

# Epothilones in patients with brain metastases from breast cancer

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Breast Cancer Brain Metastases Workshop  
Arlington, VA  
March 1, 2009



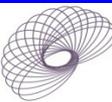
# Disclosures

- **Research funding: Novartis**



# Take home points

- **Epothilones have potential advantages over taxanes particularly for brain metastases**
- **At least 2 epothilones, patupilone and sagopilone, cross BBB**
- **Clinical trial needs**
  - **Pre-irradiation studies**
  - **Combinations with existing agents**
  - **Neurocognitive/QOL endpoints**
  - **Imaging/biomarker correlates**



# Breast ca brain metastases in the trastuzumab era

- 34% of women with MBC
- 50+ % have stable systemic disease
- 50% have CNS death
- Survival – 1-4 yrs

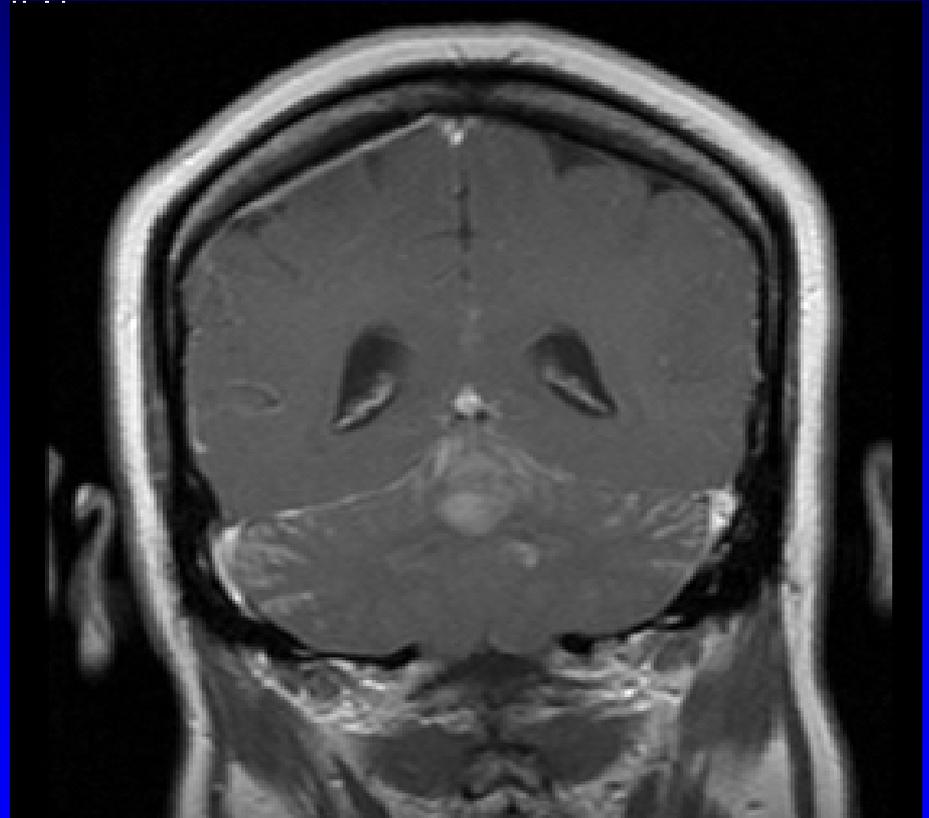
Bendell JC. Cancer 97:2972, 2003

Lai R. Cancer 101:810, 2003

