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Oral paclitaxel and encequidar in patients with breast cancer: a pharmacokinetic, safety, and antitumor activity study

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Abstract

Background: Paclitaxel is widely used for the treatment of metastatic breast cancer (MBC). However, it has a low oral bioavailability due to gut extrusion caused by P-glycoprotein (P-gp). Oral paclitaxel (oPAC) may be more convenient, less resource-intensive, and more tolerable than its intravenous form. Encequidar (E) is a first-in-class, minimally absorbed, gut-specific oral P-gp inhibitor that facilitates the oral absorption of paclitaxel.

Objectives: To investigate the pharmacokinetics (PK), overall response rate (ORR), and safety of weekly oral paclitaxel with encequidar (oPAC + E) in patients with advanced breast cancer.

Design: This is a multicenter, single-arm, open-label study in six medical centers in Taiwan.

Methods: Patients with advanced breast cancer were administered 205 mg/m^2 oPAC and 12.9 mg E for 3 consecutive days weekly for up to 16 weeks. Plasma samples were collected at weeks 1 and 4. PK, ORR, and safety were evaluated.

Results: In all, 28 patients were enrolled; 27 had MBC; 23 had prior chemotherapy; and 14 had ⩾2 lines of prior chemotherapy. PK were evaluable in 25 patients. Plasma paclitaxel area under the curve $(AUC)_{(0-52\,h)}$ at week 1 (3419 ± 1475 ng h/ml) and week 4 (3224 ± 1150 ng h/ml) were equivalent. Best overall response in 28 evaluable patients was partial response (PR) in 11 (39.3%), 13 (46.4%) stable disease (SD), and 1 (3.6%) with progressive disease (PD). No patient achieved complete response (CR). The clinical benefit rate (CR + PR + SD) was 85.7%. Major adverse events among the 28 treated patients were grade 3 neutropenia (25%), grade 4 neutropenia (18%), with febrile neutropenia in 4%, and grade 3 diarrhea (4%). No treatment-related deaths occurred. Grade 2 peripheral neuropathy occurred in 1 (4%) patient and grade 3 peripheral neuropathy in 1 (4%) patient.

Conclusions: oPAC + E produced a consistent therapeutic plasma paclitaxel exposure during treatment. There was a high rate of radiologically assessed clinical benefit, and a low rate of neurotoxicity which may provide advantages over IV paclitaxel.

Registration: ClinicalTrials.gov Identifier: NCT03165955

Keywords: efficacy, encequidar, HM30181A, oral paclitaxel, P-gp inhibitor, pharmacokinetics, safety

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Introduction

Taxanes, including paclitaxel, are among the most effective and commonly used treatments for metastatic breast cancer (MBC).[1] Taxanes require intravenous (IV) administration in a hospital setting, and neuropathy is a major dose-limiting toxicity.[2] Oral paclitaxel (oPAC) may be more convenient for patients as it would require

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fewer hospital visits, avoid many IV injections, obviate the risk of hypersensitivity reactions to Cremophor EL (CrEL), and remove the need for pre-medication with corticosteroids and antihistamines.[3] Paclitaxel is administered intravenously because it has a low oral bioavailability due to gut extrusion by P-glycoprotein (P-gp).[4] Encequidar (E) is a first-in-class, minimally absorbed, gut-specific oral P-gp inhibitor shown to enhance oral paclitaxel absorption in phase I clinical trials.[5–8] A randomized, crossover pharmacokinetics (PK) study shows that the oral administration of 205 mg/m^2 paclitaxel with E for three consecutive days produces plasma paclitaxel exposure (AUC) similar to single dose IV paclitaxel 80 mg/m^2.[9]

This study evaluated the PK, overall response rate (ORR), and safety of oral paclitaxel with encequidar (oPAC + E) in patients with advanced breast cancer.

Patients and methods

Patients

The major inclusion criteria were as follows: (1) patients with advanced breast cancer for whom IV paclitaxel 80 mg/m^2 weekly monotherapy was recommended by their oncologist; (2) measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; (3) adequate hematologic, hepatic, and renal functions; and (4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The major exclusion criteria were patients who had previously received a taxane as adjuvant therapy and relapsed within 1 year of treatment, or those previously treated with a taxane for metastatic disease.

