Vol. 34 No. 1
January 2011

THE
CLINICAL CANCER LETTER
Cancer research news for clinicians

Prostate Cancer:

XGEVA Improves Metastasis-Free Survival In Castrate-Resistant Prostate Cancer

Amgen announced top-line results from a phase III trial evaluating XGEVA (denosumab) vs. placebo in 1,432 men with castrate-resistant prostate cancer.

In the trial, known as the '147 study, XGEVA significantly improved median bone metastasis-free survival by 4.2 months (HR=0.85, 95 percent CI 0.73-0.98, p=0.03) compared to placebo, the company said. This was the primary endpoint of the study. Also, the agent significantly improved time to

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Cost of Cancer:

Cancer Care Cost To Jump by 27 Percent In a Decade, Reaching $158 Billion in 2020

The estimated total cost of cancer care in the U.S. in 2020 is expected to reach $158 billion, assuming the most recent observed patterns of incidence, survival, and cost remain the same.

This represents a 27 percent increase from 2010 due only to the projected aging and growth of the US population, according to a study published online Jan. 12 in The Journal of the National Cancer Institute.

However, the authors also note the cost of cancer care could rise even more quickly under some reasonable assumptions such as a 2 percent annual increase in costs of the initial and final phases of cancer care.

Cancer disproportionately affects the elderly population, which is expected to increase from 40 million in 2009 to 70 million in 2030.

With changes in risk factor prevalence and stage at diagnosis, and development of new diagnostic tools and treatments for cancer in the 1990s, in general cancer incidence declined and survival improved, but cancer care became more expensive.

Under a different scenario of continuing trends in cancer incidence, survival, and costs of care, the total cost of cancer care in 2020 is expected to be $173 billion, an even larger increase (39 percent from 2010).

To estimate the national medical cost of cancer care through the year 2020 for 13 cancers in men and 16 cancers in women, Angela Mariotto and colleagues from the NCI analyzed data on cancer incidence (the rates of newly diagnosed cancer in any given year) and survival from the Surveillance, Epidemiology, and End Results database http://seer.cancer.gov/ and Medicare

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Phase III Trial Shows Delay In First Metastasis Occurrence

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first occurrence of one metastasis, the company said. This was the secondary endpoint. Overall survival, a secondary endpoint, was similar between the XGEVA and placebo groups.

Overall rates of adverse events and serious adverse events were generally similar between XGEVA and placebo, with hypocalcemia and osteonecrosis of the jaw observed at increased frequencies in the XGEVA arm, the company said.

The yearly rate of ONJ in the XGEVA-treated group was similar to what has been observed in prior XGEVA trials.

"Our data demonstrate that XGEVA, which antagonizes the RANK Ligand axis, limits the ability of tumors to colonize bone, an important finding for men at risk for bone metastases and their healthcare providers," said Roger Perlmutter, executive vice president of research and development at Amgen.

The RANK Ligand pathway, first discovered by Amgen scientists in the mid-1990s, is believed to play a central role in cancer-induced bone destruction, regardless of cancer type, the company said.

Data suggest that in bone metastasis, the invasion of cancer is facilitated by bone destruction. Hence, increased bone resorption due to increased RANK Ligand expression appears to augment bone metastasis, the company said.

XGEVA is a fully human monoclonal antibody that binds to RANK Ligand, a protein essential for the formation, function and survival of osteoclasts. XGEVA prevents RANK Ligand from activating its receptor, RANK, on the surface of osteoclasts, thereby decreasing bone destruction and halting release of growth factors, making the environment less conducive to tumor growth.

Study `147 was a randomized, placebo-controlled, multi-center phase III study comparing the treatment effect of XGEVA with placebo on prolonging bone metastasis-free survival in men with hormone-refractory prostate cancer with rapidly-rising PSA levels who had no bone metastases at baseline.

The primary endpoint of the trial was time to first occurrence of bone metastasis or death from any cause, with secondary endpoints including time to first occurrence of bone metastasis (excluding death) and overall survival.

Last November, XGEVA was approved by FDA for the prevention of skeletal-related events in patients with bone metastases from solid tumors. XGEVA is not indicated to prevent SREs in patients with multiple myeloma.

Administered as a single 120 mg subcutaneous injection every four weeks, XGEVA provides an option for urologists and oncologists to prevent serious bone complications in men with prostate cancer, the company said.

Amgen has submitted marketing applications for XGEVA in the European Union, Australia, Canada and Switzerland. In Japan, Amgen is working with its licensing partner, Daiichi-Sankyo Co. Ltd. and a marketing application was submitted. XGEVA can cause severe hypocalcemia and osteonecrosis of the jaw. The most common adverse reactions in patients receiving XGEVA were fatigue/asthenia, hypophosphatemia, and nausea.

