



Integrating the Epothilones into Clinical Practice: Focus on Breast Cancer

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Disclosures

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Learning Objectives

After attending this symposium, participants should:

- Describe the mechanism of action and activity of epothilones in treatment-resistant tumors
- Summarize the data from recent clinical trials evaluating FDA-approved and investigational agents for treatment experienced breast cancer
- Identify potential adverse effects of epothilone therapy
- Develop strategies to integrate epothilones into the management of patients with breast cancer and discuss the role of pharmacists to improve therapeutic strategies and further enhance the outcomes of these patients



Epothilones: Pre-Clinical Data and Early Clinical Efficacy in Breast Cancer

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The Challenge of Breast Cancer

- **Metastatic breast cancer (MBC) remains an important medical problem**
 - More than 40,000 women will die in 2008 from metastatic disease¹
- **Anthracyclines and taxanes are the standard of care**
 - Increasing use in the adjuvant setting
 - Drug resistance

1. From the American Cancer Society. Available at: http://www.cancer.org/docroot/COM/content/div_Northwest/COM_1_1x_American_Cancer_Societys_Tell-A-Friend_Program_Can_Be_a_Lifesaver.asp?sitearea=COM. Accessed May 5, 2008.

Taxane Resistance: Mechanisms

- P-gp transmembrane protein-dependent mechanism
 - Encoded by multidrug-resistance gene (MDR1)
 - Transports xenobiotics, peptides, steroids, and phospholipids
 - Overexpressed in taxane-resistant cells
- Tubulin-dependent mechanism
 - Overexpression of certain tubulin isotypes (eg, classes II, III, and IVa) confers resistance to taxanes
 - Multiple alterations frequently present in resistant cell lines
- Tau protein-dependent mechanism
 - Microtubule-associated protein
 - Induces assembly of microtubules
 - Overexpressed in resistant cells

Epothilones: An Alternative to Taxanes

- Discovered in 1993
 - Epothilone A
 - Epothilone B
- Other Epothilones
 - Epothilone C (desoxyepothilone A)
 - Epothilone D (desoxyepothilone B)
 - Desoxyepothilone F
- Secondary metabolite macrolides produced by *Sorangium cellulosum*

Novel Agents: Epothilones

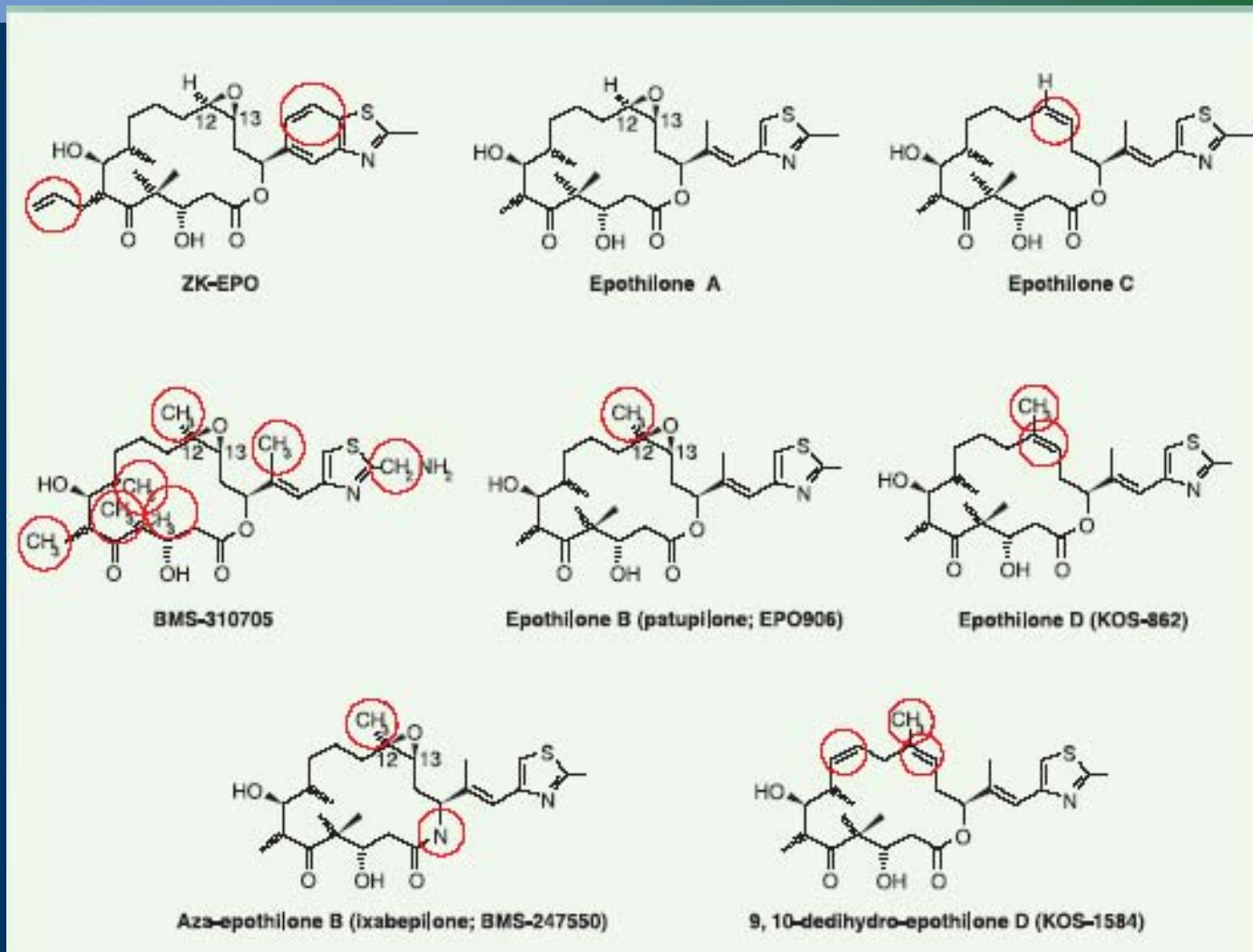
- Mechanism of action
 - Inhibit disassembly of microtubules
 - Stabilize microtubules
 - Induce apoptotic cell death
- Structurally unrelated to the taxanes
- Distinct tubulin-binding mode
- Low susceptibility to tumor resistance mechanisms
 - Multidrug resistance–associated protein 1 (MRP-1) and P-glycoprotein (P-gp) efflux pumps
 - β (III)-tubulin overexpression
 - β -tubulin mutations