Study design

This multicenter, single-arm, open-label, phase Ib study was conducted in six medical centers in Taiwan. All patients received oPAC + E (205 mg/m^2 oral paclitaxel with 15 mg encequidar methanesulfonate monohydrate, equivalent to 12.9 mg free base) for 3 consecutive days weekly for up to 16 weeks. Two dose reductions of oPAC (to 165 and 130 mg/m^2) were allowed for treatment-related toxicities. Plasma samples were collected at weeks 1 and 4 to determine paclitaxel concentration. PK, ORR, and safety were assessed. The trial is registered at ClinicalTrials.gov (Identifier: NCT03165955). In Taiwan, the approval number for this trial by Taiwan Food and Drug Administration is 1056018289.

End points

The primary end point was PK, including plasma paclitaxel exposure (AUC) at weeks 1 and 4. Secondary end points were ORR based on the investigator assessment of tumor response, and safety and toxicity.

Assessments

Pharmacokinetics. To measure plasma concentrations of paclitaxel, we collected samples at weeks 1 and 4 on days 1, 2, and 3 (pre-dose, and 1, 2, 3, and 4 h post-dose). In cases of drug toxicity, PK sampling at week 4 was delayed at the discretion of the investigator to allow for patient recovery. In cases of treatment delay, PK sampling after week 4 was immediately performed once treatment resumed. Plasma paclitaxel concentrations were analyzed using a validated liquid chromatography-tandem mass spectrometry method with lower limit of quantification of 24 ng/mL.

Antitumor response. Tumor imaging by computed tomography (CT) or magnetic resonance imaging (MRI) was performed at baseline and every 8 weeks. ORR was reported based on investigator assessments using the RECIST version 1.1[10] and reviewed by an independent central radiology review committee (ICRRC).

Safety. Safety was assessed by recording all adverse events (AEs) and serious adverse events (SAEs), hematology, biochemistry, and urinalysis test results; vital signs values; electrocardiogram (ECG) reading; ECOG performance status; and physical examination findings. AEs and SAEs were reported according to CTCAE 4.03. Adherence/compliance was measured by counting pills returned by patients.

Statistical analysis

Demographics, baseline characteristics, and drug safety were descriptively summarized. PK parameters were calculated using non-compartmental methods to determine the $AUC_{(0–52h)}$, $C_{max(0–24h)}$, $C_{max(24–48h)}$, $C_{max(48–52h)}$, $T_{max(0–24h)}$, $T_{max(48–52h)}$, and C_{trough}. Individual concentrations and the corresponding AUC time point data were tabulated for all participants. The association of

neutropenia with week-1 $AUC_{(0–52h)}$ and C_{max} each as continuous variable was assessed using logistic regression analysis. The geometric mean ratios (GMR) for the $AUC_{(0–52h)}$, C_{max}, $C_{trough(24h)}$, and $C_{trough(48h)}$; their two-sided 90% confidence intervals (CI) were calculated to compare the plasma paclitaxel exposure at weeks 1 and 4. Analysis of variance was performed on log-transformed PK parameters extracting the effects of participant and treatment (dose week). In the four participants who had dose adjustments between weeks 1 and 4, dose normalized parameters were included in the analysis. Equivalence was considered if the 90% CIs of $AUC_{(0–52h)}$, C_{max}, $C_{trough(24h)}$, and $C_{trough(48h)}$ were within 80–125%. Data were analyzed using SAS 6.0 (SAS Institute, Cary, NC, USA).

Results

Patients

In all, 28 patients with advanced breast cancer were enrolled in this study between September 2018 and March 2020. The patient characteristics are shown in Table 1. The mean age was 56.6 years. Among the patients, 27 had metastatic disease; 7 had ⩾3 metastatic sites; and 23 had prior chemotherapy, of which 14 had ⩾2 lines of prior chemotherapy.

Table 1. Patient characteristics ($n = 28$).

Mean age ± SD	**56.6 ± 9.0 (years)**
ECOG score	
0	24 (86%)
1	4 (14%)
Receptor status	
ER+ or PR+	26 (93%)
ER/PR+ and HER2+	6 (21%)
ER/PR+ and HER2–	19 (68%)
Triple negative	2 (7%)
No. of metastatic sites	
0	1 (4%)
1	13 (46%)
2	7 (25%)
⩾3	7 (25%)
Sites of metastasis	
Bone	15
Lung	11
Liver	9
Other sites	10
At least one previous chemotherapy	23 (82%)
No. of prior chemotherapy regimens	
1	9 (32%)
2	6 (21%)
⩾3	8 (29%)
Prior taxane therapy	12 (43%)
Prior hormonal therapy	25 (89%)
Other prior therapies	6 (21%)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SD, standard deviation.

