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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

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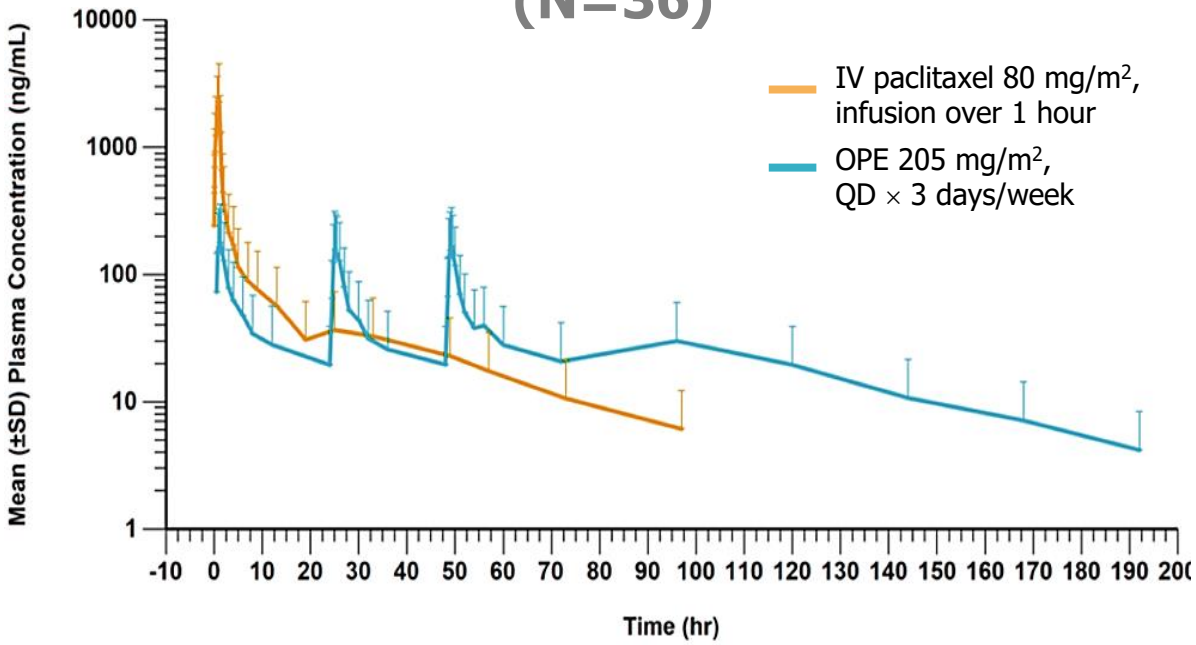
Metastatic Breast Cancer and Paclitaxel

- 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.