The most common serious adverse reaction in patients receiving was dyspnea. The most common adverse reactions resulting in discontinuation of XGEVA were osteonecrosis and hypocalcemia.

Denosumab is also marketed as Prolia in other indications.

The Clinical Cancer Letter

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202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
Website: http://www.cancerletter.com

THE CLINICAL CANCER LETTER (ISSN 164-985X). Published monthly, subscription $125 per year, by The Cancer Letter Inc.

Cost of Cancer:

Cost Could Reach $173 Billion, A 39 Percent Rise in a Decade

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expenditures associated with cancer from the linked SEER-Medicare database http://healthservices.cancer.gov/seermedicare/.

They combined prevalence (the population rates of people alive with cancer in any given year) and cancer costs by phase of care and used US Census population projections to calculate cancer care costs through the year 2020.

The researchers projected prevalence by phase of care under different assumptions about future incidence

and survival. Incidence is decreasing for most of the cancer sites. But even with declining incidence rates, the absolute number of individuals diagnosed with cancer will continue to increase because of population changes.

The researchers also projected costs by phase of care under different assumptions about future trends.

"Costs of care for cancer patients who die of their disease follows a U-shaped curve, with the highest costs in the initial phase following diagnosis and the phase before death, and the lowest costs in the period in-between, the continuing phase," the authors write.

Although the per-person cost of cancer care varies tremendously by cancer site, the overall national burden is driven by prevalence.

For example, the per-person cost of female breast cancer care in each phase is among the lowest, but the total cost of breast cancer in 2020 is projected to be the highest ($20.5 billion), because of the large number of women living with breast cancer in each phase of care.

The highest increases in costs for cancer care between 2010 and 2020 are projected for female breast cancer (32 percent) and prostate cancer (42 percent) patients in the continuing phase, representing a higher proportion of long term survivors.

"To investigate the impact of specific cancer control strategies on cancer survivorship and to estimate the societal return on investments in cancer research, more complex modeling approaches are necessary," the authors write.

One such approach is a cooperative study funded by the National Cancer Institute with the Cancer Intervention Surveillance Modeling Network, which uses micro-simulation models to investigate the impact of interventions on population-based cohorts of patients with breast, colorectal, prostate and lung cancers. http://cisnet.cancer.gov/.

The authors note that while these types of projections are "undoubtedly more reliable" than the projections used in their article, the models require substantial additional research effort, extensive data on populations in the U.S., and could only be done for a limited number of cancer sites.Melanoma:

Melanoma:

Lilly Suspends Phase III Trial Of Tasisulam in Melanoma

Eli Lilly and Co. suspended the global phase III study evaluating tasisulam, an investigational, small-molecule anti-cancer compound, as a second-line treatment for unresectable or metastatic melanoma.

Lilly, in consultation with an independent data monitoring committee, recommended a "full clinical hold," because of safety concerns.

A full clinical hold ensures that no new or existing patients in the trial receive additional doses of the compound, allowing researchers the time to fully analyze existing data.

Lilly notified regulatory agencies and contacted all trial investigators to provide details on how to manage individuals enrolled in the trial.

"We are thoroughly reviewing the clinical trial data to understand what modifications to the study protocol or dosing would be needed to improve patient safety on this trial," Richard Gaynor, vice president, oncology product development and medical affairs for Lilly, said in a statement.

Lilly continues to develop tasisulam as part of an extensive clinical development program across a wide range of tumors, including soft tissue sarcoma, breast, ovarian and renal cancers, as well as non-small cell lung cancer and acute leukemia. At this time, these trials continue without modification because the dosing of tasisulam is different. Lilly is closely evaluating patient safety within these trials on an ongoing basis.

The phase III trial sought to compare the efficacy, safety and tolerability of tasisulam versus paclitaxel, as a second-line treatment for those with metastatic melanoma. The study enrolled more than 300 patients in 18 countries. The primary endpoint of this study is overall survival.

Tasisulam was granted orphan drug status for stage 2b-IV melanoma by FDA in late 2009.

San Antonio Breast Cancer Symposium:

Genomic Health Presents Meta-Analyses of Oncotype DX

Genomic Health Inc. announced the results from seven new studies focusing on its multigene Oncotype DX breast cancer test, which has helped guide treatment decisions in more than 175,000 breast cancer patients worldwide.

Highlights from the studies presented this week by Genomic Health presented at the 33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium include:

• A meta-analysis of seven studies with a total of 912 patients presented in a poster session demonstrated a consistent and large impact of the Recurrence Score on breast cancer adjuvant treatment decisions. In these studies, physicians who use Oncotype DX in clinical

practice changed their treatment decisions in over a third of patients, leading to an overall reduction in chemotherapy use of approximately 28 percentwith the use of the Recurrence Score. It is equally important to note that the Recurrence Score led to the addition of chemotherapy to hormonal treatment in approximately 4 percent of patients who, prior to the Recurrence Score, were considered low risk but, were subsequently identified as having high Recurrence Score disease.

