficacy and safety parameters. The study results showed that median PFS was 5.6 months for patients treated with gemcitabine in combination with TH-302 at 240 mg/m2 and 340 mg/m$^2$ compared with 3.6 months for patients treated with gemcitabine alone. The PFS hazard ratio comparing the TH-302 combination to gemcitabine alone was 0.61 (95% CI: 0.43–0.87), which was highly statistically significant (P = 0.005). The response rate in the combination arms was 22% compared with 12% in the gemcitabine-alone group. Results also demonstrated greater efficacy in the higher TH-302 dose group compared with the lower-dose group. The combination was well tolerated with a safety profile that was consistent with a prior threshold study of this combination regimen.

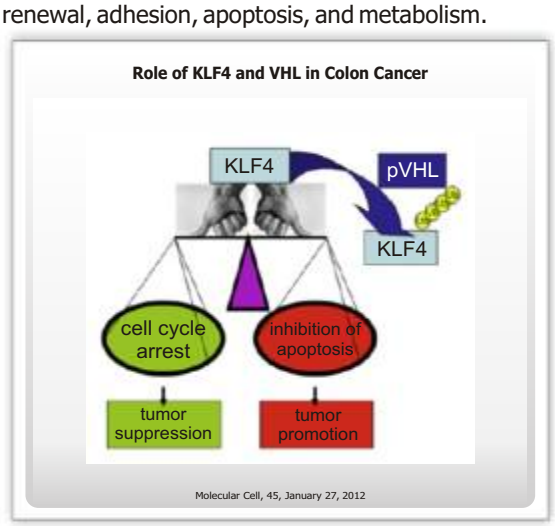
*Source: Threshold Pharmaceuticals*



# Biomarkers

### Regulation of KLF4 Turnover Reveals an Unexpected Tissue-specific Role of pVHL in Tumorigenesis

Kruppel-like factor 4 (KLF4) is a transcription factor involved in cellular responses to a variety of environmental and intracellular stress signals such as DNA damage, oxidative stress, and inflammation. KLF4 activation determines the cell fate by activating or inhibiting a network of genes involved in cellular functions as diverse as cell cycle regulation, stem cell renewal, adhesion, apoptosis, and metabolism.




In a recent study published in *Molecular Cell*, Gamper *et al.* reported that Von Hippel-Lindau gene product, pVHL, interacts directly with and degrades KLF4 via the ubiquitin–proteasome pathway. Furthermore, pVHL deficiency in colon cancer cells leads to KLF4 upregulation and concomitant increase of p21 transcription as well as to cell cycle arrest. The study findings suggest that KLF4 is a downstream mediator of HIF-independent roles of pVHL. As such, KLF4 provides a new link in the pathway leading to growth arrest triggered by the loss of pVHL observed in certain cells. In such cells, characterized by a requirement of KLF4 for proliferative control, pVHL overexpression could contribute to tumor formation, at least at the early stage of tumorigenesis. Investigators found that pVHL upregulation associated with a decrease in KLF4 levels is a common feature in colon cancers. Mechanistically, investigators identified the KLF4 amino terminus as particularly important for the regulation of KLF4 turnover by being the site of ubiquitylation and pVHL binding. Researchers pointed out that the mechanisms governing KLF4 degradation by pVHL are of interest not only for the role of KLF4 in cancer but also in differentiation and stem cell renewal.

*Source: Molecular Cell. 2012;45(2):233–243.*

### Pretreatment *EGFR* T790M Mutation Predicts Shorter EGFR TKI Response Duration in Patients with NSCLC

Patients with non-small cell lung cancer (NSCLC) with EGFR-activating mutations have excellent response to EGFR tyrosine kinase inhibitors (TKIs), but a T790M mutation accounts for most TKI drug resistance. In a recent study published in *JCO*, Kang-Yi Su *et al.* used direct sequencing, highly sensitive matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS), and next-generation

## Biomarkers (Cont'd)

sequencing (NGS) methods to investigate *EGFR* T790M in patients with NSCLC before and after TKI treatment and correlate the results with clinical outcome.

In this study, there were two cohorts of patients with NSCLC: TKI-naïve patients (n = 107) and TKI-treated patients (n = 85). Results were correlated with TKI treatment response and survival. MALDI-TOF MS was highly sensitive in detecting and quantifying the frequency of EGFR-activating mutations and T790M. MALDI-TOF MS identified more T790M than direct sequencing in TKI-naïve patients with NSCLC (25.2% vs. 2.8%, respectively; P < 0.001) and in TKI-treated patients (before TKI: 31.5% vs. 2.7%, respectively; P < 0.001; and after TKI: 83.3% vs. 33.3%, respectively; P = 0.0143). The EGFR mutations and their frequencies were confirmed by NGS. T790M was an independent predictor of decreased PFS in patients with NSCLC who received TKI treatment (P < 0 .05, multivariate Cox regression).