Lower EE. Clin Breast Cancer 4:114, 2003

Kirsch DG. J Clin Oncol 23:2114, 2005

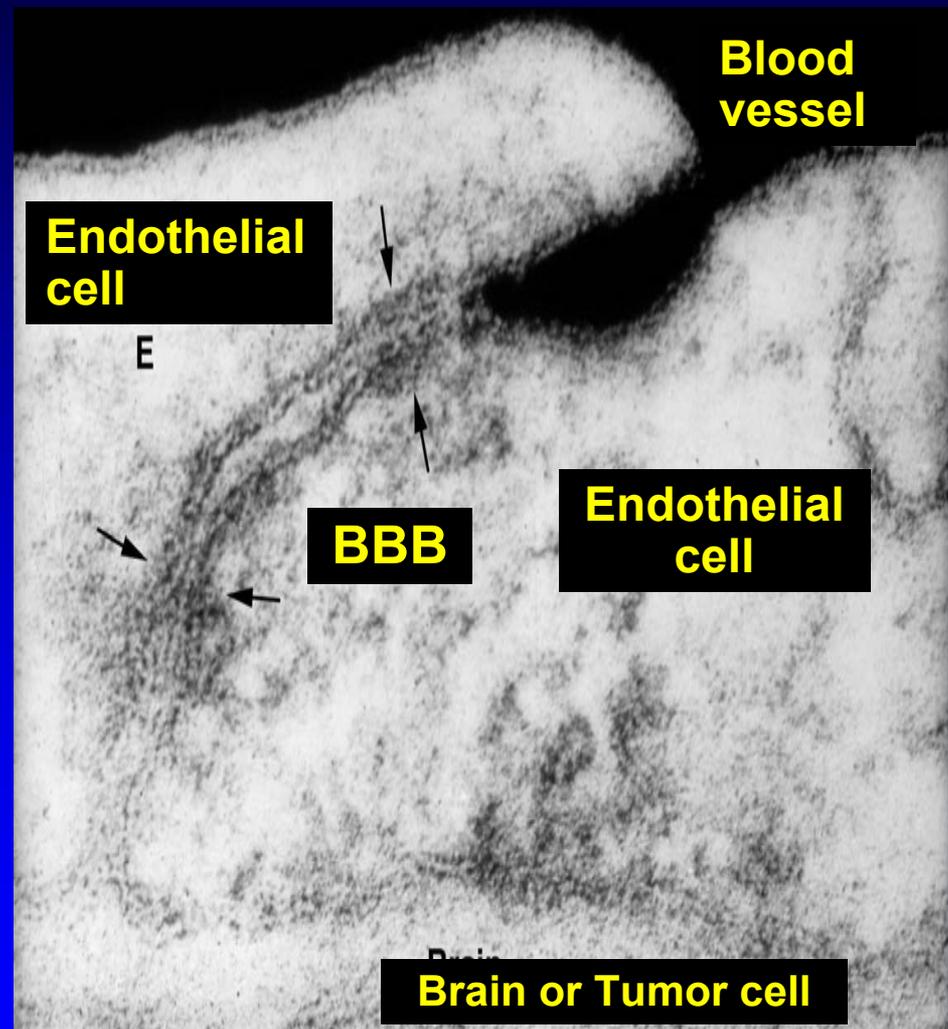
Kirsch Clin Cancer Res 9:5435, 2003



**1/3 of women with metastastatic breast ca**

# Blood-brain barrier

- **Selection of drugs**
  - lipid soluble
    - BCNU, CCNU
  - small molecules
    - cisplatin
    - hydroxyurea
    - procarbazine
    - temozolomide
- **Other issues**
  - Efflux pumps
  - Protein binding
  - Tumor interstitial pressure



# Usefulness in breast, lung cancer

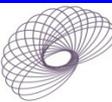
**Low**

**Intermediate**

**High**

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Nimustine	Dacarbazine	Etoposide	Taxanes
Carmustine	Methotrexate	Teniposide	Gemcitabine
Lomustine	Cytarabine	Cisplatin	Irinotecan
Procarb.	Temozolomide	Carboplatin	Cytokines
Thiotepa	Hydroxyurea	Vincristine	Doxorubicin
	Topotecan	Bleomycin	Trastuzumab



