

# 4<sup>th</sup> Annual Brain Metastases Research and Emerging Therapy Conference

September 19 & 20, 2014  
Marseille, France



## Window of Opportunity Studies in Brain Metastases

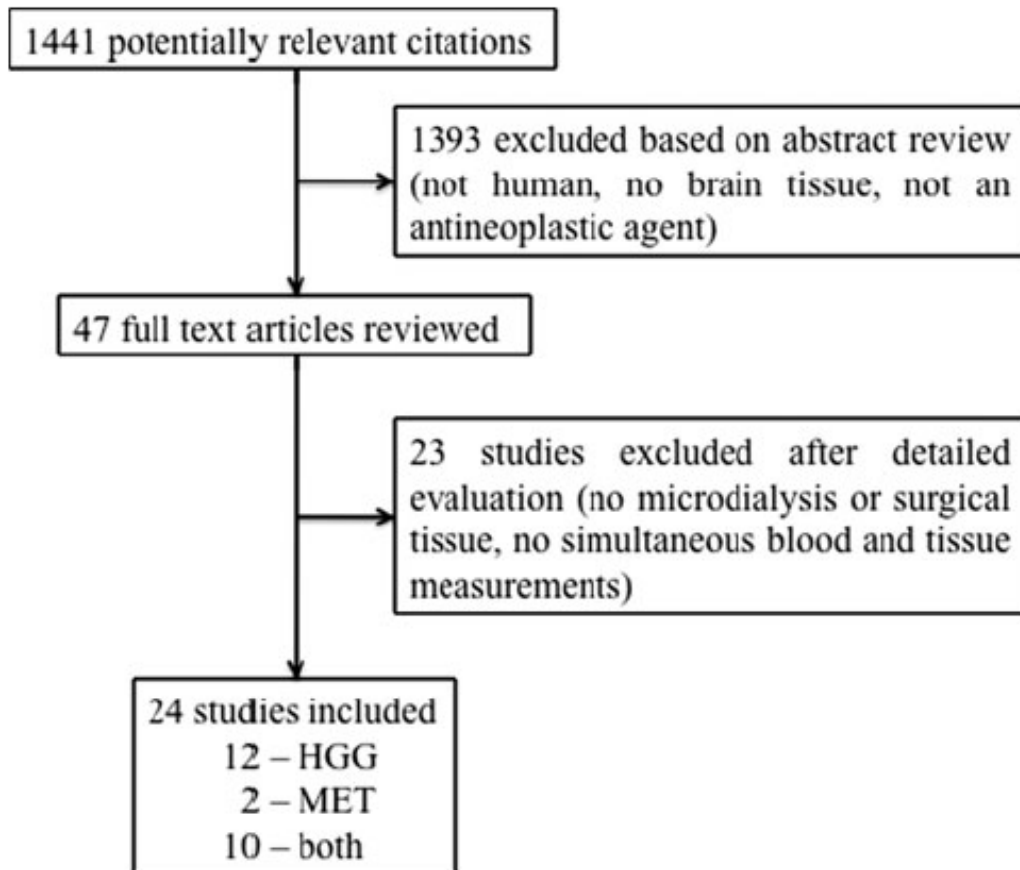
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# Tissue concentration of systemically administered antineoplastic agents in human brain tumors

Marshall W. Pitz • Arati Desai • Stuart A. Grossman •  
Jaishri O. Blakeley

J Neurooncol (2011) 104:629–638



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<b>Methods of drug tissue concentration measurements in brain metastases</b>	Microdialysis
	Surgical tissue
	Imaging
	Autopsy