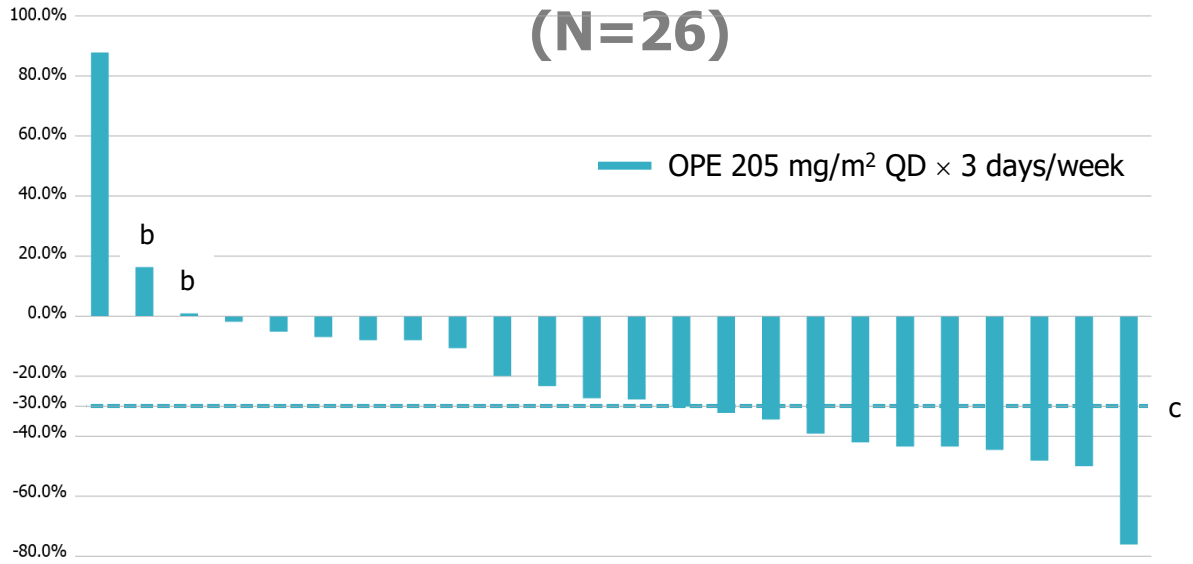
Dose Justification for OPE

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

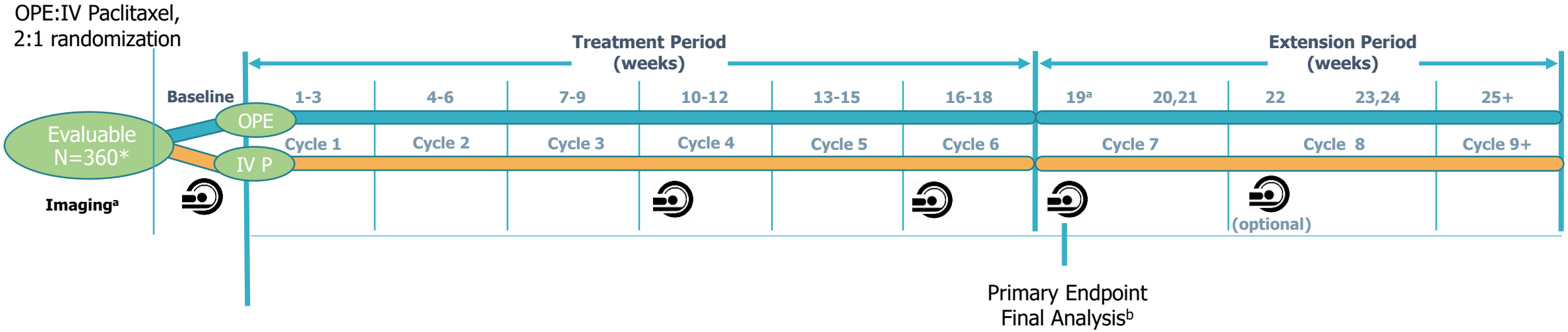
Phase II Study in Pre-treated mBC[2,a] (N=26)



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.

Study Design



***360 Evaluable Patients**
OPE (n=240)
IV Paclitaxel (n=120)
80% power, 15% difference in confirmed RR (*P*=0.045)

Primary Objectives
- *Efficacy Endpoint (Prespecified mITT Population)*
  Confirmed tumor response by week 19[a]
  - 2 consecutive scans of PR/CR using RECIST v1.1
  - Blinded and adjudicated central independent review[c]
- *Safety and Tolerability (Safety Population)*

Secondary Objectives
- *PFS*
- *OS*

[a]If first response at week 19, then week 22 scan obtained; [b]Defined as last patient, last scan; [b]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.

Patient Selection and Analysis Populations

Key Inclusion Criteria

- Histologically or cytologically confirmed breast cancer
- Measurable metastatic target lesion disease by RECIST v1.1
- ECOG PS of 0 or 1

Key Exclusion Criteria

- Central nervous system metastasis
- <1 year since previous taxane treatment (adjuvant/metastatic)

Intent-to-treat Population (ITT, N=402)

- All patients who were randomized
- OPE (n=265); IV Paclitaxel (n=137)

Safety Population (N=399)

- All patients who received ≥1 dose of OPE or IV Paclitaxel
- OPE (n=264); IV Paclitaxel (n=135)

Prespecified mITT Population (N=360)

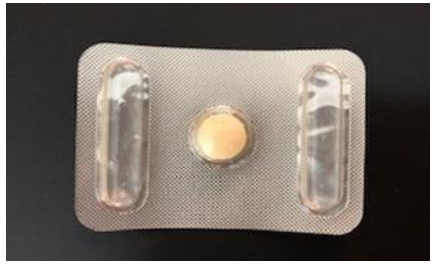
- Baseline evaluable scan: patients with metastatic RECIST lesion on central review
- All patients who received at least 7 doses of OPE or one dose of IV Paclitaxel
- OPE (n=235); IV Paclitaxel (n=125)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Paclitaxel Dosing and Administration

Oral Paclitaxel and Encequidar (OPE)

- Encequidar: 15 mg tablet

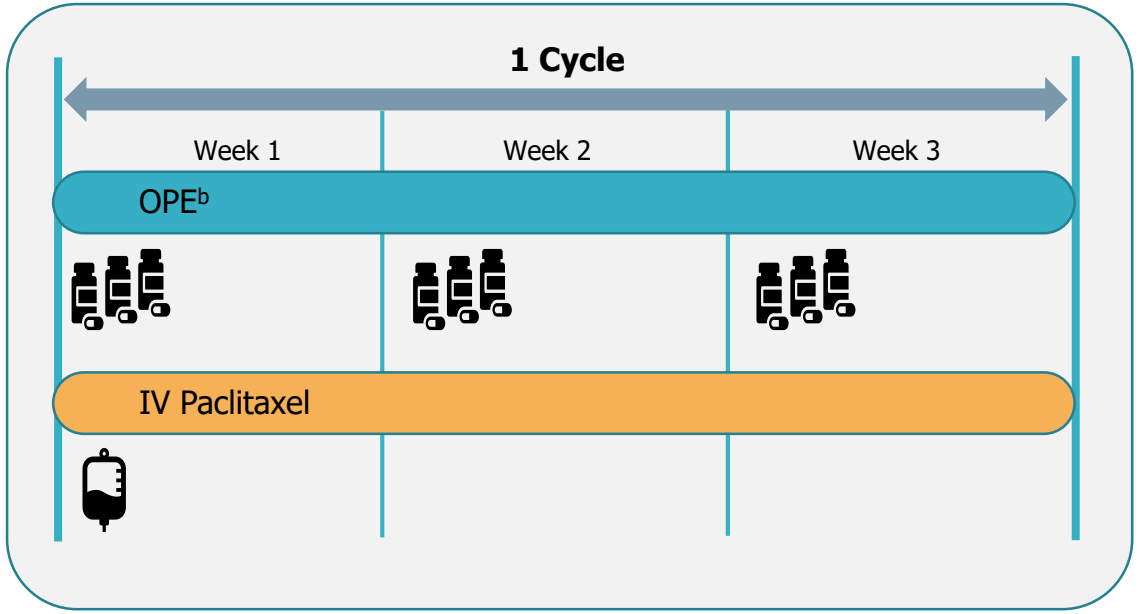


- Oral paclitaxel: each capsule contains 30 mg solubilized paclitaxel[a]

- Administered as oral paclitaxel (205 mg/m^2) and encequidar (15 mg) for 3 consecutive days/week for 3 weeks (1 cycle)

Intravenous Paclitaxel

- Administered as 175 mg/m^2 over a 3-hour infusion every 3 weeks (1 cycle)



[a]Paclitaxel solubilized in Tween-80; [b]No prophylactic corticosteroid or antihistamine premedication allowed for OPE arm.