# Ability to Cross BBB

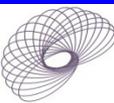
**High**

**Intermediate**

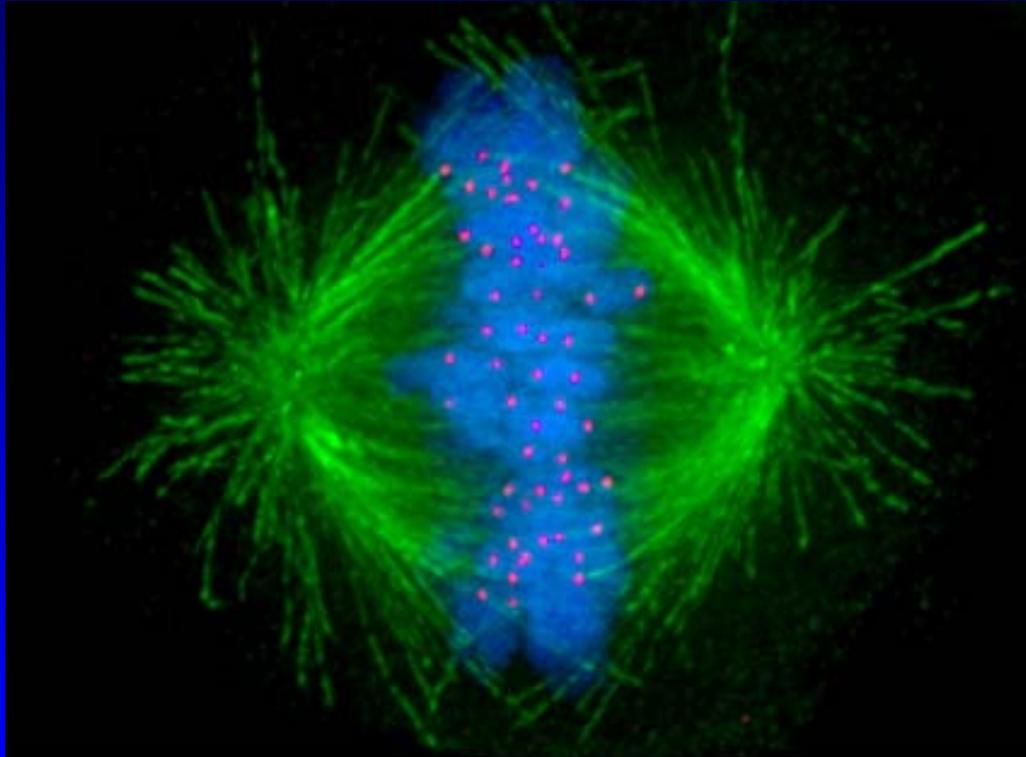
**Low**

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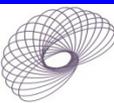
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# Microtubule Inhibitors

