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To interview Gerardo Antonio Umanzor Funez, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896. For a photo of Umanzor, click here.

Oral Paclitaxel Yielded Better Outcomes Than Intravenous Paclitaxel for Metastatic Breast Cancer Patients in Phase III Trial

SAN ANTONIO — Metastatic breast cancer patients who received an oral formulation of the chemotherapy drug paclitaxel had better response and survival and less neuropathy than patients who received intravenous paclitaxel, according to results of a phase III trial presented at the San Antonio Breast Cancer Symposium, held Dec. 10-14.

Paclitaxel is widely used to treat patients with metastatic breast cancer. It is generally administered intravenously. In this trial, researchers evaluated an oral form of the drug, given in combination with encequidar, a p-glycoprotein pump inhibitor that allows the oral paclitaxel to be absorbed into the bloodstream.

"Oral administration of cancer chemotherapy is very important for cancer patients, especially in areas where patients have difficulty accessing infusion clinics regularly," said the study's lead investigator, Gerardo Antonio Umanzor Funez, MD, medical oncologist with Centro Oncologico Integral, who conducted the study with DEMEDICA of San Pedro Sula, Honduras.

In this trial, researchers enrolled 402 metastatic breast cancer patients. The patients were randomly assigned in a 2:1 ratio to receive either 205mg/m² of oral paclitaxel plus encequidar (Pac+E) for three days a week, or 175mg/ m² paclitaxel intravenously (IV Pac) every three weeks. Their tumors were evaluated for response and confirmed at two consecutive evaluations by a blinded, independent radiology company.

The primary endpoint was radiologically confirmed tumor response rate at two consecutive timepoints; secondary endpoints were progression-free survival (PFS) and overall survival (OS).

Results showed that 35.8 percent of the Pac+E group had a confirmed tumor response, compared with 23.4 percent in the IV Pac group. In evaluating the pre-specified modified intention to treat population, which excludes patients who did not have target tumors that could be evaluated by the central radiologist per RECIST or who did not receive sufficient treatments, the response rate was 40.4 percent for the Pac+E group and 25.6 percent for the IV Pac group.

In measuring the durability of response, the researchers found that in 51 percent of the Pac+E group who had a confirmed response, the response lasted more than 150 days, compared with 38 percent of the IV Pac group who had a response. Furthermore, a higher percentage of Pac+E patients are continuing to receive treatment.

Ongoing analysis of PFS showed a median of 9.3 months for the Pac+E group, compared with 8.3 months for the IV Pac group. OS was 27.9 months for the Pac+E group, compared with 16.9 months for the IV Pac group.

The researchers said the Pac+E group reported higher rates of neutropenia, infection, and gastrointestinal side effects. They reported lower incidence and severity of neuropathy — 17 percent, compared with 57 percent in the IV Pac group. Grade 3 neuropathic symptoms were experienced by 1 percent of the patients in the Pac+E group, versus 8 percent in the IV Pac group.

Updated figures may be provided at SABCS.

“This oral form of paclitaxel provides a new therapeutic option for patients, in particular, for those who cannot easily travel,” Umanzor said. “While blood counts still need to be monitored, oral administration allows patients to remain home during therapy, and avoid spending significant time in the chemotherapy unit.

“We were pleasantly surprised that responses were durable, conferring an early survival advantage with minimal neuropathy,” he continued.

Umanzor said the next step will be testing the tolerability of oral paclitaxel in patients at high risk of developing peripheral neuropathy. The oral formulation may also be studied in other cancers, either as a monotherapy or in combination with other agents.

Umanzor pointed out that while the study’s primary endpoint of confirmed tumor response was evaluated blindly, the study could not be blinded at the clinical site. This may have created bias in the reporting of adverse events, he explained. Also, the study was statistically powered only for confirmed response rate and not for the secondary endpoints.

The study was funded by Athenex, the maker of the oral form of paclitaxel. Umanzor declares no conflicts of interest.

ABSTRACT
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Oral paclitaxel with encequidar: The first orally administered paclitaxel shown to be superior to IV paclitaxel on confirmed response and survival with less neuropathy: A phase III clinical study in metastatic breast cancer

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Intravenous paclitaxel (IV Pac) is an efficacious chemotherapeutic agent against multiple cancers including metastatic breast cancer (mBC). We hypothesized that the high peak concentration with IV Pac may be responsible for peripheral neuropathy. We have developed an orally administered Pac made bioavailable through the combination with the minimally-absorbed Pglycoprotein pump inhibitor encequidar (Pac+E). The pharmacokinetic exposure (AUC) matches that of IV Pac 80 mg/m^2 with peak concentrations that are approximately 1/10 of IV Pac.
Objective: To determine the efficacy and safety profile of oral Pac+E vs IV Pac in patients with mBC.

Patients/Methods: This is a pivotal, Phase 3, open-label, randomized study of oral 205mg/m2 Pac+E for 3 days/week vs IV Pac at the labeled dose of 175mg/m2 q3weeks (NCT02594371). Subjects were randomized 2:1 to Pac+E vs IV Pac. The primary endpoint is radiologically-confirmed tumor response rate (CR and PR) at two consecutive timepoints, 3-6 weeks apart, by study Day 160 using RECIST v1.1 criteria, as assessed by blinded, independent central radiology company (Intrinsic Imaging). Progression-free survival (PFS) and overall survival (OS) were secondary endpoints.
Results: A total of 402 mBC patients were enrolled (Pac+E 265 vs IV Pac 137); demographics were balanced. A similar percentage of subjects in each treatment group received prior taxane therapy (Pac+E, 28%; IV Pac, 31%). For the ITT population, final analysis of the primary endpoint of confirmed tumor response demonstrated a statistically significant difference between treatments; Pac+E 35.8% vs IV Pac 23.4%, a difference of 12.4%, p=0.011, favoring Pac+E. For the protocol defined mITT population (baseline evaluable scans and received first cycle of dosing) the confirmed response rates was 40.4% for Pac+E vs 25.5% for IV Pac (p=0.005). Tumor response in all clinically important subgroups was consistent with the overall confirmed response profiles. Responses were durable. Confirmed responses of >150 days was 51% of responders for Pac+E and 38% of responders for IV Pac. There is a higher percentage of Pac+E subjects receiving ongoing treatment at the time of the study endpoint vs IV Pac subjects: 51 (19%) vs 18 (13%), respectively. Ongoing analysis of PFS shows a strong trend in the protocol prespecified mITT population with a median of 8.5 and 6.9 months (p=0.065) for Pac+E and IV Pac, respectively. Ongoing analysis of OS in the mITT population favors Pac+E (p=0.02) with a median of 27.9 months vs 16.5 months for Pac+E and IV Pac, respectively. The Pac+E group had a lower incidence of alopecia and a lower incidence and severity of neuropathic AEs compared to IV Pac (17% versus 57% respectively to Week 23), with Grade 3 neuropathic symptoms observed in 1% for Pac+E vs 8% for IV Pac. The toxicity profile of Pac+E was generally similar to IV Pac. However higher rates of neutropenia, infection and gastrointestinal AEs were observed in Pac+E group. The risk of serious AEs on both treatments was highest among subjects with pre-treatment evidence of hepatic impairment and the protocol was amended to address this issue.
Conclusion: Oral paclitaxel + encequidar is the first orally administered paclitaxel shown to be superior to IV paclitaxel for confirmed response, progression-free survival, and overall survival, with minimal clinically meaningful neuropathy.

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