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Drugs in the Pipeline: What's Emerging in Late-stage Trials

SAN ANTONIO – Breast cancer continues to be a dynamic field of research, and the CTRC-AACR San Antonio Breast Cancer Symposium, now in its 32nd year, is the premier destination to present new data on emerging therapies.

C. Kent Osborne, M.D., director of the Dan L. Duncan Cancer Center and the Lester and Sue Smith Breast Center at Baylor College of Medicine and president of the symposium, will host a Drugs in the Pipeline press conference on Friday, Dec. 11, at 8:00 a.m. CT, in room 217C of the Henry B. Gonzales Convention Center.

Reporters who cannot attend in person may participate by using the following information:

- U.S. & Canada: (888) 282-7404
- International: (706) 679-5207
- Access Code: 39118522
- Topic: AACR

The following abstracts will be presented at the press conference:

48. Targeting Intrinsically-Resistant Breast Cancer Stem Cells with Gamma-Secretase Inhibitors

Treating breast cancer with a “Notch” pathway inhibitor reduced the ability of cancer stem cells to replenish themselves and promote tumor growth, researchers reported at the CTRC-AACR San Antonio Breast Cancer Symposium. These findings suggest that ongoing clinical trials testing this class of agents could offer promising results, especially when combined with other anticancer treatments.

“The Notch pathway regulates self-renewal of stem cells and our research indicates that it also regulates cancer stem cell self-renewal,” said the study’s lead author, Jenny Chang, M.D., professor of medicine at Baylor College of Medicine.

The impact of using a Notch inhibitor, she said, was to sensitize a significant proportion of otherwise treatment-resistant cancer stem cells, and this supports the notion that a select subpopulation of cells in breast cancer is largely responsible for disease recurrence and cancer spread.

Researchers from Baylor College of Medicine, University of Michigan and Dana-Farber Cancer Institute focused on “mammosphere-forming” human breast cancer cells — cells that have been found to have stem cell properties and are resistant to conventional chemotherapy. These cancer cells can be identified because of their protein signature; they express high levels of CD44, a protein involved in migration, and low or undetectable levels of the cell adhesion protein CD24. Gene analysis of these cells showed that a number of pathways are activated, such as Notch, PI3K and Hedgehog, compared to non-cancerous cells.

In this study, researchers tested gamma-secretase inhibitors in preclinical cancer stem cell models and a complementary clinical trial of a gamma-secretase inhibitor in breast cancer patients. Gamma-secretase is required for activation of the Notch signaling pathway, which regulates self-renewal of stem cells.

The research team implanted human triple-negative breast cancer obtained from patients in two independent sets of mice, and then treated them with a gamma-secretase inhibitor. They isolated the tumors in the mice and found that mammosphere formation was impaired, but tumor volume was not affected.

“Because the cancer stem cell population may be a very small percentage of the tumor cells (0.1 percent to 1 percent), tumor volume measurement is not sensitive enough to measure effects on the cancer stem cell population,” Chang said.

Researchers then studied tumor biopsies taken from a patient with metastatic breast cancer enrolled in a complementary clinical trial of a gamma-secretase inhibitor conducted at Baylor College of Medicine. They looked at biopsies before and during treatment. Findings showed that mammosphere-forming efficiency declined after the first cycle of the agent combined with chemotherapy, and tumor response was seen only after several rounds of therapy.

“The agent reduced the tumorigenic cancer cells,” Chang said. “To eliminate these cells, combination therapy that targets additional pathways regulating cancer stem cells will be essential.”

25. CONFIRM: A Phase III, Randomized, Parallel-Group Trial Comparing Fulvestrant 250 mg vs Fulvestrant 500 mg in Postmenopausal Women with

Estrogen Receptor-Positive Advanced Breast Cancer

Embargoed until 4:00 p.m. CT, Dec. 10, 2009

A higher dose of fulvestrant is well tolerated and more active than the standard, lower dose in postmenopausal patients with advanced breast cancer.

“We believe that, based on the results of this study, treatment and practice should change; patients should receive the 500 mg dose,” said Angelo Di Leo, M.D., Ph.D., director of the Department of Oncology at the Hospital of Prato, Italy.

