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Oral Paclitaxel and Encequidar (oPac+E) in the Treatment of Metastatic Breast Cancer (mBC): Management of gastrointestinal adverse events (GI AE). Study KX-ORAX-001. (Abstract PS13-11).

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Background

- Paclitaxel has poor oral bioavailability due to excretion by gastrointestinal p-glycoprotein.
- Encequidar (E) is a potent specific minimally absorbed p-glycoprotein inhibitor which enables absorption of oral paclitaxel (oPac).
- oPac+E is a combination of paclitaxel liquid-filled capsules and an encequidar tablet.
- Systemic exposure (AUC) of oPac+E 205mg/m^2/day x 3 is equivalent to IV paclitaxel (IVPac) 80mg/m^2.
- Peak concentrations (Cmax) is 1/7th of IVPac.
- The combination, oPac+E does not contain Cremophor.
- Corticosteroid and antihistamine premedication are not required for prophylaxis of hypersensitivity reactions.
- oPac +E is administered at home, minimizing clinic visits.
- Results of the pivotal phase III trial, KX-ORAX-001, including the final analysis of confirmed tumor response rate, and early PFS and OS data were presented at SABCS, 2019, Abstract # GS6-01.
- At the final analysis for the primary endpoint, the confirmed tumor response rate was significantly higher in the oPac+E group vs IVPac (35.8% vs 23.4%, p=0.011 ITT, population).

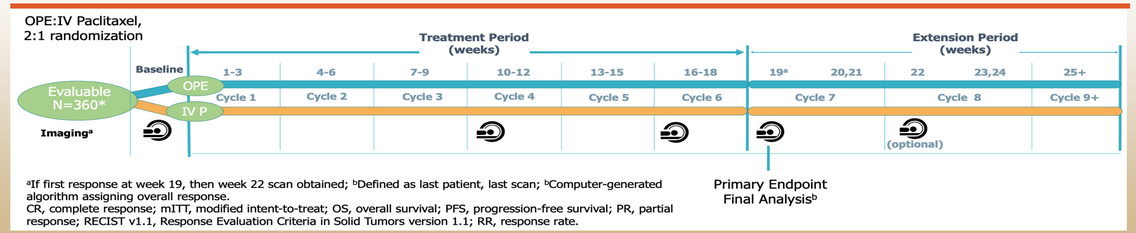
Baseline Characteristics in KX ORAX-001 (ITT Population)

402 patients were enrolled of which 399 received treatment.

	Treatment	
	IVPac N=137	oPac+E N=265
Age (Years)		
Mean (SD)	55.8 (11.51)	58.1 (11.99)
Median	56.0	60.0
Min, Max	27, 85	30, 90
Race, n (%)		
Black	2 (1)	4 (2)
Caucasian	10 (7)	22 (8)
Hispanic/Latino	123 (90)	236 (89)
Other	2 (1)	3 (1)
Baseline ECOG, n (%)		
0	79 (58)	159 (60)
1	58 (42)	106 (40)

Study Design

- Randomized, multinational study in women with metastatic breast cancer (mBC).
- Patients were randomized 2:1 to receive oPac+E (205mg/m^2/day x3 weekly) or IVPac 175 mg/m^2 every three weeks.
- Treatment continued until progressive disease or toxicity.
- Patients randomized to IVPac received prophylactic high dose corticosteroids and antihistamines both of which have significant anti-emetogenic effects.
- Patients randomized to oPac+E were not to receive prophylactic premedication or antiemetics.
- The protocol was amended after enrollment of approximately 111 patients were randomized to allow prophylactic antiemetics.
- Additionally, in the amendment patients were instructed to have loperamide at home and were to initiate antidiarrheal medication at the onset of diarrhea.

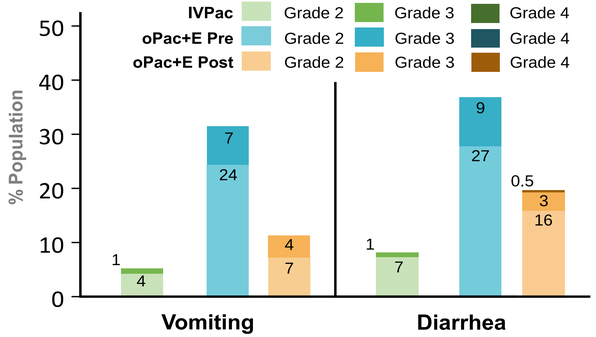


[a]If first response at week 19, then week 22 scan obtained; [b]Defined as last patient, last scan; [c]Computer-generated algorithm assigning overall response.
CR, complete response; mITT, modified intent-to-treat; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RR, response rate.

Results

- Prophylactic antiemetic therapy and early use of loperamide markedly decreased the incidence of ≥Grade 2 vomiting and diarrhea although there was a greater incidence than IVPac.
- The incidence of severe nausea, vomiting, or diarrhea was less than 1% before or after the amendment.
- Dose reductions in the oPac+E patients for nausea, vomiting, or diarrhea were few before (2.8%) and after (2.6%) the protocol amendment.

Incidence of Vomiting & Diarrhea IVPac Vs. oPac+E Pre and Post Protocol Amendment



	IVPac (N=135)			oPac+E Pre-Amendment (N=75)			oPac+E Post Amendment (N=189)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Vomiting	4%	1%	0%	24%	7%	0%	7%	4%	0%
Diarrhea	7%	1%	0%	27%	9%	0%	16%	3%	0.5%

The Most Frequently Prescribed Antiemetic Agents

IVPac	oPac+E
• ondanesteron (59%) • granisetron (24%) • palenosetron (7%) • aprepitant (2%)	• ondansetron (54%) • metoclopramide (21%) • domperidone (4%) • aprepitant (3%)

Oral administration of the NK1 inhibitor aprepitant to patients receiving oPac+E appeared to be associated with increased incidence of paclitaxel toxicity, potentially due to inhibition of metabolism of oPac.

Conclusions

- oPac+E was associated with greater efficacy in the treatment of mBC and lower rates and severity of peripheral neuropathy (SABCS, 2019, Abstract # GS6-01).
- Gastrointestinal adverse events were more frequent in oPac+E compared to IVPac.
- GI AE in oPac+E treated patients were managed by prophylactic use of antiemetics, primarily 5-HT$_3$ inhibitors and early intervention with the anti-diarrhea agent loperamide.
- Vomiting or diarrhea necessitating hospitalization or dose reduction was infrequent.
- Due to potential PK interaction, the use of the oral NK1 inhibitor aprepitant with oPac+E is not recommended.

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