Activity in Paclitaxel-Resistant Cell Lines (IC₅₀) in vitro

Cell Line	Cell Line	Patupilone	Paclitaxel	Relative Potency
Leukemia	CCRF-CEM	0.35	2.1	6
	CCRF-CEM/VBL ₁₀₀ *	2.1	4140	1971
Colon	SW620	0.1	0.2	2
	SW620AD-300*	0.3	250	833
Epidermoid	KB-31	0.19	2.31	12
	KB-8511*	0.19	533	2805
Ovarian	IA9	0.06	2.0	33
	1A9PTX22†	0.1	43	430
Breast	MCF-7	0.18	1.80	10
	MCF-7/ADR‡	2.92	9105	3118
Colon	HCT-15§	0.41	136	331

Yellow = drug-resistant cell lines; IC₅₀ = 50% inhibitory concentration. *P-gp overexpression/MDR; †Ala364→Thr mutation in β-tubulin; ‡multiple resistance mechanisms/MDR; §primarily P-gp overexpression: other mechanisms possible.
 Altman K-H et al. *Biochim Biophys Acta*. 2000;1470:M79-M91.

Epothilones Currently in Clinical Development



Patupilone (EPO906)

- Epothilone B
- Early phase clinical studies used weekly dosing schedule of 3 weeks on/1 week off
 - Most patients experienced diarrhea (onset, days 9-11)
- Confirmed partial responses in
 - Ovarian, prostate, breast, colon, gastric, renal, melanoma, and carcinoid cancer
 - Disease stabilization in small proportion of patients (2-18 months)

Patupilone (EPO906) Studies

- New phase 1 and 2 clinical trials initiated to improve safety and efficacy
 - Dosing schedule of every 3 weeks
 - Preclinical data indicated higher single doses could be more efficacious
 - Avoids dosing immediately prior to onset of predicted diarrhea
 - Improved dose intensity possible
 - Proactive antidiarrheal management
- Currently being evaluated in a phase III trial, compared with liposomal doxorubicin in patients with ovarian, primary fallopian, or peritoneal cancer

KOS-862

- Epothilone D produced by recombinant DNA technology
- Phase I studies: 100 mg/m² over 90 minutes, weekly x 3 q 4 weeks
 - Dose limiting toxicity: neuropathy
- Studies in breast cancer
 - Monotherapy in anthracycline and taxane pretreated MBC¹
 - 4 partial responses (14%)
 - Peripheral sensory neuropathy in 21 of 27 patients (3 were grade 3)
 - Phase Ib study of combined therapy with trastuzumab in HER2-positive malignancies²
 - Full doses of both agents feasible

1. Buzdar A, et al. Presented at: San Antonio Breast Cancer Symposium 2005; abstract 1087.

2. Cortes J, et al. J Clin Oncol 2006;24(18S):2028a.

KOS-1584

- Phase I studies reported
 - Administered over 1 hour on days 1, 8, & 15 every 4 weeks¹
 - DLT at 20 and 25 mg/m² was diarrhea
 - Enrolling at 16 mg/m² using antidiarrheal prophylaxis
 - Days 1 & 8 every 3 weeks²

DLT=dose-limiting toxicity.