Clinical PK

PK was evaluable in 25 patients who received at least one dose of oPAC + E and had at least one post-treatment PK evaluation at both weeks 1 and 4, or later. Four patients had dose reductions due to neutropenia; their paclitaxel concentrations at week 4 were normalized to full dose. Figure 1 shows the mean (±standard deviation) plasma concentration–time profiles of paclitaxel (dose normalized) at weeks 1 and 4.

The PK parameters of paclitaxel derived from the plasma concentration–time profiles are summarized in Table 2. The paclitaxel PK after oPAC + E administration at week 4 was equivalent to that of week 1; the GMR for the AUC was 97.03 (90% CI: 91.37–103.04), which was within the 80–125% interval that demonstrates equivalence (Table 3). Logistic regression analysis showed that the 11 subjects with grade ⩾3 neutropenia had higher $AUC_{(0–52h)}$ ($p < 0.05$) and Cmax ($p < 0.05$) than subjects with grade ⩽2 neutropenia. The median C_{max} and AUC levels in subjects with grade ⩾3 neutropenia (C_{max} 508 ng/mL, $AUC_{(0–52)}$ 4023 ng h/mL) were approximately double than those observed in subjects with grade ⩽2 neutropenia (C_{max} 248 ng/mL, $AUC_{(0–52)}$ 2382 ng h/mL).

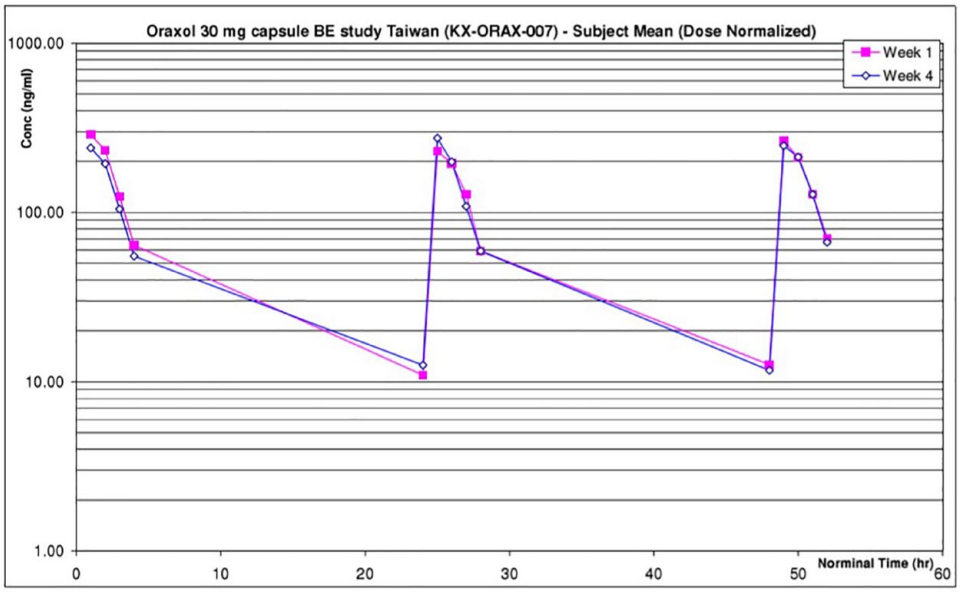

Figure 1. A semi-log scale showing the mean paclitaxel plasma concentration–time profiles at weeks 1 and 4 after oPAC + E treatment ($n = 25$).
oPAC + E, Oraxol.

Efficacy

In all, 28 patients were enrolled in the study. The ORR in the 28 patients was 39.3% (95% CI: 23.6–57.6%) based on the investigator assessment (Table 4). The investigators' ORR was comparable to the ICRRC assessment, ORR = 35.7%, (95% CI: 20.7–54.2%) (Table 4). The clinical benefit rate (CR + PR + SD) was 85.7%. Almost all patients had reduction in tumor size during treatment (Figure 2). When the study finished at 16 weeks, 3/28 patients had PD. The 22/28 patients without PD had the option of continuing treatment in a separate extension study (KX-ORAX-008).