• Another analysis showed that the Oncotype DX Recurrence Score used alone remains the recommended method to predict relative chemotherapy benefit in estrogen receptor-positive, node negative breast cancer. Researchers from the National Surgical Adjuvant Breast and Bowel Project, together with Genomic Health analyzed the value of the Recurrence Score-Pathology-Clinical risk assessment in predicting chemotherapy benefit. The RSPC integrates the Recurrence Score and clinical-pathologic factors, including tumor size, tumor grade and age to assess distant recurrence risk in early-stage patients.

RSPC has been shown to refine Recurrence Score assessment of distant recurrence risk or prognosis, especially for intermediate risk Recurrence Scores. The findings demonstrated that the Recurrence Score (interaction p=0.037) predicted chemotherapy treatment benefit, while the RSPC (interaction p=0.10) did not improve prediction of chemotherapy benefit over Recurrence Score alone. Neither tumor size (interaction p=0.32), tumor grade (interaction p=0.65) nor patient age (interaction p=0.22) was a significant predictor of chemotherapy benefit. Thus, while incorporation of traditional clinical and pathologic factors can improve the prognostic value of the Recurrence Score, these factors do not improve the ability of the Recurrence Score to predict relative chemotherapy benefit.

• In a study to determine whether age helps predict individual tumor biology, researchers examined the Oncotype DX Recurrence Score and the molecular expression of estrogen receptor, progesterone receptor, HER2 and the proliferation-related genes among 145,236 estrogen receptor-positive breast cancers. While study findings presented in a poster session showed that the Recurrence Score is slightly higher in breast cancers from younger patients (<40 years old) and lower in old patients (>70 years old), a wide range of Recurrence Score results were observed in all age groups. The results demonstrate the importance of standardized quantitative gene expression measurement delivered by the Recurrence Score, and that patient age alone does not capture the differences in the underlying individual tumor biology as the Recurrence Score does.

• Initial data from the prospective, multicenter West German Study Group Plan B trial presented in a poster session examined the relationship between tumor grade and the tumor immunohistochemistry biomarker, Ki-67, and the Oncotype DX Recurrence Score. As reported previously, there was a very weak correlation between central grade and the Recurrence Score as well as between Ki-67 and the Recurrence Score (correlation coefficients less than 0.40 for both). There were many patients with high grade and/or high Ki-67 and low Recurrence Score values. Neither tumor grade nor Ki-67 can predict the Recurrence Score status.

• An additional analysis of preliminary data from the WSG Plan B trial was presented in a separate poster session, and for the first time, compare risk groups using the Oncotype DX Recurrence Score and the invasion markers uPA (urokinase-type plasminogen activator) and its inhibitor PAI-1 (plasminogen activator inhibitor 1). uPA/PAI-1 was available in 131 of the 1,534 patients who had Recurrence Score results. Preliminary findings demonstrated a weak correlation between both uPA and PAI-1 and the Recurrence Score (correlation coefficients less than 0.30 for both).These initial results indicate that uPA/PAI-1 cannot predict the Recurrence Score. Additional recruitment and outcome assessment of the ongoing multicenter WSG Plan B trial will address the clinical significance of these initial findings.

"Based on my experience using Oncotype DX in clinical practice for the past six years, it is clear that by using only standard pathology variables, you often cannot predict the Recurrence Score without this well validated, standardized quantitative gene expression test," said Kathy Albain, professor of medicine, Division of Hematology/Oncology, Department of Medicine, Loyola University Chicago Stritch School of Medicine, Cardinal Bernardin Cancer Center, Loyola University Health System. "Just as it is critical to identify every HER2 and estrogen receptor-positive breast cancer patient for treatment selection, it is equally important to identify every patient with high Recurrence Score disease so that they can be considered for chemotherapy, and every patient with low Recurrence Score disease so that they can avoid chemotherapy and consider treatment with hormonal therapy alone."

In Phase II Study, NKTR-102 Shows Objective Response

Nektar Therapeutics announced positive results from a phase II study evaluating single-agent NKTR-

102 in metastatic breast cancer.

The results were presented at the 33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium.

NKTR-102, a topoisomerase I inhibitor-polymer conjugate, is being evaluated in multiple cancer indications.

The randomized Simon two-stage study presented at SABCS evaluated two 145 mg/m2 dose schedules of single-agent NKTR-102, every two weeks (q14d) and every three weeks (q21d), in 70 metastatic breast cancer patients who failed a prior taxane therapy. Eighty-seven percent (61/70) of patients in the study received a prior anthracycline/taxane with or without capecitabine.

A total of 66 of the 70 patients treated in the phase II study were assessable for the primary endpoint of objective tumor response rate, including confirmed complete and partial responses per RECIST.