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.

Prior Therapies and Metastatic Disease in Prespecified mITT Population

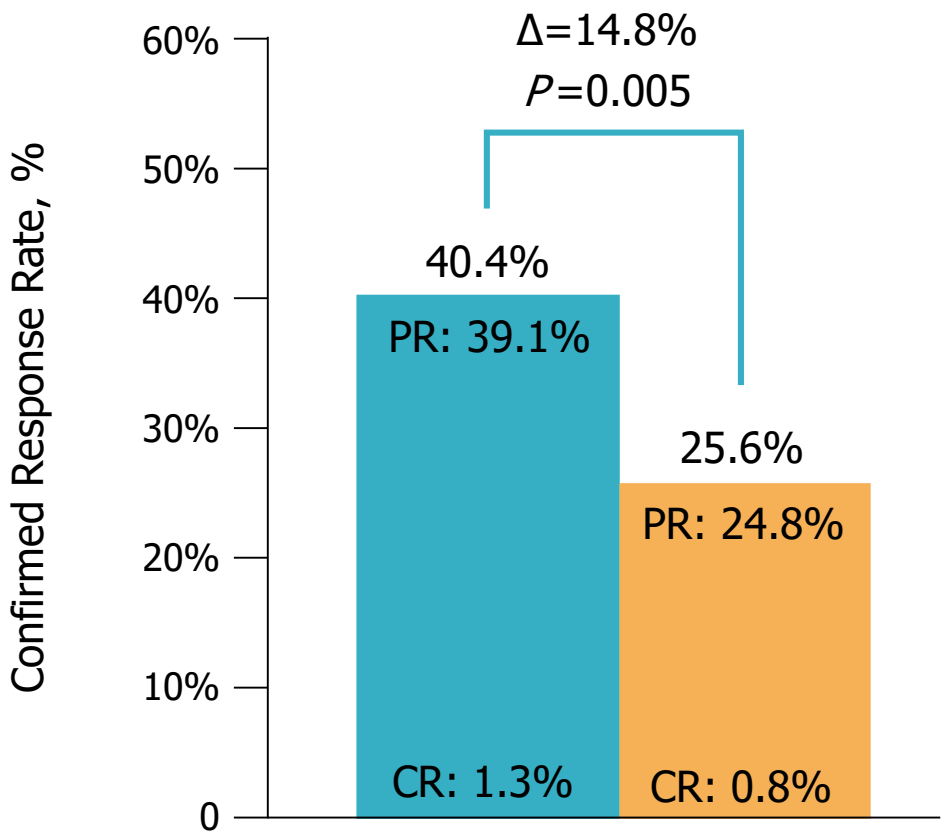
Prior Therapy Exposure		OPE (n=235)	IV Paclitaxel (n=125)
Number of prior chemotherapies in metastatic setting, %	Any	26	28
	1	14	16
	2	7	8
	≥3	4	6
Prior taxane exposure (any setting), %		29	30
Prior anthracycline exposure (any setting), %		56	55

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).

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

Confirmed Response Rate[a]