Fulvestrant, sold under the trade name Faslodex by AstraZeneca, is an estrogen receptor antagonist used for the treatment of metastatic receptor-positive breast cancer in women who have progressed or had recurrent cancer after prior endocrine therapy.

Di Leo and colleagues conducted the CONFIRM study — Comparison of Faslodex In Recurrent or Metastatic breast cancer — to compare the efficacy, response rate, clinical benefit, duration of benefit and response, quality of life and overall survival of the drug at the standard 250 mg per month dose and 500 mg per month dose. Over a two-year period, the researchers recruited 736 women from 128 centers located in 17 countries to participate in this study.

Findings showed that the 500 mg dose of fulvestrant was more active and as well tolerated as the 250 mg dose of fulvestrant, according to Di Leo, who will present further results of this randomized, phase III trial at the CTRC-AACR Annual San Antonio Breast Cancer Symposium, to be held Dec. 9-13, 2009.

The researchers are currently conducting the Trans-CONFIRM study in an effort to understand if the higher dose is mandatory in all patients, or only some.

44. A Double-Blind, Randomized, Placebo-Controlled, Phase 2b Study Evaluating the Efficacy and Safety of Sorafenib in Combination with Paclitaxel as a First-Line Therapy in Patients with Locally Recurrent or Metastatic Breast Cancer

Combining chemotherapy with a drug widely used to treat liver and kidney cancer has offered advanced breast cancer patients with HER2-negative tumors significant improvement in overall response rate and time-to-disease progression, according to new results from an international trial presented at the CTRC-AACR San Antonio Breast Cancer Symposium.

The combination of sorafenib and paclitaxel also demonstrated a favorable trend in progression-free survival, according to lead investigator William Gradishar, M.D., professor of medicine at the Robert H. Lurie Comprehensive Cancer Center at Northwestern University. Data on overall survival are not yet available.

“These data indicate that sorafenib provides added benefit when combined with paclitaxel compared to single agent paclitaxel in the first-line treatment of advanced breast cancer,” Gradishar said.

The study, a double-blind, randomized, placebo-controlled phase IIb study, was conducted in the United States (95 patients), India (170 patients) and Brazil (15 patients). It is the second in a series of four worldwide stage IIb clinical trials testing the use of sorafenib in recurrent or metastatic HER2-negative breast cancer in a program called TIES (Trials to Investigate the Effects of Sorafenib in breast cancer).

The first study to be reported demonstrated a significant progression-free survival benefit in patients with advanced breast cancer who were treated with capecitabine chemotherapy and sorafenib, compared to treatment with capecitabine alone. The other two studies are ongoing.

Sorafenib is an oral agent that has been shown to target members of two classes of kinases involved in cell growth and angiogenesis, the growth of blood vessels to feed tumors. It is approved to treat advanced kidney cancer and liver cancer. Paclitaxel is used to treat a number of different cancers, including both early and advanced breast cancer.

Early research suggested sorafenib may be a promising treatment for breast cancer, and initial clinical studies demonstrated it has a modest activity as a single agent in patients with metastatic disease.

To see if benefit improved when sorafenib was paired with chemotherapy, the researchers randomized 119 patients to the combination therapy and 118 patients to a placebo and paclitaxel.

Results showed median progression-free survival was 6.9 months (combination therapy) vs. 5.6 months (placebo/paclitaxel). Median time-to-progression was 8.1 months vs. 5.6 months for patients receiving sorafenib/paclitaxel compared to placebo/paclitaxel. The overall response rate was 67 percent vs. 54 percent, respectively.

Discontinuation of study treatment due to adverse events occurred in 23 patients in the combination arm compared to five patients in the placebo/paclitaxel arm. With the exception of neuropathy, more grade 3 and 4 toxicities occurred in patients who received sorafenib/paclitaxel. Treatment-related deaths occurred in two patients in the combination treatment arm.

“There were no new toxicities observed with the combination and adverse events were manageable,” Gradishar said.

67. Targeting Aldose Reductase: A Novel Strategy in Treating Endocrine Resistance Using Combination Therapy

Treating estrogen receptor-positive breast cancer tumors with a combination of fidarestat (an inhibitor of aldose reductase enzyme) and letrozole (an aromatase inhibitor) could delay or stop tumor resistance to endocrine therapy, according to data presented at the CTRC-AACR San Antonio Breast Cancer Symposium.