As of Oct. 26, 2010, confirmed ORR for all evaluable patients was 32 percent (10/31) for the q14d schedule and 26 percent (9/35) for the q21d schedule, including two confirmed complete responses on the q14d schedule.

An additional four patients had near CRs, with 100 percent disappearance of all target lesions. The combined ORR for all evaluable patients was 29 percent (19/66). Clinical benefit rate for the 66 evaluable patients was 41 percent (defined as CR+PR+SD greater than or equal to 6 months).

"These are important new results for NKTR-102 in patients with metastatic breast cancer," said Ahmad Awada, head of the Medical Oncology Clinic at the Institut Jules Bordet in Brussels. "The high confirmed objective response rate continues to show that NKTR-102 is one of the most active single agents in this disease. This is particularly evident given the number of patients with dramatic reduction in lung and liver metastases."

The confirmed ORR was maintained in poor prognosis and heavily pre-treated subsets within the study, including patients previously treated with anthracycline/taxane/capecitabine: 33 percent (5/15); patients with metastatic triple-negative breast cancer: 39 percent (7/18); and patients with visceral disease: 29 percent (17/58). As of Oct. 26, 2010, preliminary median progression-free survival for all patients was 20 weeks.

Patients treated in the single-agent NKTR-102 study had a median of two lines of prior cytotoxic treatments for metastatic disease. Seventy-three percent (51/70) of the patients received neoadjuvant and/or adjuvant therapy and 87 percent (61/70) had visceral disease.

Side effects were generally manageable with dose-limiting toxicity consisting primarily of grade 3 diarrhea (20-23 percent) typically occurring after three months of therapy for both schedules. One patient of 70 patients treated with NKTR-102 experienced grade 2 alopecia and no patient experienced grade 3 or 4 neuropathy. Both neuropathy and alopecia are significant adverse events commonly associated with standard breast cancer therapies.

Triple-Negative BreastCancer:
Iniparib Plus Chemo Shows Benefit In Phase II Study

The New England Journal of Medicine published the final phase II data for the investigational drug iniparib (BSI-201) demonstrating significant clinical benefit in women with metastatic triple negative breast cancer when iniparib was administered in combination with chemotherapy agents gemcitabine/carboplatin.

Although not a pre-specified endpoint, overall survival also was significantly increased in women who received iniparib.

The study, "Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer," was published in the Jan. 5, 2011, online version of the NEJM and will be published in the Jan. 20 print edition. These findings were presented at the 35th European Society for Medical Oncology Congress in Milan.

"These published data show that the addition of iniparib to gemcitabine and carboplatin provided a significant improvement in clinical benefit in women with metastatic triple negative breast cancer, an aggressive form of breast cancer with no approved standard treatments that target this particular tumor subtype," said Joyce O'Shaughnessy, lead investigator of the study and co-chair of the Breast Cancer Research Program, Baylor-Charles A. Sammons Cancer Center, Texas Oncology, US Oncology in Dallas.

The agent is being developed by Sanofi-Aventis and its wholly-owned subsidiary, BiPar Sciences.

According to the study results, 56 percent of patients in the iniparib (BSI-201) group showed a clinical benefit-defined as a complete or partial response or stable disease of at least six months - compared with 34 percent (P=0.01) of patients in the chemotherapy group alone. Median progression-free survival in the iniparib (BSI-201) group was 5.9 months compared with 3.6 months in the chemotherapy group (95% CI (0.39-0.90) HR=0.59, P=0.01). The overall response rate

was 52 percent in the iniparib (BSI-201) group versus 32 percent (P=0.02) in the chemotherapy group alone.

Although it was not a pre-specified endpoint of the trial, median overall survival among women who received iniparib (BSI-201) was 12.3 months, compared with 7.7 months among women who received chemotherapy alone - translating to a 43 percent reduction in the risk of death (95% CI, (0.36-0.90) HR=0.57, P=0.01).

In the phase II iniparib (BSI-201) study, the most common any grade adverse events in the iniparib (BSI-201) arm were neutropenia, anemia, thrombocytopenia, fatigue/asthenia, nausea and constipation.

The most common grade 3/4 adverse events in the iniparib treatment arm were neutropenia, anemia, thrombocytopenia, leukopenia and fatigue/asthenia. There were two fatal adverse events (3.4 percent) in the chemotherapy-alone group and three (5.3 percent) in the iniparib (BSI-201) group, all attributed to disease progression within 30 days of receiving study treatment.

A large phase III study is ongoing and results are expected in 2011.

"The positive iniparib phase II data in this difficult to treat form of breast cancer is encouraging and underscores the innovative science and approach we have taken as we continue to investigate iniparib's potential to address this unmet medical need," said Atul Dhir, CEO of BiPar Sciences, based in South San Francisco.