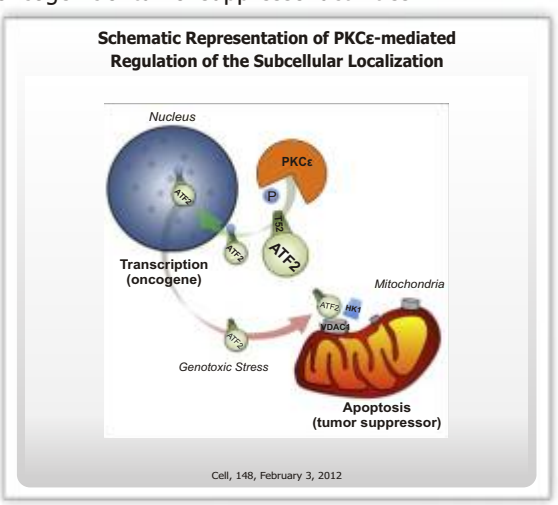
Several second-generation TKIs and other new therapies designed to overcome TKI resistance are currently under active clinical development. Despite the promise posed by the new agents, it is still necessary for physicians to accurately identify patients with T790M who can benefit from treatment. Patients can develop TKI resistance as a result of the activation of alternative pathways such as c-Met. Combination therapy with EGFR and other alternative pathway (e.g., c-Met, Her3) inhibitors can also be investigated.

*Source: Journal of Clinical Oncology. 2012;30(4):433–440.*

### PKCε Promotes Oncogenic Functions of ATF2 in the Nucleus while Blocking Its Apoptotic Function at Mitochondria

Activating transcription factor 2 (ATF2) is one of 16 Atf/Creb family transcription factors and an integral component of the activator protein-1 (AP-1) transcriptional complex, which regulates normal cellular growth and development, as well as cellular response to stress. ATF2 elicits oncogenic activities in melanoma and tumor suppressor activities in non-malignant skin cancer.

In a study published in *Cell*, Lau *et al.* demonstrated that the tumor suppressor or oncogenic activities of ATF2 result from its cytosolic or nuclear function, respectively. The present findings reveal that, following genotoxic stress, cytosolic ATF2 impairs HK1/VDAC1 complexes and mitochondrial membrane integrity, sensitizing cells to apoptosis. In contrast, the high PKCε expression in melanoma cells induces predominantly nuclear localization of ATF2, which attenuates its normal cytosolic function and correlates with resistance to genotoxic stress. The different levels of PKCε activity found in melanomas determine the extent to which ATF2 reaches the mitochondria and promotes cell death following genotoxic stress. Thus, PKCε dictates the tumor suppressor or oncogenic activities of ATF2 by directly affecting its nuclear or cytosolic localization. The study results establish the role of ATF2 at the mitochondria following genotoxic stress and reveal its contribution to stress-induced cell death. The degree of PKCε phosphorylation of ATF2 is instrumental in controlling its function. PKCε phosphorylation determines the ability of ATF2 to function at the mitochondria where its contribution to cell death is consistent with its tumor suppressor functions. Constitutively high PKCε expression/activity, as seen in melanomas, attenuates ATF2 mitochondrial function and enhances its nuclear transcriptional activity, consistent with its oncogenic activity. Thus, PKCε regulates the subcellular localization of ATF2, which dictates its ability to elicit oncogenic or tumor suppressor activities.




*Source: Cell. 2012;148(3):543–555.*

# Regulatory

### FDA Approves Axitinib for Patients with Previously Treated Advanced RCC

Pfizer announced that the FDA has approved Inlyta (axitinib), a kinase inhibitor, for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. The approval is based on data from the Phase III AXIS trial, which demonstrated that Inlyta significantly extended PFS (P < 0.0001), with a median PFS of 6.7 months compared with 4.7 months for those treated with sorafenib, a current standard of care for this patient population, representing a 43% improvement in median PFS over sorafenib.

Back to top of Biomarkers Section | Back to top of Regulatory Section | Back to Top of Document

## Regulatory (Cont'd)

Axitinib is also being investigated in a randomized clinical trial in patients with treatment-naïve as well as previously treated advanced RCC and in a randomized Phase II clinical trial for the treatment of hepatocellular carcinoma. In addition, under a collaborative development agreement between Pfizer and SFJ Pharma Ltd., SFJ will conduct a Phase III clinical trial in Asia studying axitinib for adjuvant treatment of patients at high risk of recurrent RCC following nephrectomy.