1. Stopek A, et al. J Clin Oncol 2007;25 (18s):abstract 2571.

2. Villalona-Calero M, et al. J Clin Oncol 2006;24 (18s): abstract 2003.

Sagopilone (ZK-EPO)

- Fully synthetic analog of epothilone B
- Administered as a 30 minute-infusion every 3 weeks¹
 - Dose-limiting neuropathy at 16 mg/m² and ataxia at 29 mg/m²
 - Most common adverse event reported was peripheral sensory neuropathy
 - 2 partial responses in taxane-pretreated MBC
- Randomized (30-minute or 3-hour infusion) phase II in platinum-resistant ovarian cancer
 - 4/13 responded in the 3-hour infusion
 - 1/13 responded in the 30-minute infusion
 - Peripheral neuropathy common

1. Schmid P, et al. J Clin Oncol 2005;23 (16s):abstract 2051.

2. Rustin GJ, et al. J Clin Oncol 2007;25 (18s): abstract 5527.

Ixabepilone Phase 1 Studies

- Semi-synthetic analogue of Epothilone B

	Daily × 5 every 21 days	Daily × 3 every 21 days	Weekly	Once every 21 days
Infusion duration, h	1	1	0.5-1	1
Dose (mg/m ² /d), range	1.5-8	8-10	1-30	32-65
MTD (mg/m ²)	6	8	25	50
DLT	Neutropenia, peripheral neuropathy			

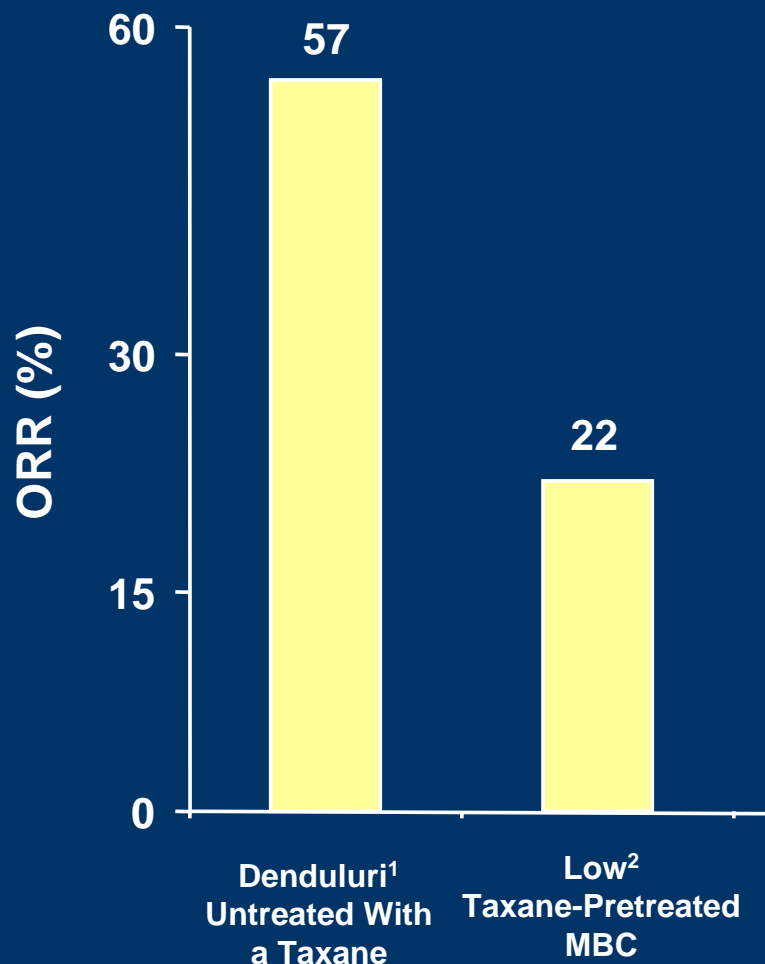
MTD=maximum tolerated dose.

Goodin S et al. *J Clin Oncol*. 2004;22:2015-2025.

Ixabepilone Phase II Studies in Breast Cancer: Daily Dosing

- Initial dosing of 8 mg/m² daily over 1 hour for days 1 to 3 for the first cycle; subsequent cycles used 10 mg/m² daily over 1 hour for days 1 to 3; cycles were q 21 days
 - No objective responses¹
- Dosing of 6 mg/m² IV over 1 hour daily X 5 days q 21 days
 - MBC, no prior taxane allowed (n=23)²
 - MBC, taxane pretreated (n=37)³