The multicenter, open-label, randomized study included 123 women with mTNBC. The primary endpoints were safety and tolerability and clinical benefit rate of iniparib (BSI-201), defined as a complete or partial response or stable disease of at least six months.

Secondary endpoints included overall response rate and progression-free survival.

Overall survival also was assessed, although it was not a pre-specified endpoint of the trial. Patients received gemcitabine/carboplatin alone (chemotherapy group) or in combination with iniparib (BSI-201) until disease progression or unacceptable toxicity.

Patients in the chemotherapy group whose disease progressed were allowed to cross over to the iniparib (BSI-201) plus chemotherapy group. Efficacy analyses were conducted on the intent-to-treat (ITT) population.

Iniparib (BSI-201) is an anti-tumor agent with poly (ADP-ribose) polymerase (PARP) inhibitory activity in preclinical models. Iniparib (BSI-201) is in phase III trials for patients with mTNBC and squamous non-small cell lung cancer, as well as in phase II trials for patients with ovarian, uterine and brain cancers.

FDA granted Fast Track designation to iniparib (BSI-201) for mTNBC. The regulatory submissions are planned for the first quarter of 2011 in the U.S. and the second quarter in the European Union, the companies said.

Colorectal Cancer:

ColoPrint Improves Prognosis In Stage II and III Colon Cancer

ColoPrint significantly improves prognostic accuracy over assessment solely based on pathologic factors and microsatellite instability in patients with stage II and III colorectal cancer, reports a paper in the Journal of Clinical Oncology.

The assay is sponsored by Agendia. The paper, which seeks to provide an independent validation of the assay, concludes that in combination with classical pathological criteria, ColoPrint facilitates the identification of stage II patients who may be safely managed without chemotherapy.

The study aimed to develop a robust gene expression classifier that can predict disease relapse in patients with early-stage colorectal cancer (CRC). ColoPrint was developed using an unbiased analysis of the entire human genome to identify recurrence-related genes.

Frozen tumor tissue from 188 untreated patients with stage I to IV CRC was analyzed using Agilent 44K oligonucleotide arrays. A nearest mean classifier was developed using a cross-validation procedure and an optimal set of 18 genes was identified. The signature was validated on an independent set of 206 samples from patients with stage I, II, and III CRC.

In the subset of patients with stage II disease, ColoPrint correctly identified most patients (63 percent) as low risk. Low risk patients had a chance of 90.9 percent to remain relapse free for 5 years while high risk patients had only a 73.9 percent five -year relapse-free survival (RFS).

In stage II patients, ColoPrint was the strongest predictor for RFS in the univariate analysis (HR 3.34; 95% CI, 1.24 to 9.00; P 0.017) and multivariate analysis.

The classifier performed independently from the ASCO risk criteria when analyzed either individually or combined (HR, 3.66; 95% CI, 1.24 to 9.08; P 0.017). Furthermore, in the analysis of all samples and of samples from patients with stage III disease only, ColoPrint remained a strong independent prognostic factor.

The study's lead author is Ramon Salazar, of the

Institut Catala'd'Oncologia-IDIBELL, L'Hospitalet de Llobregat, in Barcelona. The co-authors are from Agendia; the Netherlands Cancer Institute and Slotervaart Hospital in Amsterdam, the Netherlands; Leiden University Medical Center in Leiden; and the University of Oxford, Radcliffe Infirmary.

The results of a second independent validation study by principal investigators from the university hospital Klinikum rechts der Isar, in Munich, Germany, have been submitted to the upcoming ASCO Gastrointestinal Cancers Symposium. The lead author of the study, Robert Rosenberg, has been invited to give an oral presentation at ASCO GI.

ColoPrint is a gene expression profile that identifies Stage II or III colorectal cancer patients who are either at low risk or at high risk of experiencing a disease relapse. The development of ColoPrint follows the development and widespread clinical use of MammaPrint, the first and only FDA-cleared breast cancer recurrence assay.

Prostate Cancer:
Test May Identify Predictors For Recurrence Post-Surgery

Genomic Health Inc. announced the first results of a large prostate cancer study that identified 295 genes strongly associated with clinical recurrence following radical prostatectomy.

Top-line findings from this study, which applied the same RT-PCR technology used in Genomic Health's Oncotype DX breast and colon cancer tests were presented at the Society for Urologic Oncology annual meeting.

The company and its research partners from Cleveland Clinic plan to present complete data at the ASCO Genitourinary Cancer Symposium in February 2011.

"We have reached an important milestone in our clinical development of a test for prostate cancer by narrowing down specific genes and pathways that predict prostate cancer aggressiveness," said Steven Shak, chief medical officer at Genomic Health. "Developing a test that can address a critical dilemma in today's standard of care will require well-designed clinical studies with reproducible evidence and the ability to work with very small amounts of biopsy tissue. These study results give us confidence to move forward with full clinical development, and we are evaluating the opportunity to accelerate these efforts with our scientific advisors."