*Source: Pfizer*

### Zelboraf Receives EU Approval for the Treatment of Metastatic Melanoma

Roche announced that the European Commission has approved Zelboraf (vemurafenib) as a monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Zelboraf is designed to target and inhibit mutated forms of the BRAF protein found in about half of all cases of melanoma.

In pivotal clinical trials, Zelboraf is the only treatment to benefit patient survival in both previously untreated and previously treated people with advanced melanoma who tested positive for BRAF V600 mutations by using the Roche cobas 4800 BRAF V600 Mutation Test.

- In the pre-specified interim analysis of the Phase III BRIM3 trial, the risk of death was reduced by 63% for people who received Zelboraf compared to those who received standard first-line treatment (HR = 0.37, P < 0.0001).
- In a post-hoc analysis of BRIM3 data with a longer follow up compared with previous analyses, including crossover of patients from the placebo to the active treatment arm, Zelboraf significantly improved survival over standard first-line treatment by providing a median OS of 13.2 months compared with 9.6 months for chemotherapy (HR = 0.62).
- A survival benefit was also shown in pre-treated patients in the Phase II BRIM2 study, the data from which are planned to be published soon.

In 2011, Zelboraf became the first and the only US FDA–approved personalized medicine that is shown to improve survival in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The cobas 4800 BRAF V600 Mutation Test, a diagnostic test co-developed by Roche to identify patients eligible for treatment, was approved simultaneously with Zelboraf in the US and is CE-marked and commercially available in the EU.

*Source: Roche*

### FDA Approves Vismodegib for Adults with Advanced Basal Cell Carcinoma

Genentech announced that Erivedge (vismodegib), a hedgehog pathway inhibitor, is approved by the FDA for the treatment of adults with basal cell carcinoma (BCC) that has metastasized to other parts of the body or that has returned after surgery or that patient's healthcare provider decides cannot be treated with surgery or radiation.

The FDA approval of Erivedge is based on results from ERIVANCE BCC (SHH4476g), a pivotal international, single-arm, multicenter, two-cohort, open-label, Phase II study that enrolled 104 patients with advanced BCC, including locally advanced BCC (n = 71) and metastatic BCC (n = 33). The study showed that Erivedge shrank lesions (ORR) in 43% of patients with locally advanced BCC and 30% of patients with metastatic BCC, as assessed by independent review, the primary endpoint of the study. Roche has also submitted a marketing authorization application (MAA) for Erivedge in the EU.

*Source: Genentech*

### European Commission Approves Caprelsa (Vandetanib) for Patients with Advanced Medullary Thyroid Cancer

AstraZeneca announced that the European Commission has granted marketing authorization for Caprelsa (vandetanib) for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. Caprelsa is the first approved treatment for advanced MTC in Europe.

The marketing authorization of Caprelsa is based on data from the Phase III Caprelsa clinical trial program, including the ZETA study, a double-blind trial of 331 patients with advanced MTC that has progressed and spread to other parts of the body, which showed a 54% reduction in risk of disease progression compared with placebo (HR = 0.46; 95% CI = 0.31–0.69; P < 0.001).

Caprelsa was granted orphan drug status and approved by the US FDA in April 2011.

*Source: AstraZeneca*

### FDA Grants Pertuzumab Priority Review for Previously Untreated HER2-positive Metastatic Breast Cancer

Genentech announced that the US FDA has accepted its biologics license application for pertuzumab, a HER-dimerization inhibitor, and granted priority review. The proposed indication is pertuzumab in combination with Herceptin (trastuzumab) and docetaxel chemotherapy for people with HER2-positive metastatic or locally recurrent, unresectable

## Regulatory (Cont'd)

breast cancer, who have not received previous treatment or whose disease has relapsed after adjuvant therapy. The FDA confirmed the action date as June 8, 2012.

The pertuzumab application is based on results from the pivotal Phase III CLEOPATRA study. The study demonstrated a 6.1-month improvement in median PFS for people who received a pertuzumab-based regimen (pertuzumab combined with Herceptin and docetaxel chemotherapy) compared with those who received Herceptin and chemotherapy alone (median PFS: 18.5 vs. 12.4 months, respectively). People who received the combination also experienced a 38% reduction in the risk of their disease worsening or death (HR = 0.62, P < 0.0001, according to independent review). Roche has also submitted an MAA to the EMA for pertuzumab for people with previously untreated HER2-positive metastatic breast cancer.

*Source: Genentech*

### EMA Recommends Conditional Approval of Pixuvri for Relapsed Aggressive Non-Hodgkin's B-cell lymphoma

The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended that Pixuvri (pixantrone), a type II DNA topoisomerase inhibitor, be granted conditional approval for the cancer non-Hodgkin's B-cell lymphoma. The new medicine, which contains the active substance pixantrone, is to be used on its own in patients whose cancer is aggressive and has come back after multiple rounds of previous chemotherapy or is not responding to other treatments.

