SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio | AACR American Association for Cancer Research | Baylor College of Medicine

December 10-14, 2019

Henry B. Gonzalez Convention Center, San Antonio, Texas, USA

## HOT TOPIC:

# ORAL PACLITAXEL WITH ENCEQUIDAR IMPROVED OVERALL RESPONSE RATE AND REDUCED RATES OF NEUROPATHY AND ALOPECIA COMPARED TO INTRAVENOUS PACLITAXEL IN PATIENTS WITH METASTATIC BREAST CANCER

Oral paclitaxel plus encequidar (OPE) was the first oral taxane to show a significant improvement in overall response rate compared to intravenous (IV) paclitaxel in a phase III trial, according to data presented by Gerardo Umanzor, MD, in a presentation on Friday afternoon.

Paclitaxel is a central component of treatment for metastatic breast cancer. The potential advantages of an oral mode of administration include improved convenience for the patient and the elimination of risks for infusion hypersensitivity reactions and need for prophylactic corticosteroids. However, paclitaxel has low oral bioavailability due to its excretion by the P-glycoprotein pump (P-gp). Encequidar (HM30181A) is a highly specific and potent inhibitor of P-gp that increases absorption of oral paclitaxel. Previously, a phase I pharmacokinetic study showed that the total exposure to paclitaxel was similar between OPE 205 mg/m2 and IV paclitaxel 80 mg/m2, but the peak concentration was lower with OPE, and a phase II study showed a partial response rate of 42% in 26 patients with heavily pretreated metastatic breast cancer who received OPE 205 mg/m2 per day for 3 consecutive days each week.

The phase III trial discussed in this presentation was conducted at 45 sites in South and Central America and randomized patients with metastatic breast cancer in a 2:1 ratio to receive OPE or standard IV paclitaxel. The primary endpoint was blinded, independently reviewed, radiologically confirmed tumor response rate. Key secondary endpoints included safety and tolerability, progression-free survival (PFS), and overall survival (OS). Imaging was performed at baseline and weeks 10, 16, and 19, and patients with a complete or partial response had a confirmatory scan at week 22. The study was powered based on a modified intent-to-treat population that included 360 evaluable patients, and a p-value ≤0.045 for confirmed tumor response rate was considered significant.

Patients were included if they had a diagnosis of metastatic breast cancer and measurable disease at least 1 year removed from their previous taxane therapy (adjuvant or metastatic) and an ECOG score of 0 or 1. The 3 prespecified analysis populations included a modified intent-to-treat (ITT) population that was used for analysis of the primary endpoint (360 patients), a safety population (399 patients), and the intent-to-treat population (402 randomized patients). Patients receiving OPE took the 15-mg tablet of encequidar prior to oral paclitaxel 205 mg/m2 for 3 consecutive days each week. Nine doses of OPE corresponded to one cycle. One cycle of IV paclitaxel corresponded to a 175-mg/m2 infusion over one 3-hour period every 3 weeks.

Baseline patient characteristics of the modified ITT population were similar between treatment arms, with hormone receptor-positive, HER2-negative

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# ISSUE 4 UPDATES

## SATURDAY, DEC 14

### POSTERS WITHDRAWN

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*AT PRESS TIME

disease identified in 56% and approximately 70% of patients naïve to taxane therapy. The majority of patients had visceral disease, and 45% had ≤3 metastatic sites.

In the modified ITT population, OPE significantly improved the centrally confirmed response rate compared to IV paclitaxel (40.4% vs 25.6%, p=0.005). A significant improvement in overall response rate with OPE was also demonstrated in the ITT population, with an absolute improvement of 12.4% (p=0.011). Approximately 34% of patients in the modified ITT population with a confirmed tumor response to OPE had a response >200 days, indicating reasonably durable responses, according to Umanzor.

Data collection for PFS and OS remain ongoing, although a preliminary analysis showed a numerical trend for improved PFS and a significant improvement in overall survival with OPE (27.9 vs 16.9 months, p=0.0353, hazard ratio 0.684).

Analysis of the safety population showed that, compared to IV paclitaxel, OPE was associated with a 4-fold decrease in neuropathy and 50% decrease in complete alopecia. However, OPE was associated with higher rates of low-grade gastrointestinal toxicities, which were reduced in incidence and severity following introduction of nausea prophylaxis (which was initially prohibited in the OPE arm).

Although analysis of data for the PFS and OS endpoints is still ongoing, Dr. Umanzor concluded that the OPE will likely provide an important option for treatment of metastatic breast cancer, saying, "oral paclitaxel and encequidar provides an important oral therapeutic option for patients with metastatic breast cancer, representing a meaningful improvement in the clinical profile of paclitaxel."


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## HOT TOPIC:

### NRG-BR005 TRIAL FINDINGS DO NOT SUPPORT BREAST-CONSERVING TREATMENT WIHTOUT SURGERY

Dr Mark Basik presented findings from a primary analysis of NRG-BR005, a Phase II Trial assessing rhe accuracy of tumor bed biopsies in predicting Pathologic Complete Response (pCR) in patients with Clinical/ Radiological Complete Response after Neoadjuvant Chemotherapy (NCT), in an effort to explore the feasibility of breast-conserving treatment without surgery.