Safety

Safety was evaluable in 28 patients who received at least one dose of oPAC + E. The mean treatment duration was 13 (±3.9) weeks. The mean treatment compliance was 86%, and 61% of the patients received ⩾85% of the intended study treatment dose. Six (21%) patients had a dose reduction of oPAC from 205 to 165 mg/m^2, and four (14%) patients had a second dose reduction to 130 mg/m^2.

In all, 20 patients completed a 16-week treatment period. Eight patients discontinued the treatment. Among these patients, three withdrew their consent; one had recurrent neutropenia after two dose reductions; three had PD. One 79-year-old patient who failed previous hormonal therapy and chemotherapy died 13 weeks after oPAC + E treatment due to disease progression, pneumonia, and septic shock without chemotherapy-induced neutropenia. The investigator considered the cause of death was unrelated to treatment. Eight (29%) patients experienced SAEs, of which three were treatment related (neutropenia). Five patients had non-treatment-related SAEs, including pneumonia and septic shock (fatal), hepatitis, hydropneumothorax, femoral fracture, deep vein thrombosis, and infected breast cancer. The common treatment emergent adverse events (TEAEs) are shown in Table 5. The major treatment-related TEAEs were grade 3 neutropenia (25%), grade 4 neutropenia (18%), febrile neutropenia (4%), and grade 3 diarrhea (4%). Peripheral neuropathy occurred in 6 (21%) patients: grade 1 peripheral neuropathy in 4 (14.3%) patients, grade 2 peripheral neuropathy in 1 (4%) patient, and grade 3 peripheral neuropathy in 1 (4%) patient. No patient died from oPAC + E treatment. No hypersensitivity reactions were observed. Among the TEAEs, a total of 15 (54%) patients experienced at least 1 grade ⩾3 treatment-related AE, including neutropenia in 12 (43%) patients and anemia. The treatment-related AEs are summarized in Table 6.

Table 2. Paclitaxel PK parameters after oral paclitaxel and encequidar administration (dose normalized).

Desscriptive	$AUC_{(0-52\,h)}$ (ng h/mL)		C_{max}[a] (ng/mL)		$C_{trough(24\,h)}$ (ng/mL)		$C_{trough(48\,h)}$ (ng/mL)		$C_{max(0-24\,h)}$ (ng/mL)	
Statistics	**Week 1**	**Week 4**	**Week 1**	**Week 4**	**Week 1**	**Week 4**	**Week 1**	**Week 4**	**Week 1**	**Week 4**
Mean	3419	3224	366	356	11.0	12.5	12.6	11.7	312	267
SD	1475	1150	143	140	4.0	8.7	4.3	3.3	132	135
CV (%)	43	36	39	39	37	70	34	29	42	51
Median	3115	3216	343	328	10.5	10.3	12.6	11.6	274	243
Min	1487	1460	180	157	3.8	4.7	5.0	4.8	147	131
Max	7366	6386	678	698	20.8	48.6	22.3	20.2	649	698
	$C_{max(24-48\,h)}$ (ng/mL)		$C_{max(48-52\,h)}$ (ng/mL)		$T_{max(0-24\,h)}$ (h)		$T_{max(24-48\,h)}$ (h)		$T_{max(48-52\,h)}$ (h)	
	Week 1	**Week 4**	**Week 1**	**Week 4**	**Week 1**	**Week 4**	**Week 1**	**Week 4**	**Week 1**	**Week 4**
Mean	274	298	287	288	–	–	–	–	–	–
SD	144	127	144	144	–	–	–	–	–	–
CV (%)	53	43	50	50	–	–	–	–	–	–
Median	226	292	261	214	1.05	1.07	25.03	25.00	49.02	49.03
Min	99	132	126	127	0.97	0.93	24.47	22.78	48.22	47.05
Max	571	536	678	654	2.12	3.02	27.03	27.33	51.03	51.05

In cases of dose reduction, PK parameters were generated with paclitaxel plasma concentrations normalized to 205 mg/m^2 by assuming dose proportionality. Last sampling time point was 52 h post first-dose (4 h post third dose). Data are shown as mean (Sd) for except T_{max}, which is shown as median (min-max).
$AUC_{(0-52\,h)}$ = area under the concentration × time curve from time zero to the time of the last measurable concentration at 52 h post first-dose; C_{max} = maximum drug concentration; T_{max} = time to reach maximum (peak) concentration after drug administration.
CV, coefficient of variation; max, maximum; min, minimum; PK, pharmacokinetics; SD, standard deviation.
[a]Highest concentration of the 3-day profile week 4 = week 4 or later.