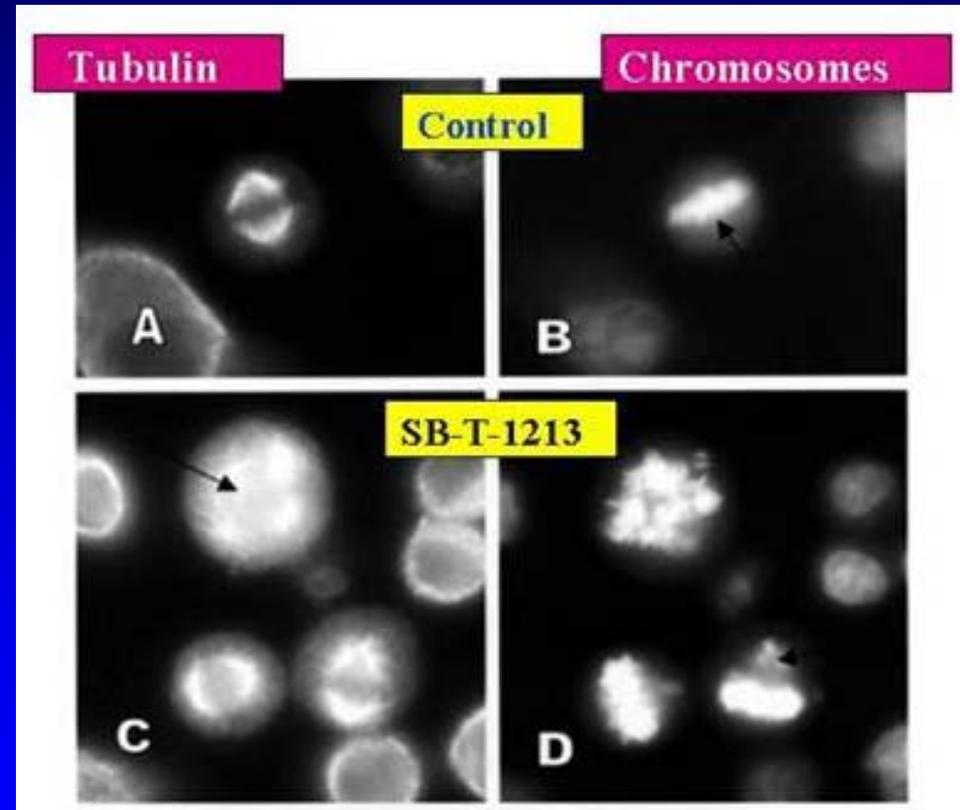


- **Inhibit tubulin polymerization**
  - vincristine
- **stabilize**
  - taxanes
  - epothilones



# Stabilization of Microtubules

- Aberrant spindle formation during mitosis
- Apoptotic cell death



Altmann K-H et al. *Biochim Biophys Acta*. 2000;1470:M79-M91;  
Rowinsky EK. *Annu Rev Med*. 1997;48:353-374.  
Jordan MA, Chem Biol 2002



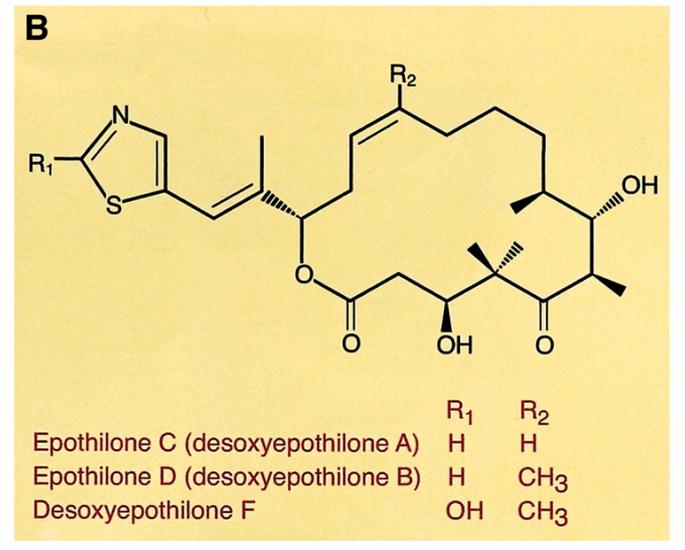
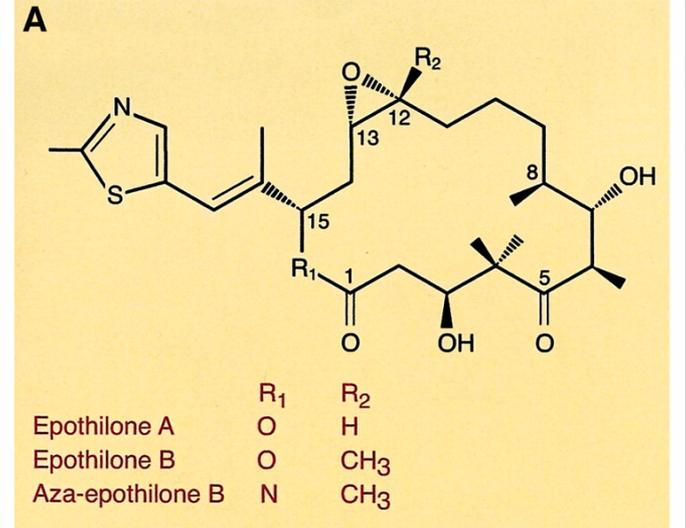
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# Epothilones