Ixabepilone Phase II Studies in Breast Cancer: Daily Dosing x 5 days



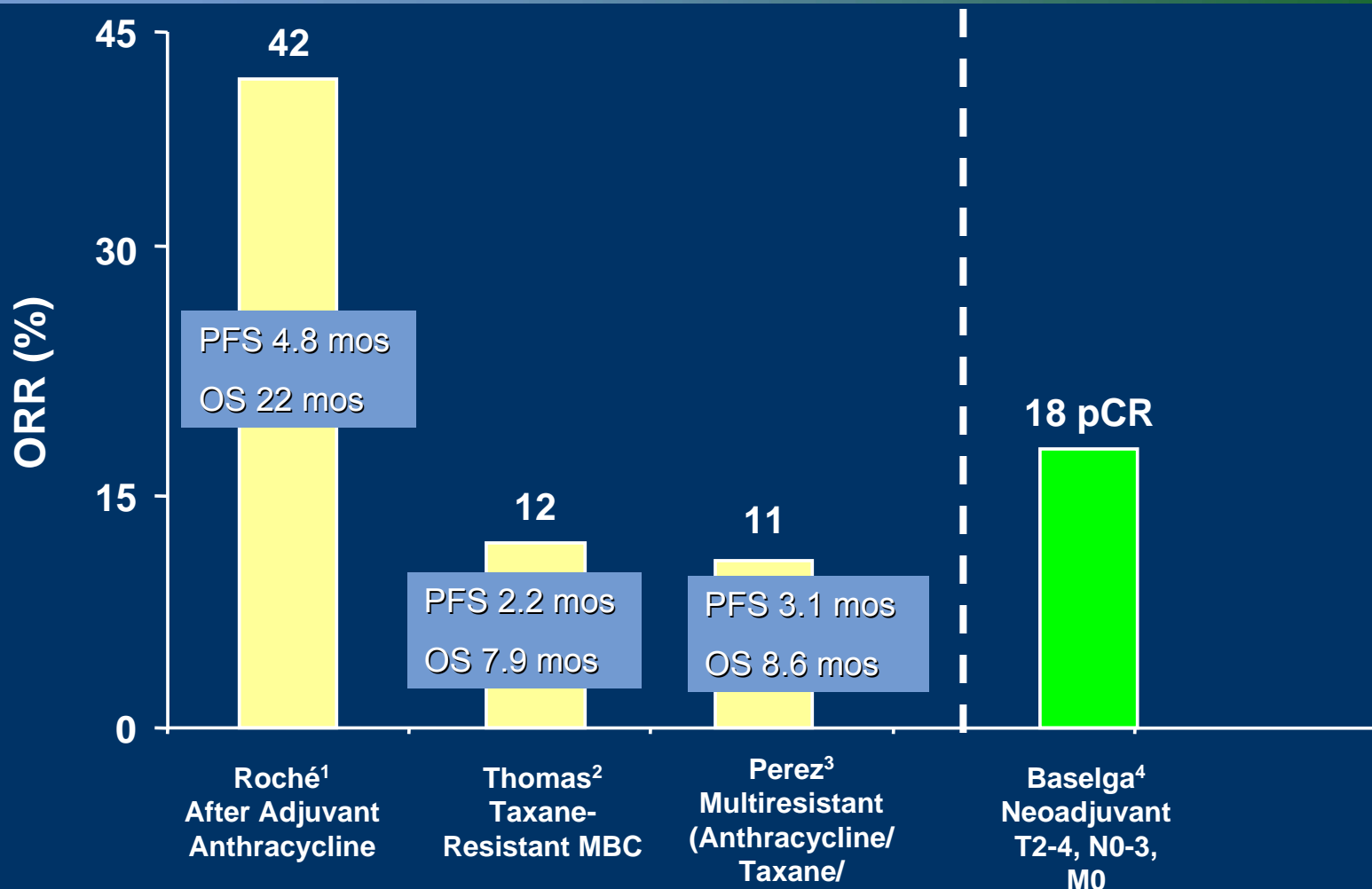
ORR = overall response rate.

1. Denduluri N, et al. *J Clin Oncol* 2007;25: 3421-3427.; 2. Low JA et al. *J Clin Oncol*. 2005;23:2726-2734.

Ixabepilone Phase II Studies in Breast Cancer – q 3 Week Dosing

- Dosing of 40 mg/m² IV over 3 hours every 3 weeks
- Patient populations
 - MBC, resistant to anthracyclines (n=65)¹
 - MBC, resistant to taxanes (n=49)²
 - MBC, resistant to anthracyclines, taxanes, and capecitabine (n=113)³
 - Invasive breast cancer, neoadjuvant therapy (n=164)

Ixabepilone Phase II Studies in Breast Cancer – q 3 Week Dosing



1. Roché H et al. *J Clin Oncol.* 2007;25:3415-3420; 2. Thomas J et al. *J Clin Oncol.* 2007;25:3399-3406; 3. Perez EA et al. *J Clin Oncol.* 2007;25:3407-3414; 4. Baselga J et al. *Breast Cancer Res Treat.* 2005;94(suppl 1):S31. Abstract 305.

Ixabepilone in combination with capecitabine in MBC

- Phase I/II study (n=50)
- Anthracycline and taxane pretreated patients
 - Ixabepilone 40 mg/m² as a 3-hour infusion on day 1 every 21 days
 - Capecitabine 1000 mg/m² twice a day on days 1 to 14 every 21 days
- Objective response rate 30% with a median progression free survival of 3.8 months

Novel Agents: Epothilones

- Mechanism
 - Unique binding to β -tubulin
 - Potent inducer of tubulin polymerization
- Resistance
 - Not a substrate for any major drug efflux pumps
 - Not susceptible to β -tubulin mutations

Novel Agents: Epothilones

■ Toxicity

- Well tolerated overall
 - Diarrhea dose-limiting toxicity for patupilone and KOS-1584
 - Neuropathy and neutropenia dose-limiting toxicity for other epothilones
- The distinct toxicity profile of agents in this class will likely influence their combination with existing agents

■ Activity

- Completed phase II clinical studies reveal activity in taxane-resistant tumors
- Ongoing clinical studies will ultimately determine the role of this novel class of agents



Epothilones: Integrating Therapy into Clinical Practice

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Epothilones – Ixabepilone

- Only FDA-approved epothilone to date
 - Approved October 16, 2007
- FDA-approved indications
 - Monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine
 - In combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane

Ixabepilone: Phase II Clinical Trials

- Single agent response rates 11%-57%
 - Prior chemotherapy exposure differs
 - Most efficacious with minimal prior therapy
 - Responses seen in taxane-resistant tumors
 - Toxicity differs based on administration schedule
 - Daily regimens – more neutropenia
 - **Every 3 week regimens – better tolerated**
- Combination with capecitabine
 - Objective response rate 30%
 - No increase in capecitabine-associated toxicities

Ixabepilone: Phase III Clinical Trials

- Locally advanced or MBC
- Anthracycline-pretreated or resistant
- Taxane-resistant (n=752)

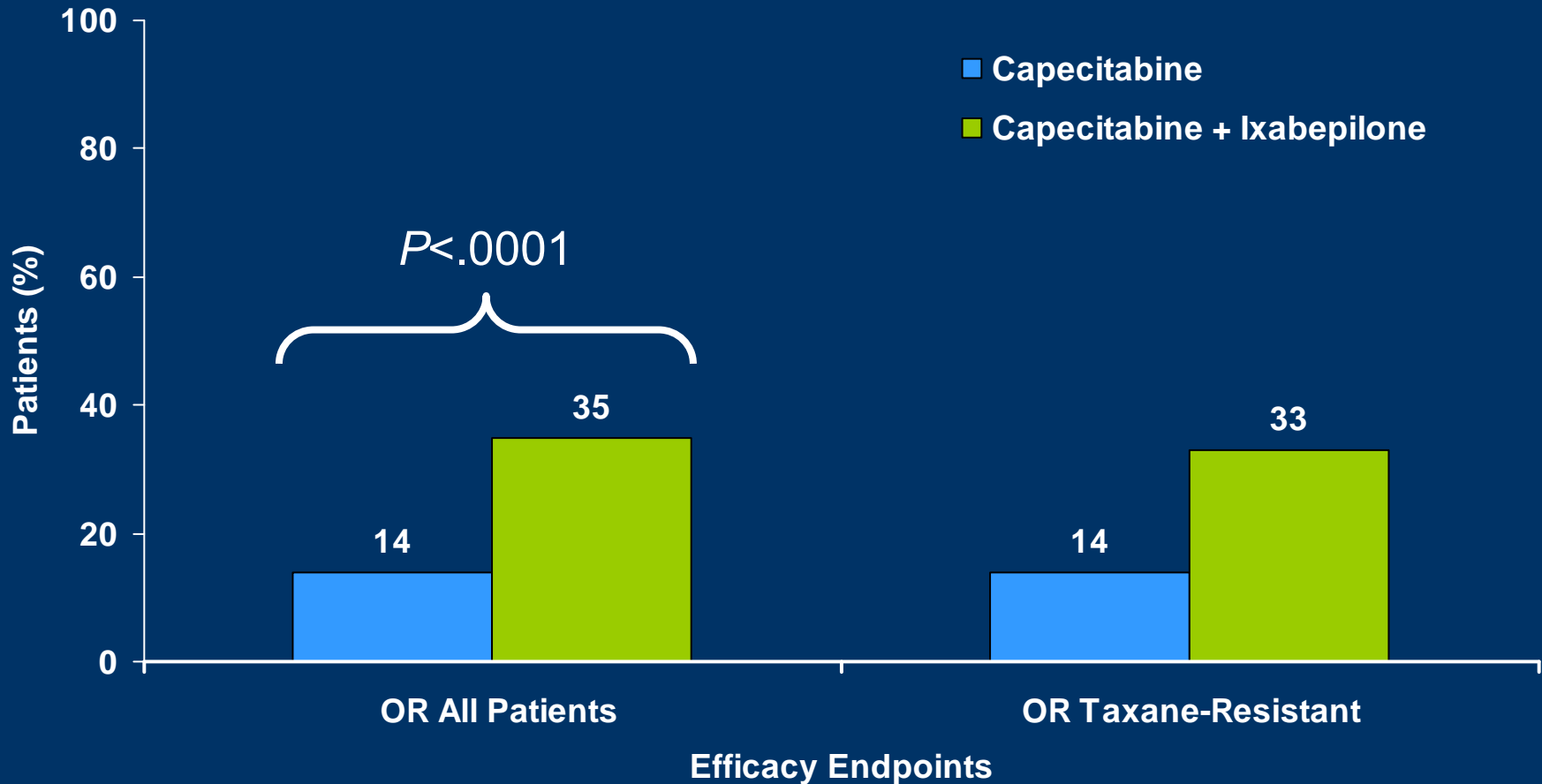
Capecitabine 2500 PO mg/m²/day x 14 d
q 21 days
(n=377)

Capecitabine 2000 PO mg/m²/day x 14 d
+
Ixabepilone 40 mg/m² IV
q 21 days
(n=375)

MBC=metastatic breast cancer.