Table 3. Paclitaxel PK analysis after oral paclitaxel and encequidar administration at week 4 *versus* week 1 (dose normalized).[a].

PK Parameter	GMR[a] (%)	90% CI	Intra-subject CV (%)
$AUC_{(0-52\,h)}$	97.03	91.37, 103.04	12.47
C_{max}	97.04	86.92, 108.32	23.05
$C_{trough(24\,h)}$	106.02	91.54, 122.77	31.04
$C_{trough(48\,h)}$	94.72	86.90, 103.25	17.98

In cases of dose reduction, PK parameters were generated with paclitaxel plasma concentrations normalized to 205 mg/m^2 by assuming dose proportionality.
[a]Week 1 dataset as the reference object and week 4 dataset as the test object.
week 4 = week 4 or later.
$AUC_{(0-52\,h)}$ = area under the concentration × time curve from time zero to the time of the last measurable concentration at 52 h post first-dose; C_{max} = maximum drug concentration; CV, coefficient of variation; CI, confidence interval; GMR, geometric metric mean ratio; PK, pharmacokinetics.

Table 4. Best overall response.

	Investigator assessment (*n* = 28)	ICRRC assessment (*n* = 28)
CR	0	0
PR	11 (39.3%)	10 (35.7%)
SD	13 (46.4%)	12 (42.9%)
PD	1 (3.6%)	3 (10.7%)
NE*	3(10.7%)	3 (10.7%)

*NE, not evaluable (two patients had no repeat CT scans after baseline, one patient did not have repeat CT scan after SD, one patient's target lesion was not measurable by ICRRC).
CR, complete response; ICRRC, independent central radiology review committee; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

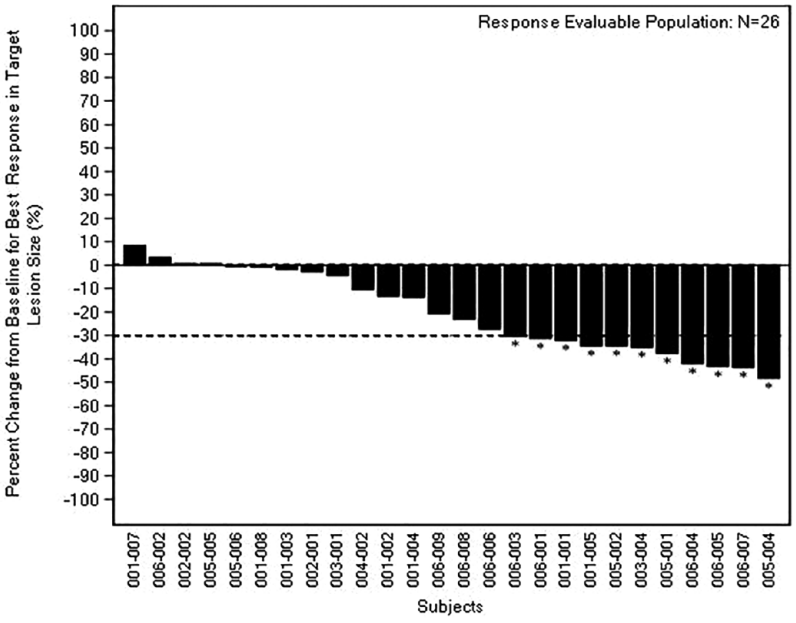

Figure 2. A waterfall plot showing the change in tumor size after oPAC + E treatment.

Discussion

Taxanes, including paclitaxel, are cornerstones in the management of MBC.[1] Paclitaxel is administered intravenously because it has a low oral bioavailability due to gut extrusion by P-gp.[4] Encequidar is a first-in-class, minimally absorbed, gut-specific oral P-gp inhibitor that enables the oral absorption of paclitaxel.[5] A randomized crossover PK study showed that 205 mg/m^2 oPAC with E once daily for 3 days produces a systemic paclitaxel exposure similar to that of 80 mg/m^2 paclitaxel IV infused over 1 h.[9]

This study showed that weekly oPAC + E can achieve therapeutic plasma paclitaxel exposure (AUC) comparable to weekly IV paclitaxel studies reported previously.[9,11] The results of this study showed that paclitaxel PK exposure at week 4 was comparable to that seen in week 1, following weekly treatment with oPAC + E, indicating that weekly administration of oPAC + E can achieve therapeutic plasma paclitaxel exposure (AUC) comparable to weekly IV paclitaxel previously reported.[9,11] This finding is important when considering long-term safety and efficacy of continued oPAC + E treatment of cancer patients. These data also imply that that there is no P-gp induction with long-term oPAC + E therapy.