- Discovered in 1993
- Produced by *Sorangium cellulosum*
- Analogs of taxanes (paclitaxel, docetaxel)
- 16-member ring macrolides

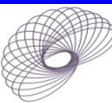
Nettles JH. *Science*. 2004;305:866-869;  
Altmann K-H et al. *Biochim Biophys Acta*. 2000;1470:M79-M91.  
Goodin, S. et al. *J Clin Oncol*; 22:2015-2025 2004



# Epothilones

## Potential advantages over taxanes

- More potent *in vitro* especially against taxane resistant cell lines
- Overcome mechanisms of taxane resistance
  - P-glycoprotein protein efflux
  - $\beta$ -tubulin gene mutations
- No need for Cremophor formulation
- Some cross the BBB



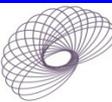
# Epothilone family

- **1<sup>st</sup> generation - natural**
  - epothilone B (patupilone)
  - epothilone D (KOS-862)
- **2<sup>nd</sup> generation - semisynthetic**
  - ixabepilone, KOS-1584, BMS-310705
- **3<sup>rd</sup> generation - fully synthetic**
  - sagopilone (ZK-EPO), ABJ-879



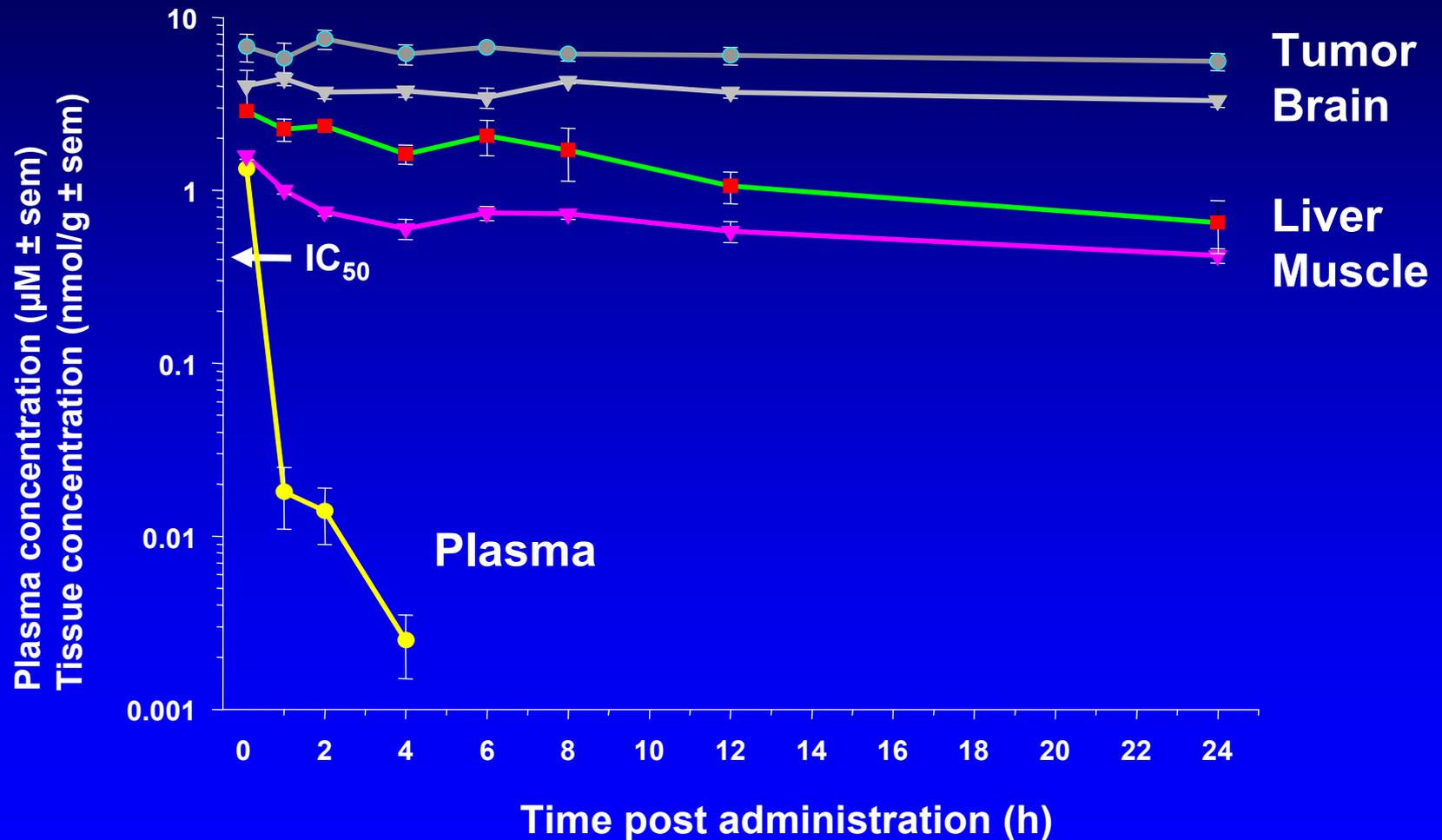
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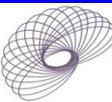