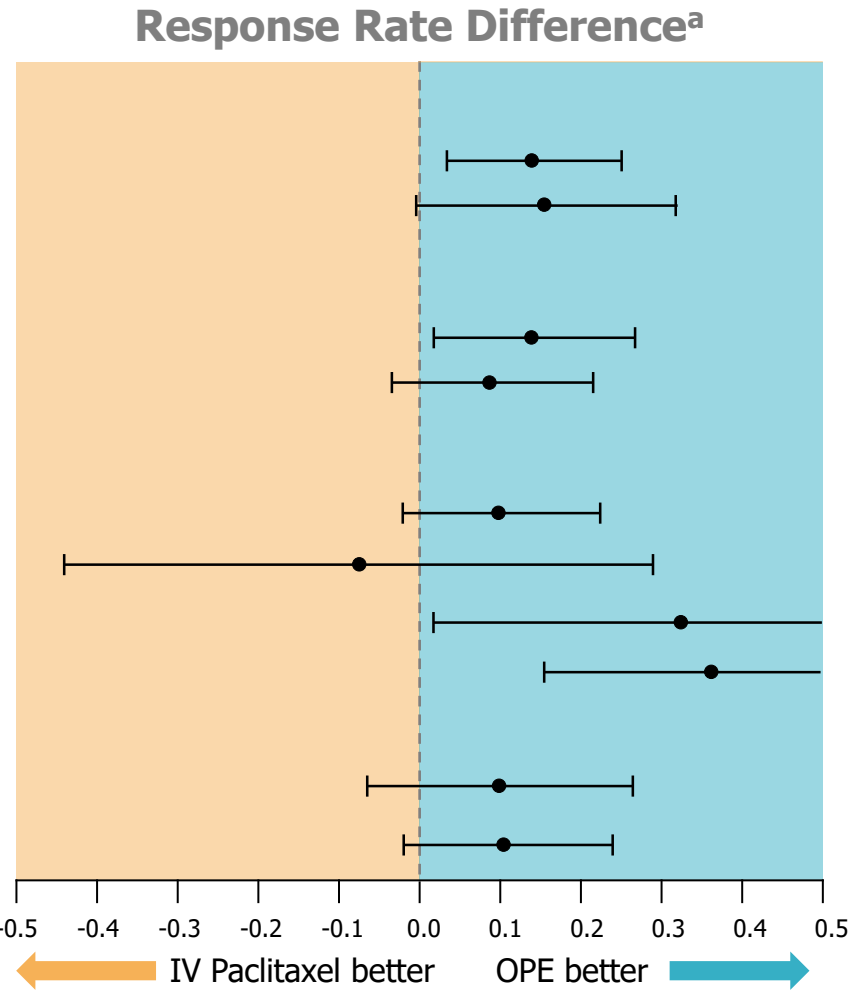


Tumor Evaluations	OPE	IV Paclitaxel
Stable disease, %	23.8	39.2
Progressive disease, %	16.2	21.6

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

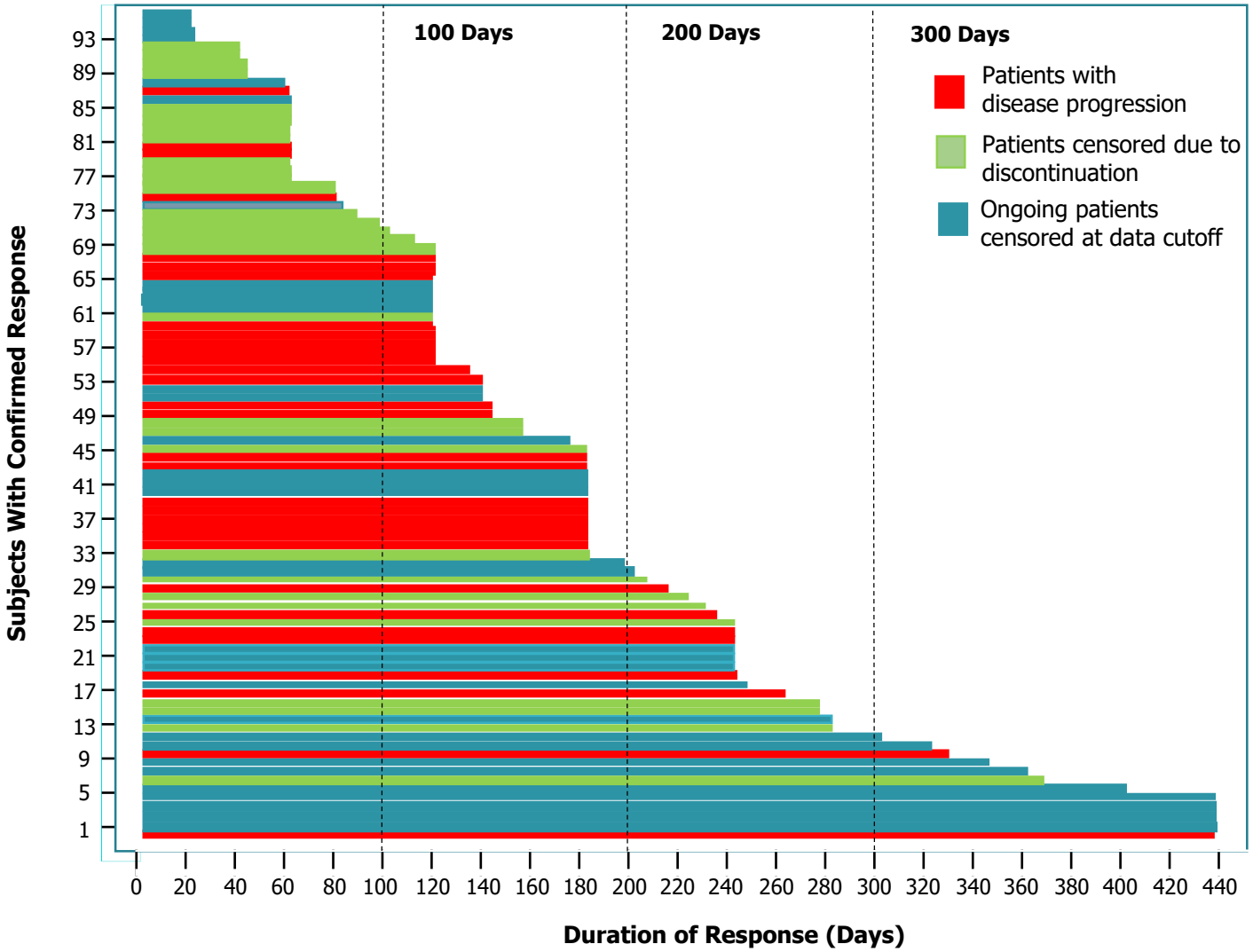
Subgroup Analysis in Prespecified mITT Population: Tumor Response by Central Review

	OPE (n=235)	IV Paclitaxel (n=125)	Estimate
Age, years			
<65, % (n/total)	42.3 (74/175)	27.7 (26/94)	0.146
≥65, % (n/total)	35.0 (21/60)	19.4 (6/31)	0.156
Baseline ECOG PS			
0, % (n/total)	48.6 (67/138)	29.7 (22/74)	0.189
1, % (n/total)	28.9 (28/97)	19.6 (10/51)	0.093
Hormone receptor status			
HR positive/HER2 negative, % (n/total)	31.1 (41/132)	21.3 (13/61)	0.097
HR positive/HER2 positive, % (n/total)	52.4 (11/21)	60.0 (6/10)	-0.076
Triple negative, % (n/total)	52.6 (10/19)	21.1 (4/19)	0.315
HR and HER2 unknown, % (n/total)	61.0 (25/41)	23.1 (6/26)	0.379
Prior therapies			
Taxanes, % (n/total)	34.3 (23/67)	24.3 (9/37)	0.100
Anthracycline, % (n/total)	33.6 (44/131)	23.2 (16/69)	0.104



[a]Response rate difference is calculated as the rate from the OPE group minus the rate from the IV Paclitaxel group.

