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Pharmacology Updates

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Disclosures

- None

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Objectives

- Review data on the use of oral paclitaxel with encequidar in patients with metastatic breast cancer
- Identify the potential role of oral paclitaxel with encequidar as well as clinical considerations
- Discuss the mechanism of action of tucatinib and compare to currently approved small molecular tyrosine kinase inhibitors used in breast cancer

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San Antonio Breast Cancer Symposium®, December 10-14, 2019

Oral paclitaxel with encequidar (OPE): 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

Umanzor G[1], Rugo HS[2], Barrios FJ[3], Vasallo RH[4], Chivalan MA[5], Bejarano S[6], Ramirez JR[7], Fein L[8], Kowalyszyn RD[9], Cutler DL[10], Kramer D[10], Goldfinch J[10], Wang H[10], Moore T[10], Kwan RMF[10]

1. Liga Contra el Cancer, Honduras; 2. University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 3. Instituto Nacional de Cancerologia (INCAN), Guatemala City, Guatemala; 4. Clinical Research RD, Santo Domingo, Dominican Republic; 5. CELAN Clinica Medica, Guatemala City, Guatemala; 6. Excel Medica, San Pedro Sula, Honduras; 7. CRESEM, Quetzaltenango, Guatemala; 8. Instituto de Oncologia de Rosario, Rosario, Argentina; 9. Centro de Investigaciones Clinica, Clinica Viedma, Argentina; 10. Athenex Inc., Buffalo, NY, USA

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Metastatic Breast Cancer and Paclitaxel

- Taxanes remain a foundation of breast cancer treatment[1]
  - IV Paclitaxel FDA-approved schedule for mBC[2,3]: 175 mg/m^2 Q 3 weeks
  - IV Paclitaxel US clinical practice[3]: 80 mg/m^2 IV Q week (varies by site, Q 3-4 weeks)
- Benefits of an oral mode of administration include patient convenience, home treatment, lack of IV access, removal of the risk of infusion hypersensitivity reactions and the need for prophylactic corticosteroids[4,5]
- Paclitaxel is not orally absorbed because it is excreted by the P-glycoprotein (P-gp) pump[6]
- Encequidar (HM30181A) is a highly specific, potent inhibitor of P-gp and increases the absorption of oral paclitaxel[7]
- Oral paclitaxel and encequidar (OPE) is composed of 30 mg capsules of solubilized paclitaxel and a 15 mg tablet of encequidar

1. Gradishar WJ. *Breast Cancer (Auckl)*. 2012;6:159-171; 2. Taxol [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011; 3. NCCN 2019 Guidelines, https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf accessed on November 25, 2019; 4. Liu G, et al. *J Clin Oncol*. 1997;15(1):110-115; 5. Eek D, et al. *Patient Prefer Adherence*. 2016;10:1609-1621; 6. Jang SH, et al. *J Pharmacol Exp Ther*. 2001;298(3):1236-1242; 7. Kwak JO, et al. *Eur J Pharmacol*. 2010;627(1-3):92-98.

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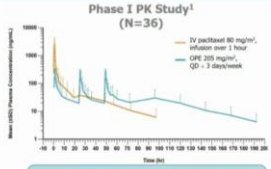
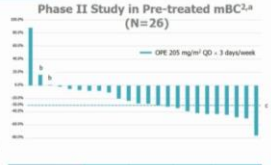
Dose Justification for OPE

Phase I PK Study[1] (N=36)



- AUC was comparable[1]: OPE 205 mg/m^2 QD × 3 versus IV paclitaxel 80 mg/m^2 × 1
- OPE peak concentration ~1/7 of IV paclitaxel

Phase II Study in Pre-treated mBC[2,a] (N=26)



Best Tumor Response	Complete Response	Partial Response	Stable Disease	Disease Progression
% Population (N=26)	0	42.3	46.2	11.5

[a]Median=2 lines of therapy; [b]Patient had a new lesion; [c]30% is clinically meaningful.
AUC, area under the curve; mBC, metastatic breast cancer; PK, pharmacokinetic; QD, once daily.
1. Jackson C, et al. ESMO, Barcelona, Spain, 2019, 477-P; 2. Dai MS, et al. ASCO, Chicago, IL, USA, 2019, 1084-P.