"Patients undergoing neoadjuvant chemotherapy (NAC) have high pCR rates – up to 66.7% with HER2-directed therapy," Dr. Basik pointed out. "and we see very low rates of local recurrence in pCR patients as well -- 7% at 10 years. Women are asking, 'Why do I need surgery when the tumor has disappeared?' The question is, can we define a group who can safely be treated with primary chemo-radiotherapy by developing a tool highly predictive of pCR?" MRI, Dr. Basik pointed out, is insufficient for this purpose. What is the additive value of tumor bed/clip biopsy?

The NRG-BR005 was a Phase II Trial designed to assess the accuracy of post-neoadjuvant systemic therapy (NST) image-directed tumor bed biopsy for pathologic complete response in cases of clinical and radiological near-complete response with tri-modality imaging. Its goal is to assess whether post-NST tumor bed core needle biopsies in addition to clinical examination and tri-modality imaging can identify appropriate patients after NST – patients who are optimal candidates to proceed with radiotherapy treatment without formal breast-conserving surgery (lumpectomy). Selected eligibility for the study included operable invasive ductal carcinoma (T1-T3, stage I/IIIA), completed neoadjuvant chemotherapy, and cCR and rCR or near rCR by tri-modality imaging – either mammography, ultrasound, or MRI. Eligible patients also were required to have a biopsy marker placed within the tumor bed with image confirmation of marker placement.

Study enrollment opened in June of 2017; as of June 2019, 2 of the 105 enrolled patients reported residual disease at surgery (non-pCR), which triggered a temporary accrual suspension for futility analysis. Ultimately, 105 patients enrolled. Four declined a core biopsy, and three had not had biopsy or surgery as of July 21, 2019, leaving 98 evaluable patients. Upon review of all pathology reports, 36 patients had either invasive cancer or ductal carcinoma in situ (DCIS) residual disease, which surpassed the required number of non-pCRs for the primary analysis.

A Negative Predictive Value (NPV) of 90% or greater for the inclusion of biopsy was chosen a priori to support the feasibility of foregoing breast-conserving surgery. Planned accrual was 175 patients, in order to obtain 35 patients who had residual tumor at surgery. In accordance with the two-stage design, one interim analysis was planned for the time when 27 patients failed to achieve pCR at surgery.

The study concluded that the addition of biopsy to the tri-modality imaging package did not achieve an NPV equal to or greater than 90%. Biopsy identified 50% of the patients who had residual disease at surgery. "The findings do not support breast-conserving treatment without surgery based on the study criteria for cCR, rCR/near rCR, and negative tumor bed biopsies," concluded Dr. Basik, but noted that they have just begun to analyze these results. He and the research team suggested further analyses, including central review of tri-modality imaging and assessment of the imaging algorithm with and without the addition of biopsy.

## HOT TOPIC:

# WOMEN'S HEALTH INITATIVE RANDOMIZED CLNICAL TRIALS OUTCOMES INDICATE CONJUGATED EQUINE ESTROGEN ALONE AND CONJUGATED ESTROGEN PLUS MEROXYPROGESTERONE ACETATE HAVE OPPOSITE EFFECTS ON INCIDENCE OF BREAST CANCER

Rowan Chlebowski, MD, presented the long-term findings from the Women's Health Initiative Randomized Clinical Trials examining the effects of Conjugated Equine Estrogen (CEE) alone vs. CEE plus Meroxyprogesterone Acetate (MPA) on the incidence of breast cancer and deaths from breast cancer.

"After a half-century, hormone therapy's influence on breast cancer remains controversial," Dr. Chlebowski said, "with discordant findings from observational studies compared to randomized clinical trials." For instance, he pointed out, a collaborative group meta-analysis of 58 observational studies found that both estrogen plus progestin and estrogen alone significantly increased breast cancer incidence, while the Million Women Study reported both estrogen plus progestin and estrogen alone significantly increased breast cancer mortality. Against this background, the Women's Health Initiative sought to update breast cancer findings from the WHI randomized trials through over 19 years follow-up.

The WHI Hormone Therapy (HT) Randomized Trials was a placebo-controlled double-blind design focusing on postmenopausal women, ages 50-79, with no prior breast cancer and whose mammograms were not suggestive. 10,739 women with prior hysterectomy received .625 mg/d Conjugated Equine Estrogen alone; 16,608 women with no prior hysterectomy received .625 mg/d CEE with 2.5 mg/d medroxyprogesterone acetate (MPA). The primary monitoring outcomes were reduced coronary heart disease for benefit and invasive breast cancer for harm. The study was implemented at 40 US clinical centers, entering postmenopausal women from 1993-1998. An annual mammography protocol was mandated; breast cancers were verified by central medical record and pathology report review, and deaths were verified by central death certificate and medical record review enhanced by 9 serial National Death Index (NDI) queries which capture 98% of US deaths.

Dr. Chlebowski reported the study's conclusions: CEE-alone and CEE plus MPA have opposite effects on breast cancer. CEE-alone significantly decreases breast cancer incidence and deaths from breast cancer, which persist over decades after discontinuing use, while CEE plus MPA significantly increases breast cancer incidence and associated mortality, which persist over a decade after discontinuing use.

"These findings, in conjunction with other hormone therapy effects on clinical outcomes, should inform clinical decision making," he said. A colleague at the presentation pointed out the importance of these findings, calling it a breakthrough in "breast cancer prevention that also improve all-cause mortality."