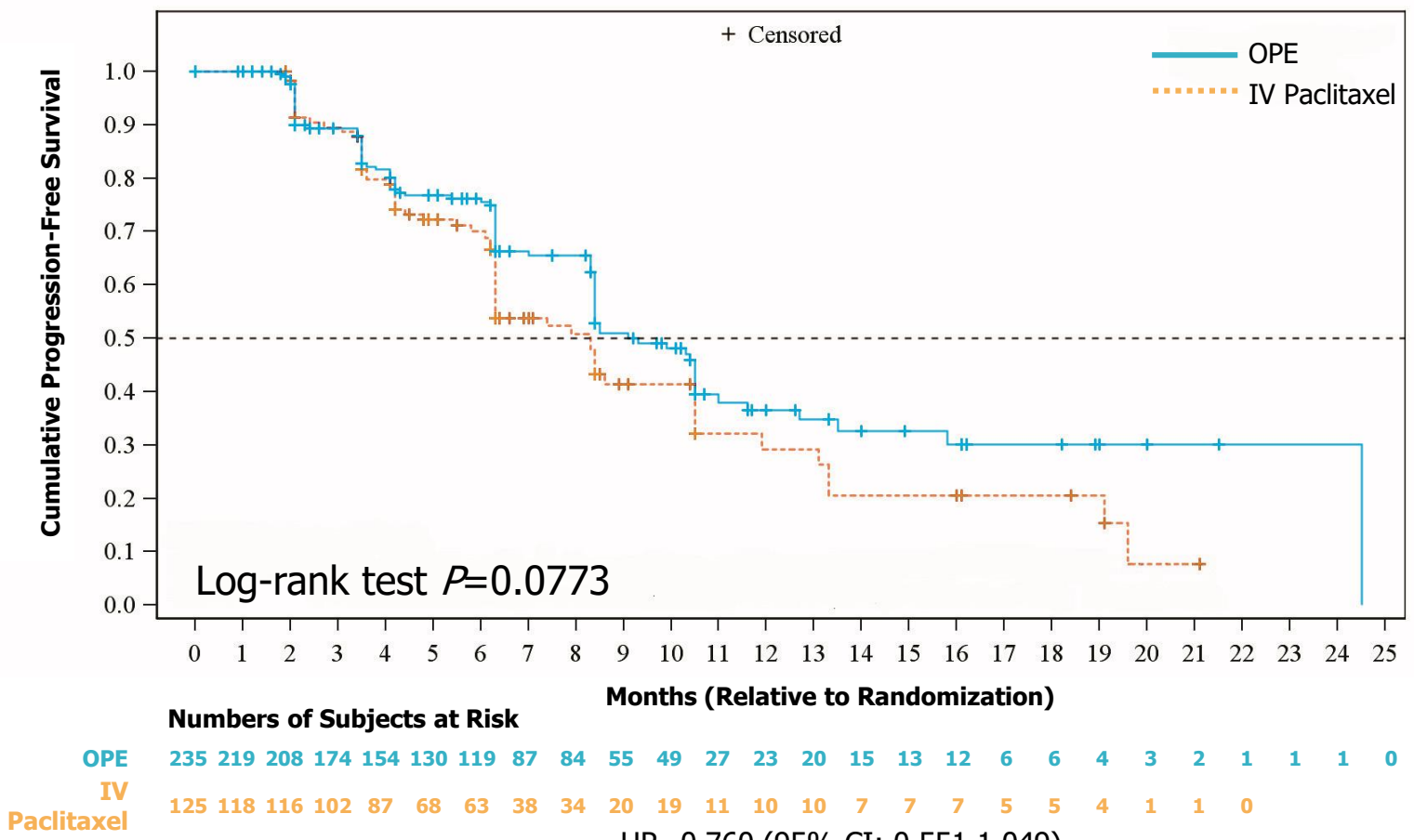
Ongoing Duration of Response in Prespecified mITT Population: Trend for OPE in Patients With Confirmed Tumor Response



Duration of Response, days			
	>100	>200	>300
Duration of response, %	**74.7**	**33.7**	**12.6**

	1-100	101-200	>200
Patients with disease progression, %	4.2	22.1	8.4
Patients censored due to discontinuation, %	13.7	9.5	14.7
Ongoing patients censored at data cutoff, %	7.4	9.5	10.5