The committee recommended conditional approval because the data supplied showed that the medicine's benefits outweigh its risks but are not yet comprehensive and that more information is needed on the benefits of the medicine in patients who have received rituximab in the past. Results showed that a greater proportion of patients responded to Pixuvri than a comparator chemotherapy medicine (20% vs. 6%) and that patients receiving Pixuvri survived for longer without their disease getting worse (an average of 10.2 vs. 7.6 months). The committee also noted that the benefit of Pixuvri appeared to be lower in patients who had received rituximab in the past and that its benefit was not established in patients when used as the fifth or later round of chemotherapy in patients whose disease did not respond to the last treatment.

The conditional approval will be renewed on a yearly basis until the obligation to provide additional data on rituximab-pretreated patients has been fulfilled. The applicant, CTI Life Sciences Ltd., has informed the committee that it expects to be able to provide the results of the additional study by mid-2015.

*Source: European Medicine Agency*

### GSK Withdraws Its Application for an Extension of the Indication for Tyverb

The EMA has been formally notified by GlaxoSmithKline (GSK) Research & Development of its decision to withdraw its application for an extension of the therapeutic indication for Tyverb (lapatinib) 250 mg film-coated tablets.

On April 14, 2011, GSK submitted an application to extend the marketing authorization for Tyverb in combination with paclitaxel for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 (ErbB2). Patients in the registration study were not previously treated with trastuzumab in either the adjuvant or metastatic setting. At the time of withdrawal, the application was under review by the CHMP.

Tyverb was given conditional approval and was first authorized in the EU on June 10, 2008. It is currently authorized for treatment of patients with breast cancer whose tumors overexpress HER2 (ErbB2):

- In combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines, taxanes, and therapy with trastuzumab in the metastatic setting
- In combination with an aromatase inhibitor for postmenopausal women with hormone receptor–positive metastatic disease not currently intended for chemotherapy

In its official letter, the company stated that its decision to withdraw the application was based on the CHMP's assessment that the lack of an active-controlled trial hampers the proper assessment of the benefit–risk balance in European patients in the applied indication.

Tyverb continues to be authorized in the currently approved indications.

*Source: European Medicine Agency*

- **A SMART Synopsis of Today's Oncology Headlines. We find the stories that matter most, *so you don't have to.***
- **An E-Newsletter that both educates *and* informs.**
- **SmartAnalyst is a strategic consulting firm** that has supported multiple pharma client engagements **over a ten-year history. Oncology has been a core indication of analytical focus.**
- **SMARTOncology is a reflection of SmartAnalyst's Oncology experience and expertise.** We inform our readers **about headlining news that matters most,** while also **educating our audience with "Tumor of The Month"** articles and supplementing issues **with our own Key Insights.**



# SmartOncology E-Newsletter

## Product of SmartAnalyst

SMARTANALYST®
INTELLIGENT INSIGHTS. SMART RESULTS.

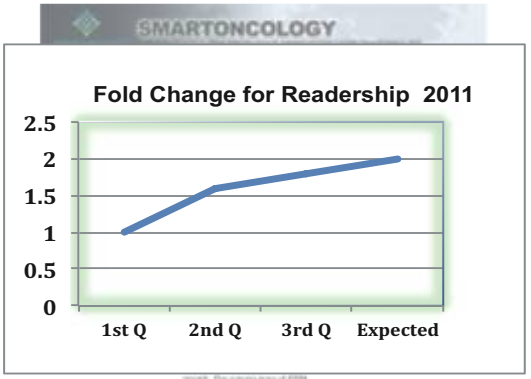
### Become A SmartOncology Sponsor

Offering Biotech and Pharma companies a viable opportunity to share their products and services with their key target market.

Please review our sponsorship rates and placement choices. Feel free to contact our team at any point in time. We would be more than happy to answer any questions. cveenis@smartanalyst.com

### Readership 3,000+ and Growing… Targeting:

- Academics
- Physicians
- KOLs
- Pharma
  - Marketing
  - R & D




### Key Sponsors include:

- Advocacy groups
- Vendors
- Congresses

.


| Ad Type | Size | Price/Issue | Price/Quarter | Price/6-month | Price/Anum |
|---|---|---|---|---|---|
| Banner/Logo | Full Page (7"x0.7") | $650 | $1625 | $2925 | $5200 |
| Banner/Logo | Half Page (3.5"x0.7") | $325 | $800 | $1450 | $2600 |
| Logo + 1-3 sentences (~50 Words) | (Approx. 2.7"x1.5") | $825 | $2025 | $3650 | $6500 |

Back to top of Newsletter Sponsorship Section | Back to Top of Document