Researchers analyzed RNA from 431 prostate cancers among patients previously treated with radical prostatectomy (RP) at Cleveland Clinic between 1987 and 2004.

Of the 732 cancer-related and reference genes assessed, 295 were significantly predictive (unadjusted $p<0.05$) of clinical recurrence-free interval using Cox PH regression.

The number of genes predicting clinical recurrence was well in excess of that expected by chance alone. In addition, the majority of these 295 genes were strongly associated with additional endpoints including prostate-specific antigen recurrence (75 percent of the genes); prostate cancer-specific survival (84 percent of genes) and upgrading/upstaging from biopsy to RP (68 percent of the genes).

Increased expression of cytoskeleton genes (i.e. FLNA) and epithelia genes (i.e. KRT5) were associated with lower risk of recurrence; whereas increased expression of extracellular matrix genes (i.e. COL3A1) were associated with higher risk of recurrence.

"Using a standardized quantitative technique combined with rigorous central review of pathology and clinical data, this study clearly demonstrates a strong association between tumor gene expression and clinical recurrence," said Eric Klein, chairman of the Glickman Urological and Kidney Institute at Cleveland Clinic. "A genomic test that distinguishes between clinically indolent and aggressive disease could help men with localized prostate cancer and their doctors decide between active surveillance and immediate prostatectomy or radiation therapy, or decide on the need for adjuvant therapy after initial treatment."

Gene Expression:
Tissue of Origin Test Consistent With Diagnosis In Blinded Validation Study

The Journal of Medical Diagnostics published the results of a Tissue of Origin Test validation and reproducibility study.

In the large blinded, multi-site study employing 462 formalin-fixed, paraffin-embedded tumor specimens, the Tissue of Origin Test results were in agreement with the available diagnosis in 89 percent of cases.

These results show that the gene expression based Tissue of Origin Test can assist in accurately and reliably identifying the origin of metastatic or poorly differentiated tumors using FFPE tissue, which is the most common clinical specimen type used in testing of cancer tumors, the company said.

The test is marketed by Pathwork Diagnostics Inc., a privately held molecular diagnostics company.

When a tumor's tissue of origin is not identified, patients may not receive the most appropriate tumor-specific, standard-of-care treatment.

The study is the largest and most rigorously conducted validation of a gene expression based test for helping to identify a tumor's primary site using FFPE specimens, the company said.

The Tissue of Origin Test measures the gene expression levels of more than 2,000 genes and compares the gene expression pattern of the specimen to that of 15 tissues in the test database, to indicate the most likely match.

The validation study published in JMD is titled "Validation and Reproducibility of a Microarray-Based Gene Expression Test for Tumor Identification in FFPE Specimens."

In the study, 462 metastatic and poorly differentiated FFPE tumor tissue specimens from tissue banks, all of which had an available diagnosis identifying their tissue of origin as one of the 15 tissues in the test database, were analyzed using the Tissue of Origin Test. The test results were compared to the available diagnoses and were in agreement in 89 percent of the cases. In addition, the study showed that an average of 12 cancer tissue types for each specimen could be ruled out, with >99 percent probability.

The Tissue of Origin Test received FDA clearance earlier this year for use with FFPE tissues.

Clinical Trials Approved By NCI CTEP Last Month

The NCI Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigators listed.

Phase I

8274 O6-Benzylguanine (BG) and Temozolomide (TMZ) Therapy of Glioblastoma Multiforme (GBM) with Infusion of Autologous P140KMGMT+ Hematopoietic Progenitors to Protect Hematopoiesis, Case Western Reserve University Sloan, Andrew Edward (216) 844-6054

8335 A Phase I, Open Label, Dose Escalation Study of the Safety, Tolerability and Pharmacokinetic Properties of the Combination of Cilengitide and Paclitaxel in Patients with Advanced Solid Malignancies, Mayo Clinic Rochester, Molina, Julian R. (507) 284-2511

8590 Phase I Pharmacodynamic and "High Content" Study of the Gamma-Secretase Inhibitor RO4929097 in Patients with Recurrent Malignant Gliomas (MGs) Targeting p75NTR to Inhibit Brain Tumor Initiating Cells (BTICs) and Recurrent Invasive Gliomas, University Health Network-Princess Margaret Hospital, Forsyth, Peter A.J. (403) 210-6559

8739 Phase Ib Dose Escalation and Biomarker Study of MK-2206 in Combination with Standard Doses of Weekly Paclitaxel in Patients with Locally Advanced or Metastatic Solid Tumors with an Expansion in Advanced Breast (713) 792-2817

8813 A Phase I Study of Veliparib (ABT-888) in Combination with Low-dose Fractionated Whole Abdominal Radiation Therapy (LDFWAR) in Patients with Advanced Solid Malignancies with Peritoneal Carcinomatosis, Johns Hopkins University, Azad, Nilofer S. (410) 614-9169