Ongoing Analysis PFS in Prespecified mITT[a] Population

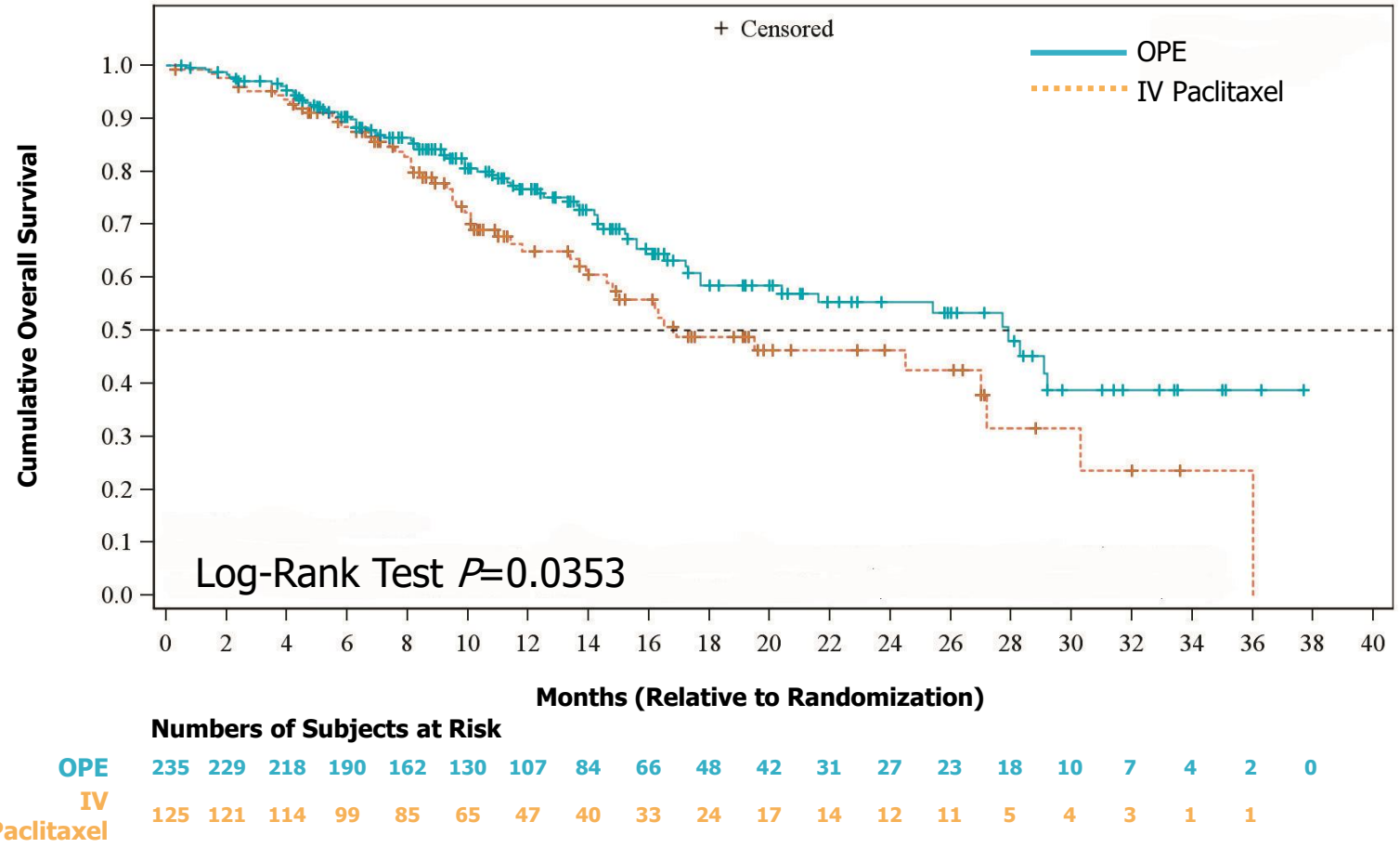


HR=0.760 (95% CI: 0.551,1.049)

PFS, mITT (N=360)	OPE (n =235)	IV paclitaxel (n=125)
Median estimate, months	**9.3**	**8.3**
Censored summary, %	58.3	48.0
Patients with event[b], %	41.7	52.0
Patients discontinued with no event[b] (censored), %	40.4	36.8
Patients ongoing with no event[b] (censored), %	17.9	11.2

[a]In the ITT analysis, a nonsignificant numerical trend was seen for the median PFS favoring the OPE median.
[b]Event is defined as radiological disease progression by central review or death collected in eDC within 90 days of the last tumor assessment.
CI, confidence interval; HR, hazard ratio.