“Single agents are less effective,” said Rajeshwar Rao Tekmal, Ph.D., professor of obstetrics and gynecology at the University of Texas Health Science Center at San Antonio. “Many tumors develop resistance, so this combination approach could prolong that window when endocrine therapy is effective.”

About two-thirds of breast cancer tumors initially are hormone sensitive or estrogen receptor-positive and respond well to endocrine therapy. However, close to half of those tumors develop resistance to endocrine therapy, said Tekmal.

In this preclinical study, researchers treated estrogen receptor-positive tumors already resistant to letrozole with letrozole and fidarestat. As an inhibitor of aldose reductase enzyme, fidarestat blocks the metabolism of glucose in cancer cells.

Together, the combination effectively re-sensitized the cells to letrozole, allowing for effective endocrine therapy and more cell death.

Researchers believe increased glucose metabolism (polyol accumulation) contributes to oxidative stress, which, in turn, could alter intracellular signalling by affecting the regulation of protein kinases that are known to be involved in therapy resistance. Blocking the path of glucose metabolism may help to restore sensitivity to endocrine therapies or it may stop or delay the development resistance endocrine therapies in first place.

While this is a preclinical study, Tekmal believes it could lead to future drug treatments that will make endocrine therapy more effective for longer periods of time.

“This is a very promising study showing that combination treatments seem to work on resistance and re-sensitizing tumors that are resistant to endocrine therapies,” he said.

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The mission of the CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for breast cancer patients. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR) and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor, and the AACR's scientific prestige in basic, translational and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. The 32nd annual symposium is expected to draw more than 8,500 participants from more than 90 countries.

Presenter Name: Jenny Chang, M.D.

Institution: Baylor College of Medicine

Abstract Number: 48

Abstract Title: Targeting Intrinsically-Resistant Breast Cancer Stem Cells with Gamma-Secretase Inhibitors

Abstract Body:

Background: We showed previously that tumorigenic, mammosphere-forming human breast cancer cells characterized by high CD44 and low or undetectable CD24 levels (CD44⁺/CD24^{-/low}) are intrinsically resistant to conventional chemotherapy, and therefore may be responsible for cancer relapse. Our goal is identify novel drugs that selectively target these chemotherapy-resistant, tumor-initiating cells. Gene expression analysis of CD44⁺/CD24^{-/low} cells vs. non-tumorigenic cells implicated the Notch, PI3K, and the Hedgehog signaling pathways in regulating CD44⁺/CD24^{-/low} cells. Thus, Notch, PI3K-AKT, and/or Hedgehog inhibitors may eliminate this unique subpopulation of cancer cells, either alone or in combination with chemotherapy, and could improve patient outcome. To test this hypothesis, we are carrying out a series of preclinical and clinical studies using a gamma-secretase inhibitor (GSI) to target the Notch pathway.

Methods: For preclinical studies, stable xenograft lines were generated by transplantation of human tumor biopsy fragments into immunocompromised mice. Mice with tumors (n = 32, 150-300 mm³) were randomized to four treatment groups: 1) vehicle control, 2) chemotherapy: docetaxel 3) drug: GSI (Merck-003) or 4) combination: docetaxel + Merck-003 During treatment, mice were monitored for tumor volume, body weight, and toxicity. At the end of the treatment cycle, residual tumors were characterized by FACS for the percentage of CD44⁺/CD24^{-/low} cells, as well as for mammosphere-forming efficiency (MSFE) and tumor-initiating capacity. In a complementary clinical trial, breast cancer biopsies taken before and after treatment with GSI (Merck-0752) were characterized for expression of CD44, CD24, and ALDH by FACS and for MSFE.