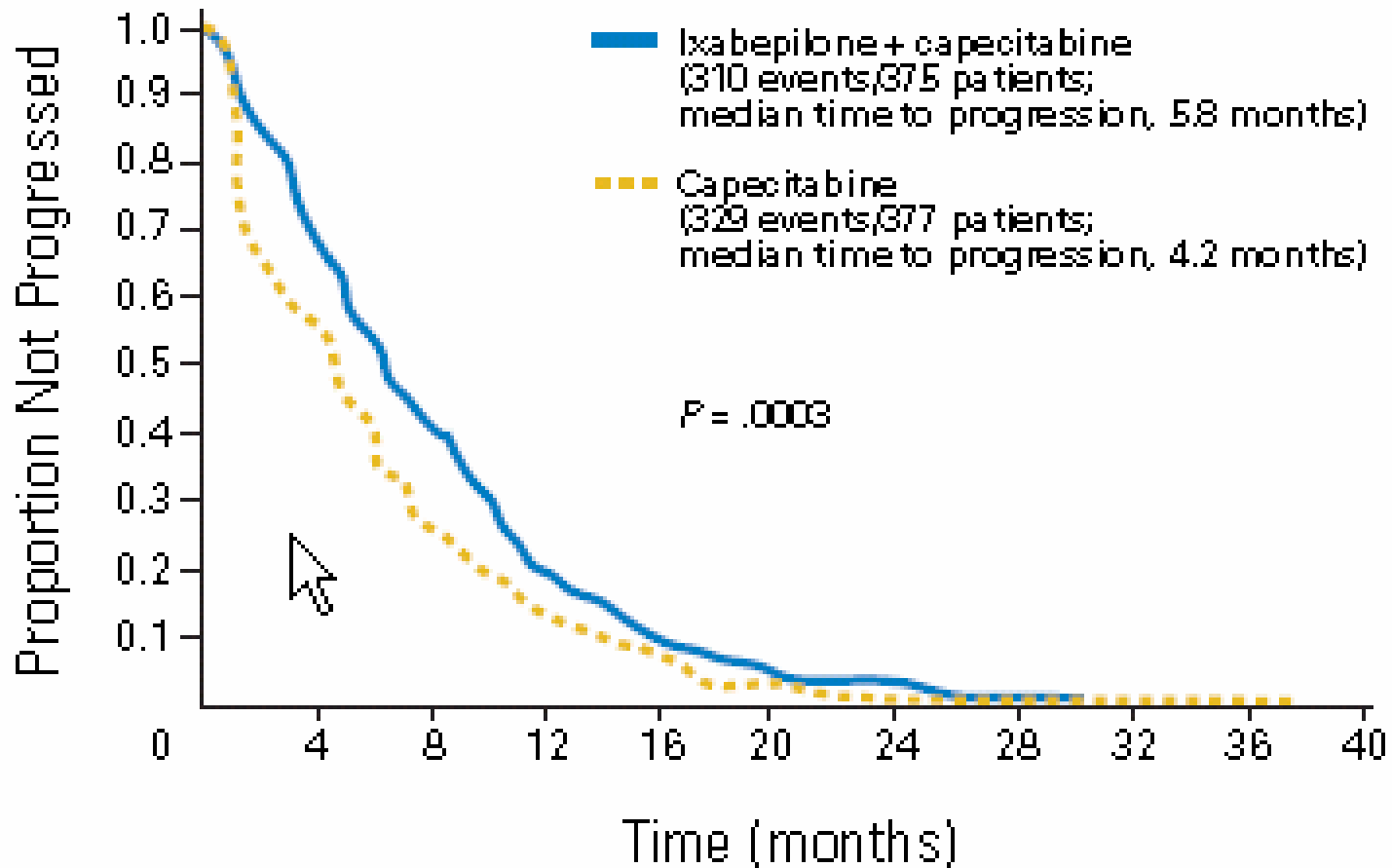
Thomas E, et al. *J Clin Oncol* 2007;25: 5210-5217.

Ixabepilone + Capecitabine IRR-Assessed Response Rates



IRR=independent radiologic review; OR=objective response rate.
Thomas E, et al. *J Clin Oncol* 2007;25: 5210-5217.

Ixabepilone + Capecitabine Progression-Free Survival (PFS)



Capecitabine ± Ixabepilone : Safety

Grade 3/4 Toxicity (%)	CAPE + IXA (n=369)	CAPE (n=368)
Hematologic		
Neutropenia	68	11
Febrile Neutropenia	4	1
Anemia	10	5
Thrombocytopenia	8	4
Nonhematologic		
Peripheral Sensory Neuropathy*	21	0
Hand-Foot Syndrome	18	17
Fatigue	16	4
Diarrhea	6	9

*Grade 3/4 treatment related motor neuropathy (5% IXA + CAPE vs 0% CAPE).

Ixabepilone Pharmacy Issues

- Formulated in Cremophor EL + ethanol
 - Premed with H₁ and H₂ antagonists
 - Steroid premedication required if patient has a hypersensitivity reaction
- pH- and concentration-dependent solubility
 - Dilute in Lactated Ringer's Injection (pH=6-7.5)
 - Optimal final concentration 0.2-0.6 mg/mL
- Requires DEHP-free bags/tubing and in-line filter with microporous membrane at least 0.2-1.2 μm

DEHP= di-(2-ethylhexyl)phthalate

Ixempra™ [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company,; 2007.