IV paclitaxel is insoluble and formulated with CrEL, which can cause hypersensitivity reactions. Premedication with corticosteroids and antihistamines in the hospital setting is required to prevent these effects. However, despite the pre-medications, life-threatening hypersensitivity reactions still occur in 2–3% of patients.[12] oPAC + E does not contain IV CrEL and no hypersensitivity reactions were observed in this study and no premedications were required. The lack of hypersensitivity reactions is reassuring, and suggests that oPAC + E can safely be administered at home rather than in a hospital setting.

Neuropathy is a major dose-limiting side effect of IV paclitaxel which may be persistent and significantly affect the quality of life of patients.[2,13] Neuropathy may be mediated by the solvent CrEL in IV paclitaxel or high blood concentration of paclitaxel. However, oPAC + E does not require IV CrEL. The peak paclitaxel plasma concentration of oPAC + E is approximately 15% that of IV paclitaxel.[9] Peripheral neuropathy of 21% (4% grade 2 peripheral neuropathy, 4% grade 3 peripheral neuropathy) observed with oPAC + E in this study appear much less than the 50% reported with weekly IV paclitaxel (grades 2 and 3 sensory neuropathy of 21% and 12%, and grade 2 and 3 motor neuropathy of 8% and 9%, respectively).[13] Reducing the frequency and severity of chemotherapy-induced neuropathy improves patient tolerability and quality of life may facilitate a longer duration of treatment and give opportunity to prolong clinical responses. Avoiding persistent neuropathy is especially important in neo-adjuvant and adjuvant therapy, where it is important to avoid permanent toxicity that impacts on quality of life. In the I-SPY 2 clinical trial, the combination of oPAC + E and

Table 5. Treatment emergent adverse events (TEAE) ⩾ 10%.

SOC preferred term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total ($n = 28$)
Patients with at least one TEAEs	1 (4%)	7 (25%)	12 (43%)	6 (21%)	1 (4%)	27 (96%)
Gastrointestinal disorders	13 (46%)	8 (29%)	1 (4%)	0	0	22 (79%)
Diarrhea	10 (36%)	5 (18%)	1 (4%)	0	0	16 (57%)
Nausea	9 (32%)	0	0	0	0	9 (32%)
Vomiting	4 (14%)	0	0	0	0	4 (14%)
Hemorrhoids	3 (11%)	0	0	0	0	3 (11%)
Blood and lymphatic system disorders	2 (7%)	6 (21%)	7 (25%)	5 (18%)	0	20 (71%)
Neutropenia	2 (7%)	5 (18%)	7 (25%)	5 (18%)	0	19 (68%)
Anemia	2 (7%)	2 (7%)	2 (7%)	0	0	6 (21%)
Leukopenia	0	0	3 (11%)	0	0	3 (11%)
Skin and subcutaneous tissue disorders	7 (25%)	10 (36%)	0	0	0	17 (61%)
Alopecia	4 (14%)	8 (29%)	0	0	0	12 (43%)
Nervous system disorders	7 (25%)	2 (7%)	1 (4%)	0	0	10 (36%)
Peripheral neuropathy	4 (15%)	1 (4%)	1 (4%)	0	0	6 (21%)
Investigation	1 (4%)	6 (21%)	3 (11%)	0	0	10 (36%)
Increased alanine aminotransferase	1 (4%)	3 (11%)	1 (4%)	0	0	5 (18%)
Increased aspartate aminotransferase	1 (4%)	3 (11%)	1 (4%)	0	0	5 (18%)
Metabolism and nutrition disorders	3 (11%)	2 (7%)	1 (4%)	1 (4%)	0	7 (25%)
Decreased appetite	2 (7%)	1 (4%)	1 (4%)	0	0	4 (14%)

If a subject experienced more than one episode of an AE, the subject was counted only once within a preferred term. If a subject experienced more than one AE within a SOC, the subject was counted once for each preferred term and once for the SOC.
AE, adverse event; SOC, System Organ Class.

dostarlimab, with or without carboplatin or trastuzumab, is being investigated as neoadjuvant therapy for breast cancer (ClinicalTrial.gov Identifier: NCT01042379). The study results appear encouraging and is expected to be available in the near future.