Results and Conclusions: In preclinical studies using two independent triple negative xenograft lines, Notch pathway inhibition reduced mammosphere formation but did not affect tumor volume, with no consistent change in marker expression by FACS. In patient samples, MSFE also declined after the first cycle of GSI/chemotherapy and remained low after subsequent cycles. This response corresponded with a stasis of metastatic growth during five cycles of treatment, but metastatic burden began to increase coincident with the sixth cycle of treatment. Marker analysis suggests that GSI treatment chemo-sensitizes a significant proportion of the otherwise chemo-resistant CD44⁺/CD24^{-/low} cell population indicating that they are dependent on the Notch pathway for survival. The decrease of MSFE in both preclinical and clinical studies suggests that inhibition of the Notch pathway by GSI may reduce the number of tumorigenic cancer cells that would otherwise remain after chemotherapy.

Presenter Name: Angelo Di Leo, M.D., Ph.D.

Institution: Hospital of Prato

Abstract Number: 25

Abstract Title: CONFIRM: A Phase III, Randomized, Parallel-Group Trial Comparing Fulvestrant 250 mg vs Fulvestrant 500 mg in Postmenopausal Women with Estrogen Receptor-Positive Advanced Breast Cancer

Abstract Body:

Background: Fulvestrant (Faslodex®) is an estrogen-receptor (ER) antagonist with no known agonist effects licensed for the treatment of postmenopausal women with advanced breast cancer who have progressed or recurred following prior endocrine therapy. The efficacy of fulvestrant at the approved dose (AD, 250 mg/month) is well established; however, increasing the dose to 500 mg (high dose, HD: 500 mg i.m. on Day 0, then 500 mg i.m. on Days 14 and 28 and every 28 days thereafter) may further improve clinical outcome. Data from the NEWEST (Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors) study provided the first indication that fulvestrant HD has significantly greater biological activity than AD in the neoadjuvant setting. Further data are required to clarify the clinical role of fulvestrant HD in ER+ advanced breast cancer.

Methods: CONFIRM (COmparisoN of Faslodex In Recurrent or Metastatic breast cancer) is a randomized, double-blind, parallel-group, multicenter, Phase III study (9238IL/0064; NCT00099437) comparing fulvestrant AD with HD in postmenopausal women with ER+ advanced disease recurring or progressing after prior endocrine therapy. Eligible patients were randomized 1:1 to fulvestrant AD or HD. The primary objective was to compare the efficacy of fulvestrant AD and HD in terms of time to progression. Secondary objectives included: objective response rate, clinical benefit rate (complete or partial response or stable disease lasting ≥ 24 weeks), duration of response, duration of clinical benefit (all by RECIST criteria), and overall survival. Safety and tolerability were also assessed. Treatment with fulvestrant continued until disease progression, or until discontinuation for any other reason. All patients were followed up for disease progression and survival, regardless of treatment discontinuation, unless consent was withdrawn.

Results: In total, 736 women were recruited between 8 February, 2005 and 31 August, 2007 from 128 centers in 17 countries.

Discussion: CONFIRM was designed to elucidate any benefit of fulvestrant HD over AD in postmenopausal women. The findings will clarify the role of fulvestrant in the treatment of patients with ER+ advanced breast cancer. Clinical outcomes and safety and tolerability data will be reported.

Presenter Name: William Gradishar, M.D.

Institution: Robert H. Lurie Comprehensive Cancer Center

Abstract Number: 44

Abstract Title: A Double-Blind, Randomized, Placebo-Controlled, Phase 2b Study Evaluating the Efficacy and Safety of Sorafenib in Combination with Paclitaxel as a First-Line Therapy in Patients with Locally Recurrent or Metastatic Breast Cancer

Abstract Body:

Introduction: Sorafenib is a targeted therapeutic agent indicated for advanced renal cell carcinoma and hepatocellular carcinoma. Sorafenib targets multiple kinases involved in tumor growth and angiogenesis. Initial clinical studies with sorafenib have demonstrated modest activity as a single agent in patients with heavily pretreated metastatic breast cancer (BC). We describe the study design and patient accrual of a phase 2b study evaluating the efficacy and safety of sorafenib as part of a first-line regimen for patients with locally recurrent or metastatic BC.