Ongoing Analysis OS in Prespecified mITT Population

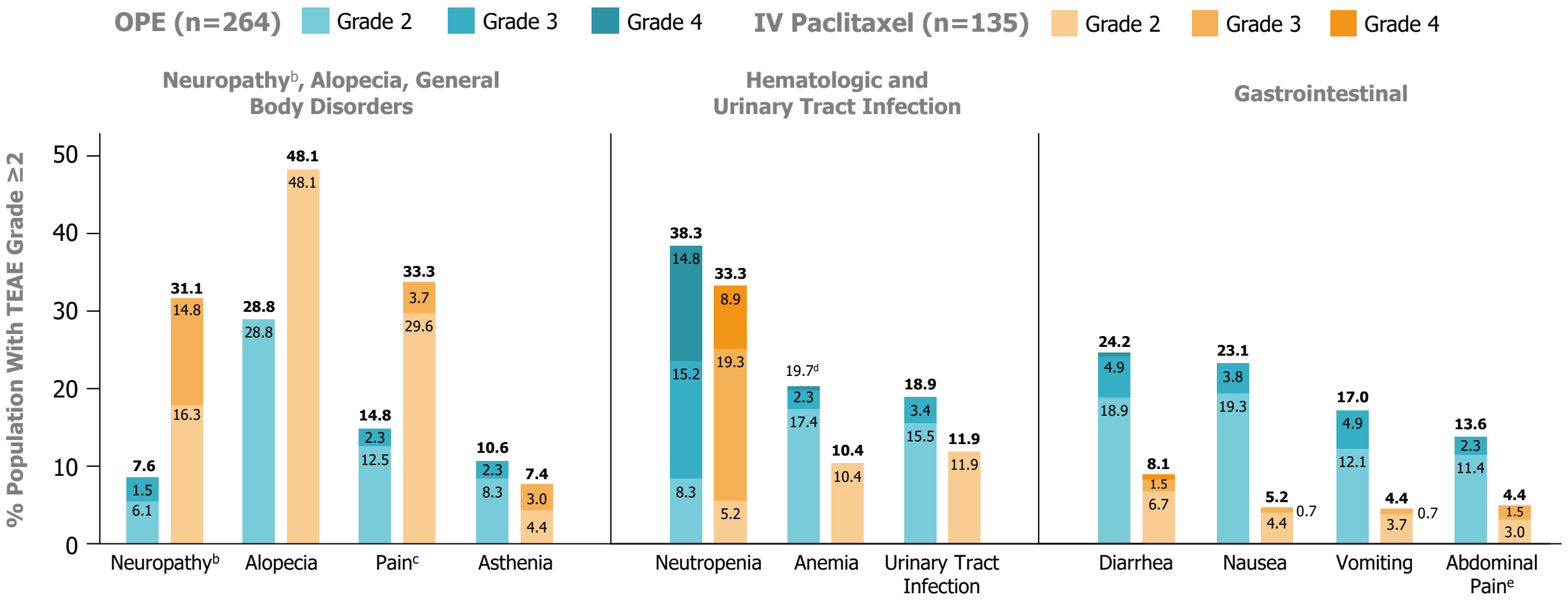


HR=0.684 (95% CI: 0.475, 0.985)

OS, mITT (N=360)	OPE (n =235)	IV paclitaxel (n=125)
Median estimate, months	**27.9**	**16.9**
Censored summary, %	68.9	58.4
Patient deaths (events), %	31.1	41.6
Discontinued patients and survival status unknown (censored), %	17.9	18.4
Patients ongoing or being followed up (censored), %	51.1	40.0

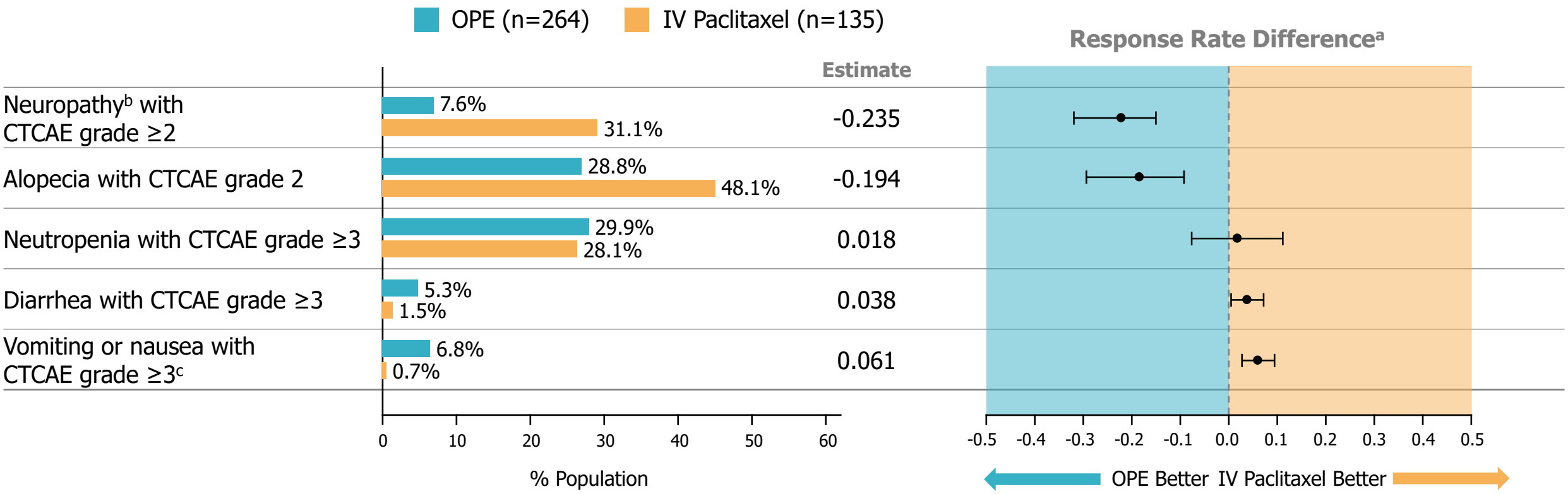
ITT results: Median estimate (months),
OPE (27.7), IV Paclitaxel (16.9); Log-rank test *P* =0.114
HR=0.762 (95% CI: 0.540,1.077)

TEAEs (CTCAE Grade ≥2) With ≥10% Overall Incidence Rate[a]: Safety Population (N=399)