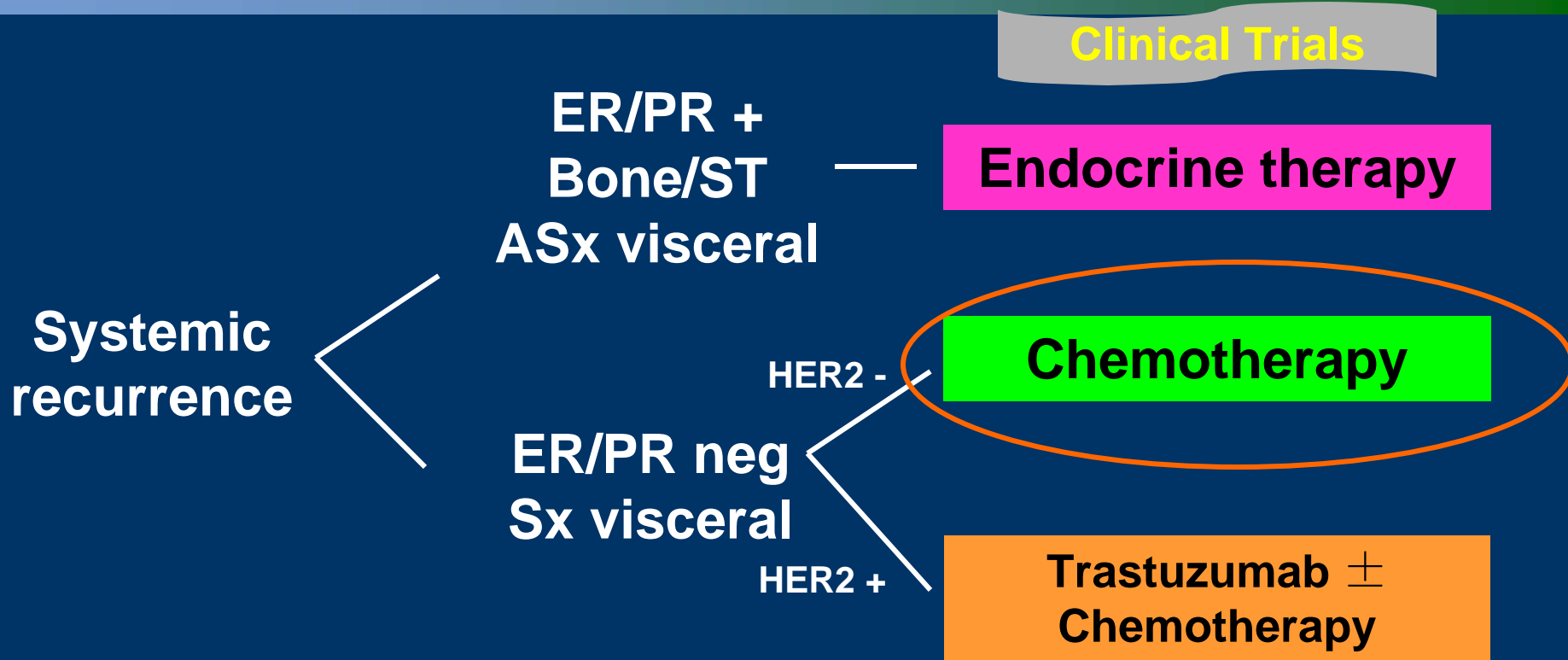
Ixabepilone: Drug Interactions

- Formal drug interaction studies in humans not completed
- Ixabepilone *in vitro*:
 - Weak inhibitor of human CYP3A4
 - Minimal potential to interact with drugs metabolized by CYP3A4
 - Following incubation with known inhibitors of P450, significant inhibition seen only with 3A4 inhibitors (troleandomycin, ketoconazole)
- Dose reduction with strong inhibitors (50%)

Ixabepilone...

Place in Therapy?

MBC Treatment Decisions



ASx=asymptomatic; Sx=symptomatic; ER=estrogen receptor; PR=progesterone receptor; ST=soft tissue; HER2=human epidermal growth factor receptor-2.

Adpated from NCCN Breast Cancer Management Guidelines, v.2.2008.

Principles of Treating MBC With Systemic Chemotherapy

- Initial anthracycline or taxane therapy
 - Objective response rates (complete + partial responses) ~40%-50%
 - Median duration of response (MDR) ~9-11 months
- Each successful treatment with chemotherapy results in a shorter MDR
- Combination vs sequential single agent
 - Widely debated

Chemotherapy for Metastases

Combination vs Single Agent

■ Combination regimens

- Generally associated with higher response rates
- Improvements in survival seen with few regimens
 - $A \rightarrow T$ vs $T \rightarrow A$ vs AT (paclitaxel)¹
 - Similar survival
 - Docetaxel vs docetaxel/capecitabine²
 - Improved OS, but only 15% crossed over to capecitabine
 - Paclitaxel vs gemcitabine/paclitaxel³
 - Improved OS, but only 15% crossed over to gemcitabine
- Greater toxicity with all combinations

■ Patients who require rapid response may benefit from combo despite added toxicity

A=doxirubicin; T=paclitaxel; OS=overall survival.