Study Design: This is a multinational, double-blind, randomized, placebo-controlled, phase 2b trial performed in adult patients with HER-2 negative, locally recurrent or metastatic BC. The trial is part of a program of 4 Phase 2b trials investigating the use of sorafenib in advanced BC. Patients must have discontinued adjuvant chemotherapy, hormonal therapy, or radiation therapy within 3 weeks, and taxane therapy within 12 months of randomization. Patients are eligible if they have not received chemotherapy for locally recurrent or metastatic BC. Previous therapy that targets vascular endothelial growth factor (ligand/receptor) is not allowed. Patients are randomized 1:1 to sorafenib (400 mg, orally, twice daily, continuously) or placebo in combination with paclitaxel (90 mg/m² weekly, IV, 3 weeks on/1 week off). Randomization strata are based on site of metastatic disease (visceral vs non-visceral). Patients remain on study treatment until disease progression, unable to tolerate the treatment, or withdraw consent. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival, time to progression, response rate, duration of response, and safety. Quality of life is an exploratory endpoint. The sample size is estimated at 220 patients based on patient accrual projections (14-month duration) and the estimated rate of PFS events (120 events within 21 months). The study is registered at ClinicalTrials.gov (NCT00499525).

Patient Accrual: Enrollment began in January 2008 and has been completed as of January 2009. A total of 237 patients have been randomized. Preliminary efficacy and safety data are expected by Sept. of 2009 and will be presented.

Conclusions: Efficacy and safety data from this phase 2b study will help evaluate a potential role for sorafenib as part of a first-line, multimodal regimen for patients with HER-2 negative, advanced BC, and will determine whether phase 3 studies should be pursued.

Presenter Name: Rajeshwar Rao Tekmal, Ph.D.

Institution: UT Health Science Center at San Antonio

Abstract Number: 67

Abstract Title: Targeting Aldose Reductase: A Novel Strategy in Treating Endocrine Resistance Using Combination Therapy

Abstract Body: Breast cancer is the most commonly diagnosed form of cancer in women. Among breast cancer patients about 2/3 are initially hormone sensitive or estrogen receptor (ER) positive and respond to endocrine therapy. Aromatase inhibitors (AI's) are superior class of hormonal therapeutic agents effectively control ER positive breast cancer in postmenopausal women. Acquired resistance to AI's is expected to be an emerging serious problem in clinics and recent studies have shown that tumors use adaptive signaling mechanisms to overcome AI sensitivity. Thus there is an urgent need for newer treatment modalities. Combination of endocrine and non endocrine agents that block these signaling pathways may prevent or delay the adaptive mechanism and thereby onset of resistance to hormonal therapy. In our study we have found that Fidarestat, an aldose reductase (enzyme which catalyzes the rate limiting step of glucose to fructose or sorbitol formation in polyol pathway) inhibitor effectively re-sensitize letrozole resistant LTLT-Ca breast cancer cells to letrozole. 1 μ M of fidarestat + 1 μ M letrozole was found very effective in inducing maximum cell death in LTLT-Ca cells when compared to fidarestat alone. The combination treatment not only restored ER- α levels but also down regulated HER2/MAPK signaling proteins. Aldose reductase siRNA (100nM)- treated MCF-7/Aro and MCF-7 cells upregulated ER- α in western blot and ER-functionality assays. On the other hand in aldose reductase-siRNA- treated LTLT-Ca cells, ER- α levels were down-regulated as in fidarestat treatment. Pretreatment of LTLT-Ca with fidarestat for one week showed reduced proliferation of cells and the effect was maintained until four passages with 1 μ M letrozole alone. Fidarestat treatment up-regulated E2-mediated transcription in LTLT-Ca cells. In order to enhance the efficacy and targeted delivery of fidarestat in LTLT-Ca cells we have used a nanoparticle-based therapeutic formulation. Folate receptor, highly expressed on epithelial carcinomas, could be a potential molecular target for tumor selective drug delivery. Physico-chemically well characterized Fidarestat-folate nanoparticles (FFNP's) were prepared to increase the tumor selective intracellular delivery. FFNP's were found superior in exerting cytotoxicity when compared to fidarestat alone. Combination therapy was equally effective in controlling LTLT-Ca cell growth using xenograft model. Taken together, the increased glucose metabolism in LTLT-Ca cells may be critically contributing to chemotherapeutic resistance by increasing drug metabolism and decreasing uptake. Hence targeting aldose reductase in endocrine resistance may be attractive alternative to increase the sensitivity of hormonal therapy.