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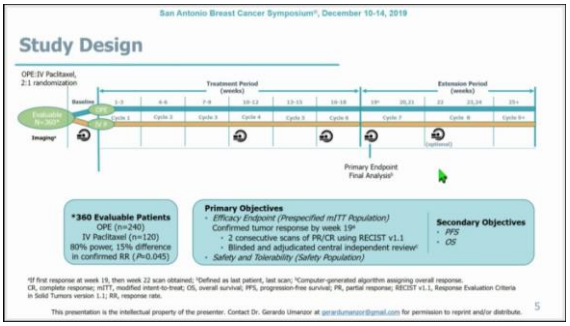

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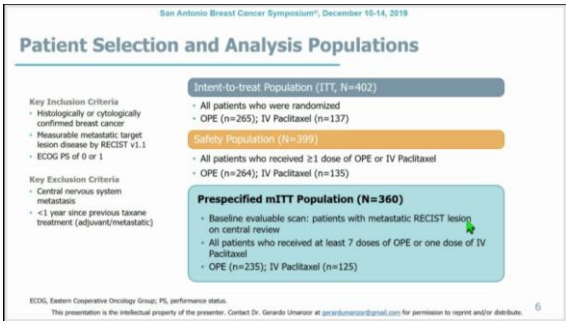

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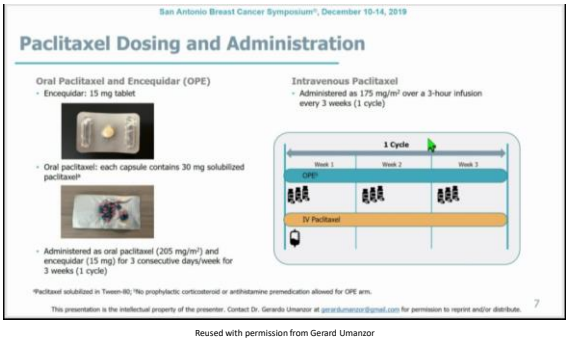

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Baseline Patient Characteristics and Demographics: Prespecified mITT Population (N=360)

Patient Characteristics		OPE (n=235)	IV Paclitaxel (n=125)
Age, years, mean (range)		57.2 (30-90)	55.7 (32-85)
Age category ≥65, %		26	25
Race/ethnicity, %	Hispanic/Latino	88	90
	Other[a]	12	10
ECOG status, %	PS 0	59	59
	PS 1	41	41
Hormone receptor status[b], %	HR positive/HER2 negative	56	49
	HR positive/HER2 positive	9	8
	Triple negative	8	15
	HR and HER2 unknown[c]	17	21

[a]Black, Caucasian, other; [b]In addition, approximately 5% for each HR positive/HER2 unknown and other; [c]Data unavailable or missing.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

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Prior Therapies and Metastatic Disease in Prespecified mITT Population

Prior Therapy Exposure		OPE (n=235)	IV Paclitaxel (n=125)
Number of prior chemotherapies in metastatic setting, %	Any	26	28
	1	14	16
	2	7	8
	≥3	4	6
Prior taxane exposure (any setting), %		29	30
Prior anthracycline exposure (any setting), %		56	55

Metastatic Disease		OPE (n=235)	IV Paclitaxel (n=125)
Number of metastatic sites, %	1	17	20
	2	37	36
	≥3	46	44
Visceral metastases, %	All[a]	75	78
	Liver	39	41
	Lung	58	52
Lymph node involvement, %		69	66

[a]Liver, lung, pleura, heart, pancreas, adrenal, brain, bowel, ovaries, bladder; bone metastases, n (%): OPE, 1 (<1); IV paclitaxel, 0 (0).

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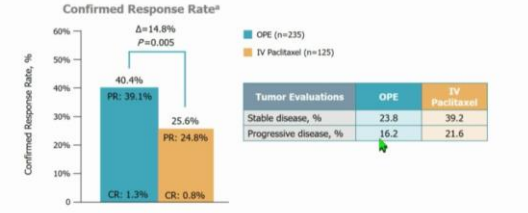
Primary Endpoint in Prespecified mITT Population (Final Analysis): OPE Increased Confirmed RR Compared to IV Paclitaxel



Tumor Evaluations	OPE	IV Paclitaxel
Stable disease, %	23.8	39.2
Progressive disease, %	16.2	21.6

[a]ITT analysis of the primary endpoint is also significant.

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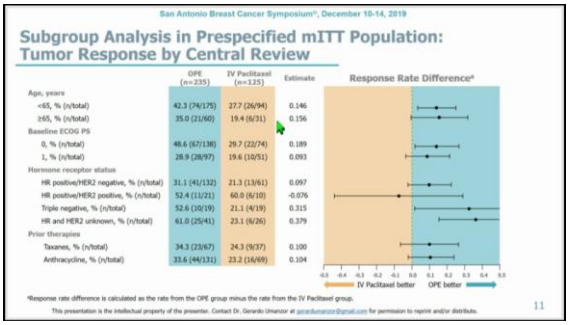