1. Sledge G, et al. *JCO* 2003;21(4):588-592. 2. O'Shaughnessy J, et al. *JCO* 2002; 20(12):2812-23.

3. Melemed AS, et al. Paper presented at: ASCO 2007;Abstract 150.

MBC Chemotherapy

Preferred agents*

Anthracyclines

Taxanes

Capecitabine

Vinorelbine

Gemcitabine

Preferred Combinations*

CAF/FAC

AC

AT

Docetaxel/capecitabine

Gemcitabine/paclitaxel

FEC

EC

CMF

CAF/FAC= cyclophosphamide/doxorubicin/fluorouracil; FEC= fluorouracil/ epirubicin/ cyclophosphamide; AC=doxorubicin/cyclophosphamide; EC=epirubicin/cyclophosphamide; AT=doxorubicin + paclitaxel or docetaxel; CMF=cyclophosphamide/ methotrexate/ fluorouracil; *No compelling evidence shows that combination regimens are superior to sequential single agents. NCCN Clinical Practice Guidelines in Oncology™ v.2.2008.

MBC Chemotherapy

Exposure in
Adjuvant Setting

Preferred Agents*

~~Anthracyclines~~

~~Taxanes~~

Capecitabine

Vinorelbine

Gemcitabine

Preferred Combinations*

CAF/FAC

AC

AT

Docetaxel/capecitabine

Gemcitabine/paclitaxel

FEC

EC

CMF

CAF/FAC= cyclophosphamide/doxorubicin/fluorouracil; FEC= fluorouracil/ epirubicin/ cyclophosphamide; AC=doxorubicin/cyclophosphamide; EC=epirubicin/cyclophosphamide; AT=doxorubicin + paclitaxel or docetaxel; CMF=cyclophosphamide/ methotrexate/ fluorouracil; *No compelling evidence shows that combination regimens are superior to sequential single agents. NCCN Clinical Practice Guidelines in Oncology™ v.2.2008.

MBC Other Active Agents

Other
Active
Agents

Platinoids

Etoposide (po)

Vinblastine

Fluorouracil
(cont. inf.)

Ixabepilone ±
capecitabine



Clinical
Trials

Ixabepilone Monotherapy

Place in Therapy

Regimen	Patients	RR (%)	mTTP (mo.)
Ixabepilone ¹	Anthracycline-, taxane-, & capecitabine pretreated	11	3.1
Capecitabine ²	Anthracycline- & taxane-pretreated	20	~3
Gemcitabine ²	Anthracycline- & taxane-pretreated	17-20	4.5
Vinorelbine ²	Anthracycline- & taxane-pretreated	25	6

- Cape=Hand-foot syndrome; GI toxicities
- Gem=neutropenia; thrombocytopenia; flu-like syndrome
- Vin= neuropathy, neutropenia (mild)

Ixabepilone + Capecitabine Place in Therapy

Regimen	Patients	RR (%)	mTTP (mo)
Ixa + Cape ¹	Anthracycline- & taxane-pretreated	35	5.8
Doc + Cape ²	Anthracycline-pretreated	42	6.1
Gem + Pac ³	Anthracycline-pretreated	41	6.1

- Ixa + Cape=febrile neutropenia (4%); neuropathy; HFS; GI toxicities.
- Doc + Cape=febrile neutropenia (~15%); HFS; GI toxicities.
- Gem + Pac=neutropenia; thrombocytopenia; flu-like syndrome.

Doc=docetaxel; Gem=gemcitabine; Pac=paclitaxel.

1. Thomas E, et al. *J Clin Oncol*. 2007;25:5210-5217. 2. O'Shaughnessy J, et al. *JCO*. 2002;20(12):2812-2823.
3. Melemed AS, et al. Presentation at: ASCO 2007;Abstract 510.

Actual Clinical Practice

- Refractory breast cancer
 - Locally advanced or MBC
 - Resistant to anthracyclines and taxanes
 - Progressed rapidly with neoadjuvant or metastatic treatment
 - Recurred within 6 months of adjuvant therapy
- Salvage therapy
 - Patients who previously may have responded to chemotherapy but have since progressed
- Adequate performance status
- NCCN: consider no further cytotoxic therapy when no response to 3 sequential regimens or $PS \geq 3$

ASCO 2008 Updates

- ZK-EPO (sagopilone)
 - No activity in GBM; some activity in melanoma
 - Safe in combination with cisplatin in SCLC
- Patupilone
 - Some activity in brain metastases from MBC
 - Dosing in mild liver dysfunction
- Ixabepilone
 - Some activity in RCC; no activity in variety of pediatric malignancies
 - Safe in combination with epirubicin in MBC
 - Safe (?) in combination with mitoxantrone/pred in HRPC; weekly for HRPC (?)

ASCO = American Society of Clinical Oncology; GBM = glioblastoma multiforme; SCLC = small cell lung cancer; MBC = metastatic breast cancer; RCC = renal cell carcinoma; HRPC = hormone-refractory prostate cancer; pred = prednisone.

Future Directions

- Ongoing clinical trials
 - Confirming role in MBC
 - Exploring role in early stage breast cancer
- Other combinations
 - Chemotherapy
 - Biologic therapy
 - Trastuzumab
 - Lapatinib
 - Bevacizumab
- Expanding role in other cancers