8866 An Early Phase I Study of IPdR Absorption, Metabolism, and Safety in Patients with Advanced Solid Tumors and Lymphomas, National Cancer Institute Developmental Therapeutics Clinic, Kummar, Shivaani (301) 435-5402

Phase I/II

8331 A Phase I/II Study of Azacitidine Combined with Mitoxantrone and Etoposide (A-NOVE) Chemotherapy for Patients Age >= 60 with Poor Prognosis Acute Myeloid Leukemia (AML), (416) 946-2824

Phase II

8254 Lenalidomide for the Treatment of CLL Patients with High-Risk Disease Roswell Park Cancer Institute, Chanan-Khan, Asher Alban A. (716) 845-3360

8408 A Phase 2 Study of GDC-0449 in Patients with Advanced Chondrosarcomas

Institut Bergonie Cancer Center, Italiano, Antoine 33 5 56 33 33 33

8446 A Randomized Discontinuation Phase 2 Study of AZD0530 as a Metastasis Inhibitor in Castrate Resistant Prostate Cancer, University of Chicago,

Posadas, Edwin Melencio (773) 834-5137

8467 A Phase II Study of RO4929097 (NSC 749225) in Combination with FOLFOX plus Bevacizumab Versus FOLFOX Plus Bevacizumab Alone for the First-Line Treatment of Patients with Metastatic Colorectal Cancer, Memorial Sloan Kettering Cancer Center, Segal, Neil Howard (212) 639-6237

8540 Phase II Study of RO4929097 to Eradicate Residual Disease in Patients with Multiple Myeloma Post Single Autologous Stem Cell Transplant Cancer Institute of New Jersey, Gharibo, Mecide Meric (732) 235-8776

8601 A 2-arm Randomized Phase II Study of Carboplatin, Paclitaxel plus Reovirus Serotype-3 Dearing Strain (Reolysin) vs. Carboplatin and Paclitaxel in the First Line Treatment of Patients with Recurrent or Metastatic Pancreatic Cancer Ohio State University Medical Center, Bekaii-Saab, Tanios Sam (614) 293-9863

8611 A Single-Arm Phase II Clinical Trial with the Novel MEK Inhibitor AZD-6244 for the Treatment of MCT-1 Related Relapsed or Refractory Diffuse Large B-cell Lymphoma, Northwestern University, Evens, Andrew M. (312) 695-4537

8617 Pilot Phase II Study of 5-Azacytidine in Previously Treated Patients with Advanced NSCLC, Ohio State University Medical Center, Otterson, Gregory A. (614) 293-2887

8628 A Randomized Phase II Study of Sequential Biotherapy with Aflibercept and High Dose IL-2 Versus High Dose IL-2 Alone in Patients with Inoperable Stage III or Stage IV Melanoma: Efficacy and Biomarker Study, City of Hope, Tarhini, Ahmad A. (412) 648-6507

GOG-0127W A Phase II Evaluation of ABT-888 (IND# 77840, NCI Supplied Agent: ABT-888, NSC #737664), Topotecan (NSC #609699) and Filgrastim or Pegfilgrastim in the Treatment of Persistent or Recurrent Squamous or Non-Squamous Cell Carcinoma of the Cervix, Gynecologic Oncology Group, Kunos, Charles Andrew (216) 844-3103

GOG-0265 A Phase II Evaluation of ADXS11-001 (NSC 752718, BB-IND#13,712) in the Treatment of Persistent or Recurrent Squamous or Non-Squamous Cell Carcinoma of the Cervix, Gynecologic Oncology Group, Huh, Warner King (205) 934-4986

Phase III

N0949 Randomized Phase III Trial of mFOLFOX7 or XELOX Plus Bevacizumab Versus 5-Fluorouracil/ Leucovorin or Capecitabine Plus Bevacizumab as First-line Treatment in Elderly Patients with Metastatic Colorectal Cancer North Central Cancer Treatment Group, Grothey, Axel (507) 284-3121

Phase Other

NCCTG-N9831E-NCCTG-ICSC Automated Quantitated Analyses (AQUA) of Epidermal Growth Factor Receptor (EGFR), p95/HER2, HER3, HER4, PTEN, and PI3Kp110alpha in N9831 Primary Breast Tumors using Tissue Microarrays, North Central Cancer Treatment Group, Perez, Edith A. (507) 284-1159

NCIC-MA.27C-MGH-ICSC A Genome-Wide Association Study in Patients Experiencing Bone Fractures While Receiving Aromatase Inhibitors for Early Breast Cancer on NCIC CTG Trial MA.2, National Cancer Institute of Canada Clinical Trials Group, Goss, Paul E. (617) 724-3118

Phase Pilot

8414 A Phase 1b Study of GDC-0449 Following Autologous Transplantation in Patients with High Risk First Remission or Relapsed Multiple Myeloma, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital, Huff, Carol Ann (443) 287-7104

8804 Using Proton MRS to Predict Response of Vorinostat Treatment in Glioblastoma, Emory University, Olson, Jeffrey J. (404) 778-5770

FDA Approvals:

FDA Approves SNDA For Gardasil For Anal Cancer And Precancerous Lesions

GARDASIL was approved by FDA for the prevention of **anal cancer and associated precancerous lesions** due to human papillomavirus types 6, 11, 16, and 18 in people ages 9 through 26.