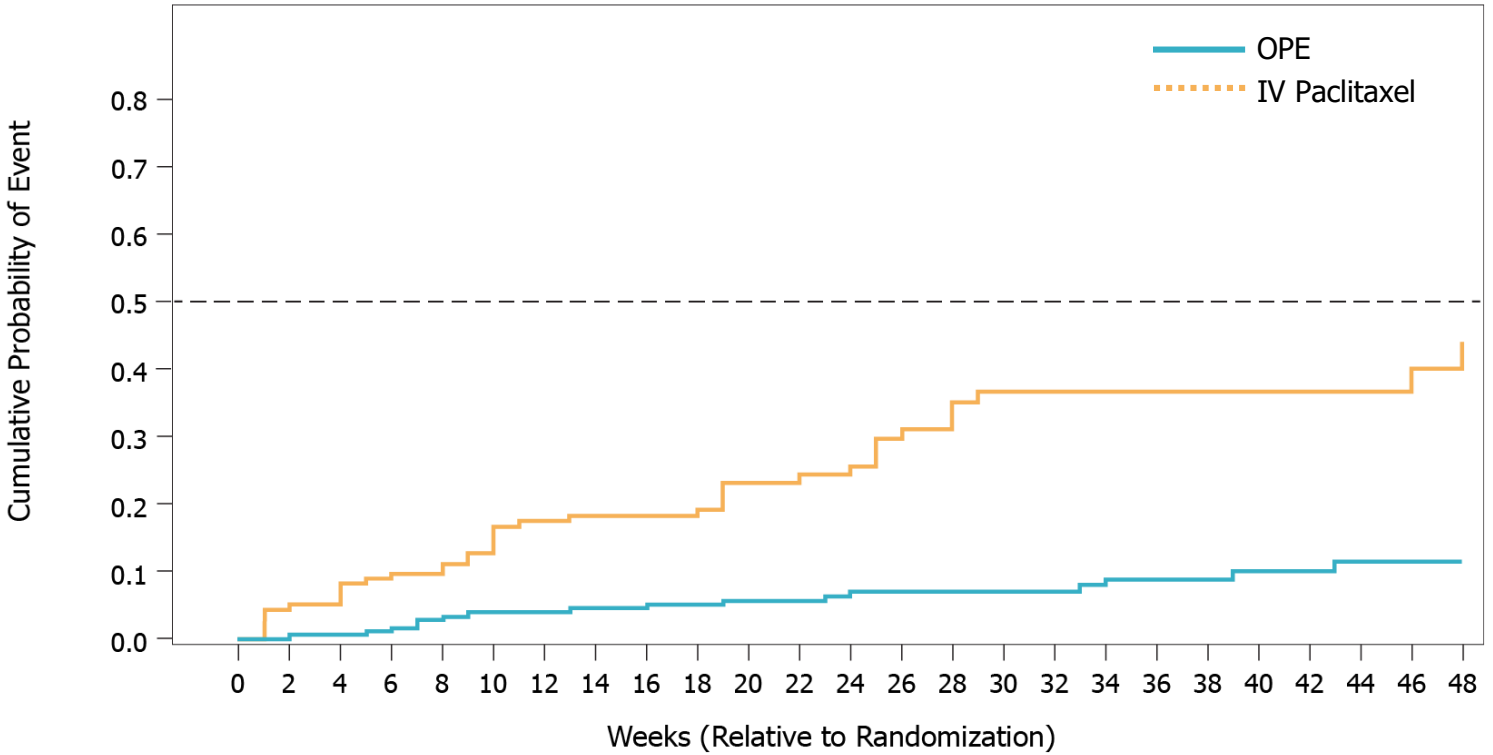
[a]Data for hyperuricemia and hypertriglyceridemia are not presented; [b]Includes burning sensation, dysesthesia, hypoesthesia, hyporeflexia, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy; [c]Includes arthralgia, back pain, pain in extremity; [d]Grade 5 anemia, n (%): OPE, 1(0.4); IV paclitaxel, 0(0); [e]Includes abdominal pain, upper abdominal pain, and abdominal pain upper.
CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Treatment-emergent Adverse Events of Interest: Safety Population (N=399)



[a]Incidence rate difference is calculated as the rate from the OPE group minus the rate from the IV Paclitaxel group; [b]Includes burning sensation, dysesthesia, hypoesthesia, hyporeflexia, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy
c. The protocol initially did not allow patients in the OPE arm to receive prophylactic antiemetic therapy. With the introduction of appropriate prophylaxis of nausea, the rates and severity of these adverse events decreased.

Neuropathy[a] TEAEs (CTCAE Grade ≥2): Safety Population (N=399)



Numbers of Subjects at Risk

OPE	264	263	248	239	225	215	198	185	180	171	158	149	137	128	121	114	103	95	85	78	71	65	60	57	51
IV Paclitaxel	135	129	126	120	117	111	103	96	92	86	70	67	58	52	49	40	34	33	33	29	24	20	20	19	15

[a]Neuropathy TEAEs include burning sensation, dysesthesia, hypoesthesia, hyporeflexia, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Conclusions

- Oral paclitaxel and encequidar is the first oral taxane in a Phase III trial to demonstrate a significant improvement in confirmed overall response rate compared to IV paclitaxel
  - In the modified intent-to-treat population, centrally confirmed ORR increased from 25.6% with IV paclitaxel to 40.4% with OPE (P=0.005)
  - Response with OPE was durable with 33.7% of patients responding for >200 days
- Although PFS was similar, oral paclitaxel and encequidar was associated with improved overall survival in the modified intent-to-treat population
- Oral paclitaxel and encequidar was associated with a lower incidence of neuropathy and alopecia but a higher incidence of low-grade gastrointestinal adverse events compared to IV paclitaxel
- 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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