# Patupilone tissue distribution



# Patupilone phase I trials anti-tumor activity

- Q week or q 3-week regimens
- DLT: Diarrhea
  - grade 3 neuropathy 2%
  - no grade 3/4 myelosuppression
- Responses
  - Breast, NSCLC, colon, ovarian, unknown primary, carcinoid



# Phase II trial of patupilone in patients with breast cancer brain metastases

Cleveland Clinic, Cleveland (D Peereboom)

Memorial Sloan Kettering Cancer Center, New York (A Seidman)

Massachusetts General Hospital, Boston (A Eichler)

University of Michigan, Ann Arbor (C von Poznak)



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# Objectives

- **Primary**
  - 3-month CNS-progression free survival (PFS) > 35%
- **Secondary**
  - Toxicity
  - CNS response rate\* and duration of response
  - Systemic disease response rate\*\* and duration
  - Overall survival

\*McDonald criteria

\*\*bidimensional measurements



# Study Population

- **Recurrent or progressive CNS disease after whole brain radiation therapy (WBRT)**
  - 40 pts
- **Asymptomatic, unirradiated brain metastases and/or leptomeningeal metastases**
  - 10 pts



# Eligibility

- Patients may continue hormone therapy and trastuzumab
- No prior epothilones
- No neuropathy or diarrhea  $>$  grade 1 at entry



# Treatment

- **Patupilone**
  - 10 mg/m<sup>2</sup> IV over 20 min q 3 weeks
- **Follow up**
  - MRI brain q 6 weeks
  - CT Chest/abd q 6 weeks



# Statistics

- **Primary endpoint: 3-month CNS-progression free survival (PFS)**
  - Goal: > 35%
  - Rate < 15% considered negative
- **N = 40 evaluable to achieve acceptable confidence limits\* on % PFS in brain**

\*max  $\frac{1}{2}$  width of 95% confidence interval quantile 0.16



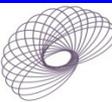
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# Patupilone in breast cancer brain metastases

## Summary

- Patupilone has activity against breast cancer brain metastases
- Early data shows 3-month CNS PFS of ~30%
- Main toxicity: diarrhea
- Worthy of further study
  - Before WBRT
  - In combination regimens



# Take home points

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