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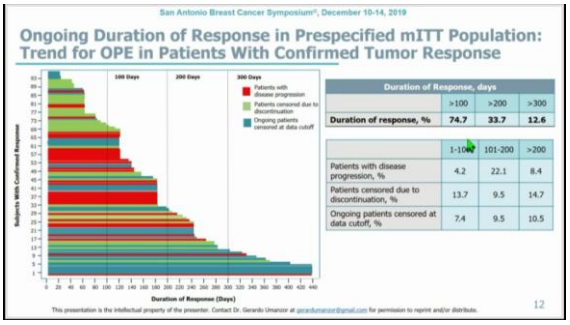

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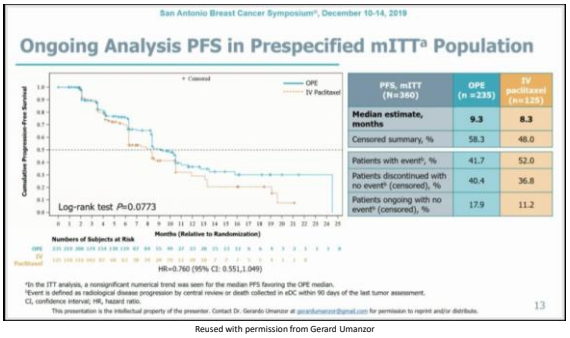

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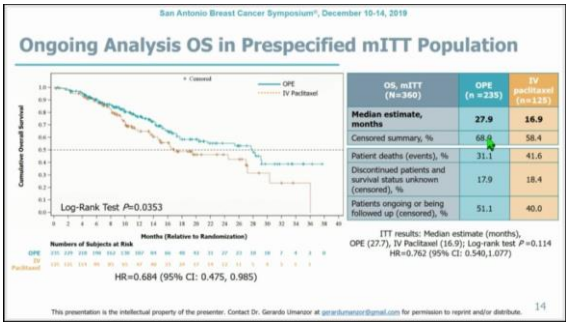

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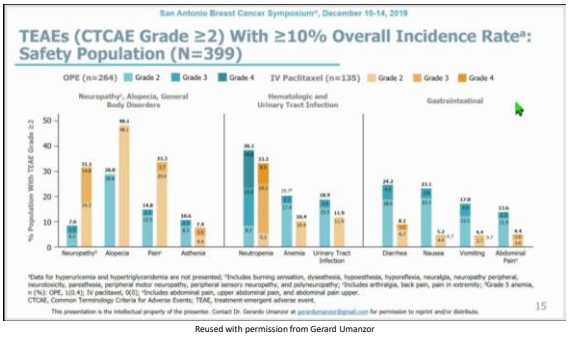

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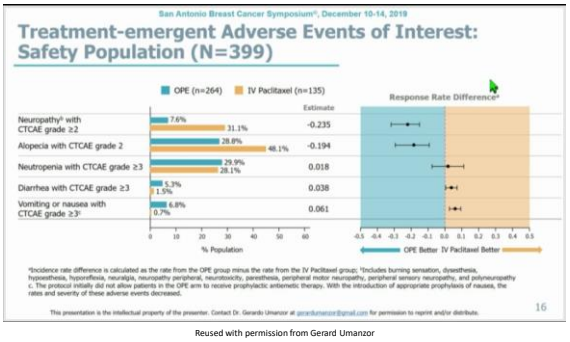

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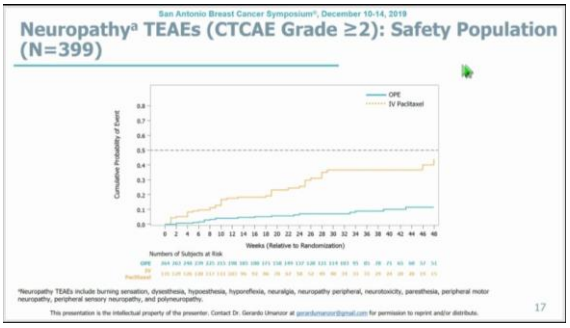

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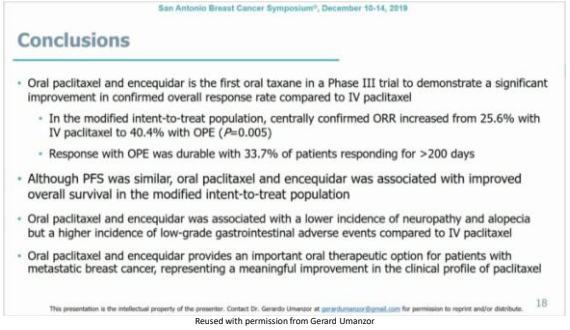

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Tucatinib

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Tucatinib MOA

- Oral reversible tyrosine kinase inhibitor
  - Selectively inhibits HER2
  - Minimal inhibition of EGFR
    - ↓ rates of diarrhea
- Crosses BBB

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Murthy R, et al. *Lancet Oncol.* 2018;19:880-88.
Murthy RK, et al. *N Eng J Med.* 2019; [epub ahead of print].

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