In this study, oPAC + E achieved a confirmed response rate of 39.3% and clinical benefit rate of 85.7% which are encouraging because most of the patients had received prior chemotherapy, and 50% of the patients had received ⩾2 lines of prior chemotherapy. However, efficacy was not the primary end point of this study, the sample size was relatively small and the follow-up time was short, but clinically meaningful objective responses were observed. The ORR in this study was confirmed in a phase III clinical trial of oPAC + E *versus* IV paclitaxel Q3W in the treatment of MBC, with a ORR of 35.8% for oPAC + E *versus* 23% for IV paclitaxel ($p = 0.01$).[14]

The response to paclitaxel has been shown to be related to the duration of paclitaxel exposure over a threshold level of 0.05 μM ($T > 0.05\,\mu M$).[15,16] Population PK model simulations indicate that the paclitaxel AUC was similar between oPAC + E and IV paclitaxel dosing regimens but the duration of paclitaxel exposure ($T > 0.05\,\mu M$) is twice as long with oPAC + E compared to IV paclitaxel.[11]

Table 6. Treatment-related adverse events (AEs) ⩾ 10%.

SOC preferred term	Total ($n = 28$)
Patients with at least one treatment-related AEs	27 (96%)
Gastrointestinal disorders	19 (68%)
Diarrhea	14 (50%)
Nausea	9 (32%)
Vomiting	4 (14%)
Blood and lymphatic system disorders	20 (71%)
Neutropenia	12 (43%)
Anemia	2 (7%)
Skin and subcutaneous tissue disorders	14 (50%)
Alopecia	12 (43%)
Nervous system disorders	8 (29%)
Peripheral neuropathy	4 (14%)
Investigation	10 (36%)
Increased alanine aminotransferase	5 (18%)
Increased aspartate aminotransferase	5 (18%)
Metabolism and nutrition disorders	3 (11%)
Decreased appetite	3 (11%)

If a subject experienced more than one episode of an AE, the subject was counted only once within a preferred term. If a subject experienced more than one AE within a SOC, the subject was counted once for each preferred term and once for the SOC.
AE, adverse event; SOC, System Organ Class.

This may explain the good response observed in this study and the phase III clinical trial.[14]

The most frequent toxicity of oPAC + E in this study was grade 3/4 neutropenia, and is higher than that reported in other studies of IV paclitaxel.[11] However, the high rate of grade 3/4 neutropenia did not translate into high rates of febrile neutropenia, with only one patient experiencing febrile neutropenia, and no treatment-related deaths were observed. This is reassuring, especially in this population where patients were heavily pre-treated. The mechanism of increased neutropenia after oPAC + E treatment may be related to the prolonged plasma paclitaxel exposure. Neutropenia following IV paclitaxel therapy is associated with the duration of paclitaxel exposure over a threshold level of 0.05 μM ($T > 0.05$ μM).[15–17] As highlighted above, the duration of exposure ($T > 0.05$ μM) is twice as long with oPAC+E compared to IV paclitaxel.[11] As well as explaining the higher response rate, these data may explain the increase in neutropenia of oPAC + E observed.[14]

Conclusions

Weekly oPAC + E enabled paclitaxel to be administered orally. The combination treatment achieved a therapeutic systemic paclitaxel exposure with a high rate of response in patients with MBC. The systemic paclitaxel PK exposure did not change during the course of treatment consistent with continued and consistent inhibition of p-glycoprotein. oPAC + E showed a toxicity profile with some advantages over IV paclitaxel. Peripheral neuropathy, a dose-limiting toxicity of taxane therapy, was less frequent and severe than reported with IV treatment. Hypersensitivity reactions were not observed; prophylaxis for hypersensitivity reactions with antihistamines and corticosteroids was not required. Neutropenia was higher but manageable without treatment-related deaths, and febrile neutropenia was rare. The use of oPAC + E as an emerging cancer treatment and alternative to IV paclitaxel warrants further investigation.

Declarations

Ethics approval and consent to participate

The Institutional Review Board (IRB) of study participating hospitals approved the protocol and informed consent form (ICF). ICF was agreed by and obtained from all patients prior to participation. The IRB names of the participating hospitals and their ethical approval numbers/IDs are Taipei Medical University-Joint IRB (No. N201609012), China Medical University Hospital Research Ethics Committee (No. CMUH105-REC1-082), Research Ethics Committee of National Taiwan University Hospital (No. 201601054MSB), Taipei Veterans General Hospital IRB (No. 2016-10-001AU), and Tri-Service General Hospital IRB (No. 1-105-01-013).