Gardasil already is approved for the same age population for the prevention of cervical, vulvar, and vaginal cancer and the associated precancerous lesions caused by HPV types 6, 11, 16, and 18 in females. It is also approved for the prevention of genital warts caused

by types 6 and 11 in both males and females.

"Treatment for anal cancer is challenging; the use of Gardasil as a method of prevention is important as it may result in fewer diagnoses and the subsequent surgery, radiation or chemotherapy that individuals need to endure," said Karen Midthun, director of the FDA's Center for Biologics Evaluation and Research.

Although anal cancer is uncommon in the general population, the incidence is increasing. HPV is associated with approximately 90 percent of anal cancer. The American Cancer Society estimates that about 5,300 people are diagnosed with anal cancer each year in the U.S., with more women diagnosed than men.

Gardasil's ability to prevent anal cancer and the associated precancerous lesions [anal intraepithelial neoplasia grades 1, 2, and 3] caused by anal HPV-16/18 infection was studied in a randomized, controlled trial of men who self-identified as having sex with men.

This population was studied because it has the highest incidence of anal cancer.

At the end of the study period, Gardasil was shown to be 78 percent effective in the prevention of HPV 16- and 18-related AIN. Because anal cancer is the same disease in both males and females, the effectiveness data was used to support the indication in females as well.

As of May 31, 2010, more than 65 million doses of Gardasil had been distributed worldwide, since its approval in 2006 according to the manufacturer, Merck and Co. Inc, of Whitehouse Station, N.J.

The most commonly reported adverse events include fainting, pain at the injection site, headache, nausea, and fever. Fainting is common after injections and vaccinations, especially in adolescents.

ACCURAY INC. said FDA granted the company 510(k) clearance to market **Lung Optimized Treatment**, a new component of the CyberKnife VSI System.

The 510(k) clearance enables Accuray to provide physicians with greater flexibility in delivering radiosurgery treatments of lung cancer.

Lung Optimized Treatment offers the accuracy and steep dose fall off required to safely treat lung tumors, even those close to such critical structures, the company said.

Simulation and comparison workflows, combined with unique tracking modes, allow the clinician to select from multiple, non-invasive options, providing lung SBRT patients the optimal non-invasive treatment option, regardless of tumor location.

Because fiducial implantation is no longer required, CyberKnife radiosurgery with Lung Optimized Treatment offers a completely non-invasive option, which is particularly important for medically or surgically inoperable patients, the company said.

ABSTRAL (fentanyl) transmucosal tablets to manage breakthrough pain for adults with cancer, received FDA approval.

Fentanyl immediate-release transmucosal medications are administered on the soft surfaces of the mouth (inside of the cheek, gums, tongue), or the nasal passages or throat, where they dissolve and are absorbed.

"This is an important step for patients with cancer pain to have options for the treatment of their breakthrough pain," John Jenkins, director of FDA Office of New Drugs in the Center for Drug Evaluation and Research, said in a statement.

Abstral is indicated for the management of breakthrough pain in patients with cancer, ages 18 years and older, who already use opioid pain medication around the clock and who need and are able to safely use high doses of an additional opioid medicine. Breakthrough pain is pain that comes on suddenly for short periods of time and is not alleviated by a patient's normal pain management plan.

These patients are considered opioid tolerant because of their current opioid medication use. Only health care professionals skilled in the use of Schedule II opioids to treat pain should prescribe this drug product.

Abstral is available only through a Risk Evaluation and Mitigation Strategy program, which is intended to minimize the risk of misuse, abuse, addiction and overdose.

Under the program, pharmacies, distributors, and health care professionals who prescribe to outpatients are required to enroll in the program to prescribe, dispense and distribute this product.

The safety of Abstral was evaluated in 311 opioid-tolerant cancer patients with breakthrough pain. Two hundred and seventy of these patients were treated in multiple-dose studies. The duration of therapy for patients in multiple-dose studies ranged from 1-405 days with an average duration of 131 days and with 44 patients treated for at least 12 months.

Common adverse reactions include nausea, constipation, drowsiness and headache.

Serious adverse events, including deaths, have been reported in patients with other immediate-release transmucosal fentanyl products.The deaths occurred as a result of improper patient selection and/or improper dosing.

Abstral is manufactured by ProStraken Inc.