Consent for publication

Not applicable.

Author contributions

Ming-Shen Dai: Conceptualization; Data curation; Formal analysis; Investigation; Methodology;

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Competing interests

M-SD, T-CC, C-FC, Y-SL, H-SS, C-GJ, NH, and T-YC declare that they have no conflict of interest. JZ, DLC, RD, DK, and W-KC work for Athenex Inc. AQ works and K-CT worked for PharmaEssentia Corporation. HT works for Zenith Technology.

Availability of data and materials

Data and materials will be available to external researchers who have been approved by Athenex, Inc., and PharmaEssentia Corporation, depending on the nature of the request, merit of the research proposed, data availability, and intended use of the data.

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References

1. Gradishar WJ. Taxanes for the treatment of metastatic breast cancer. *Breast Cancer (Auckl)* 2012; 6: 159–171.
2. Rivera E and Cianfrocca M. Overview of neuropathy associated with taxanes for the treatment of metastatic breast cancer. *Cancer Chemother Pharmacol* 2015; 75: 659–670.
3. Eek D, Krohe M, Mazar I, *et al.* Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a

review of the literature. *Patient Prefer Adher* 2016; 10: 1609–1621.

4. Sparreboom A, van Asperen J, Mayer U, *et al.* Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. *Proc Natl Acad Sci USA* 1997; 94: 2031–2035.
5. Smolinski MP, Urgaonkar S, Pitzonka L, *et al.* Discovery of encequidar, first-in-class intestine specific P-glycoprotein inhibitor. *J Med Chem* 2021; 64: 3677–3693.
6. Kim JC, Kim KS, Kim DS, *et al.* Effect of HM30181 mesylate salt-loaded microcapsules on the oral absorption of paclitaxel as a novel P-glycoprotein inhibitor. *Int J Pharm* 2016; 506: 93–101.
7. Kwak JO, Lee SH, Lee GS, *et al.* Selective inhibition of MDR1 (ABCB1) by HM30181 increases oral bioavailability and therapeutic efficacy of paclitaxel. *Eur J Pharmacol* 2010; 627: 92–98.
8. Lee HJ, Heo DS, Cho JY, *et al.* A phase I study of oral paclitaxel with a novel P-glycoprotein inhibitor, HM30181A, in patients with advanced solid cancer. *Cancer Res Treat* 2014; 46: 234–242.
9. Jackson CGCA, Hung T, Segelov E, *et al.* Oral paclitaxel with encequidar compared to intravenous paclitaxel in patients with advanced cancer: a randomised crossover pharmacokinetic study. *Br J Clin Pharmacol* 2021; 87: 4670–4680.
10. Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer (version 1.1)* 2009; 45: 228–247.
11. He J, Jackson CGCA, Deva S, *et al.* Population pharmacokinetics for oral paclitaxel in patients with advanced/metastatic solid tumors. *CPT Pharmacom Syst Pharmacol* 2022; 11: 867–879.
12. Gelderblom H, Verweij J, Nooter K, *et al.* Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. *Eur J Cancer* 2001; 37: 1590–1598.
13. Seidman AD, Berry D, Cirrincione C, *et al.* Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008; 26: 1642–1649.
14. Rugo HS, Umanzor GA, Barrios FJ, *et al.* Open-label, randomized, multicenter, Phase III study comparing oral paclitaxel plus encequidar versus intravenous paclitaxel in patients with metastatic breast cancer. *J Clin Oncol* 2023; 41:65–74.
15. Joerger M, Huitema ADR, Richel DJ, *et al.* Population pharmacokinetics and pharmacodynamics of paclitaxel and carboplatin in ovarian cancer patients: a study by the European Organization for Research and Treatment of Cancer-Pharmacology and molecular mechanisms group and new drug development group. *Clin Cancer Res* 2007; 13: 6410–6418.
16. Mielke S, Sparreboom A, Behringer D, *et al.* Paclitaxel pharmacokinetics and response to chemotherapy in patients with advanced cancer treated with a weekly regimen. *Anticancer Res* 2005; 25: 4423–4427.
17. Gianni L, Kearns CM, Giani A, *et al.* Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. *J Clin Oncol* 1995; 13: 180–190.

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