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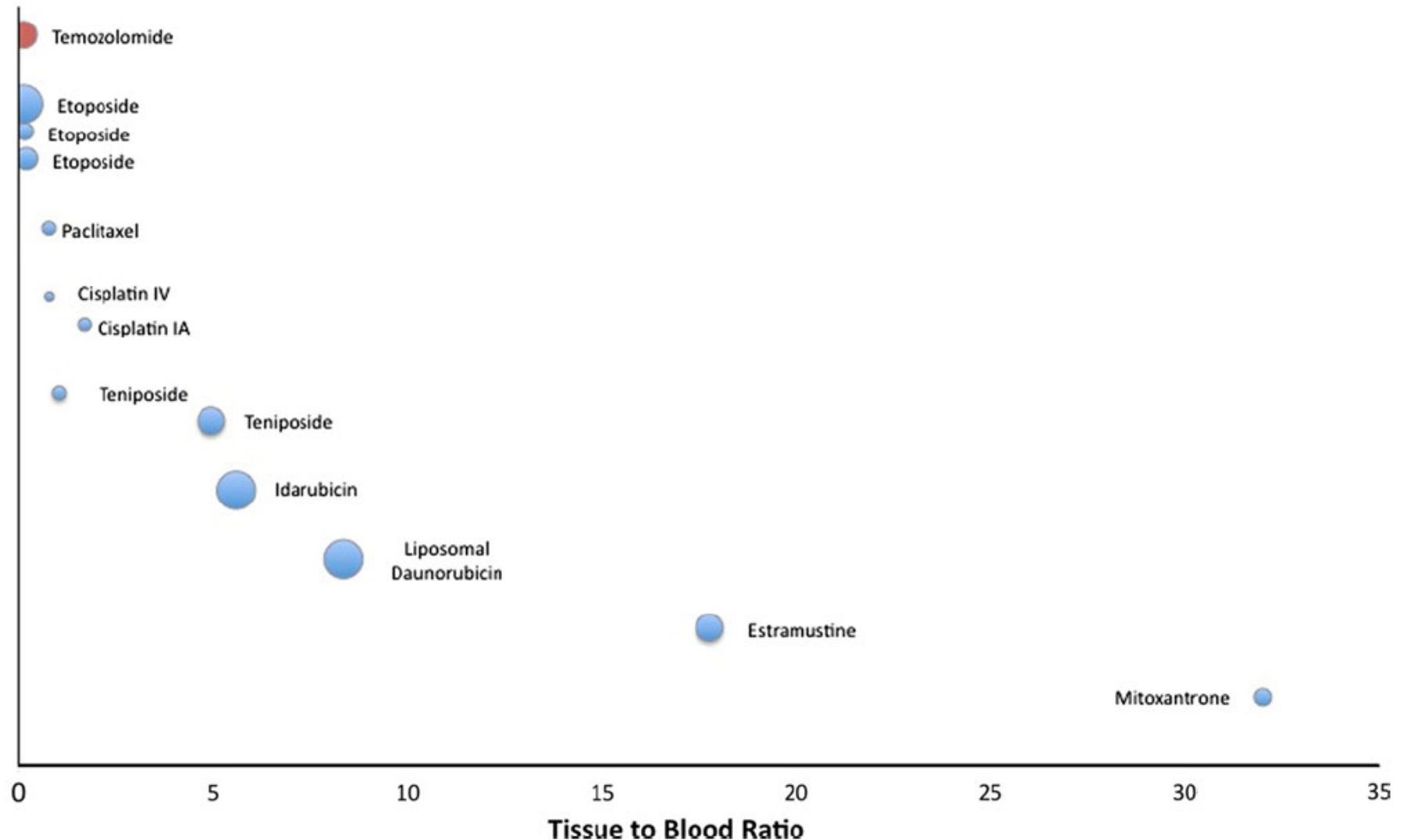
**Table 4** Metastatic brain tumor tissue concentration of agents

Drug	MW	Lipophilicity <sup>a</sup>	N	O	TBR	<i>n</i>	Primary cancer
Cisplatin [30]	298	−2.1939	2	0	0.78	18	Lung
					1.68 <sup>b</sup>	9	Lung
Liposomal Daunorubicin [31, 32]	564	0.1 <sup>c</sup>	1	10	8.36	1	Adenocarcinoma NOS
Estramustine [34]	440	5.7	1	3	17.8	2	Melanoma, Thyroid
Etoposide [35–37]	589	1	0	13	0.116	1	Adenocarcinoma NOS
					0.155	5	Not stated
					0.199	3	Lung, Melanoma
Idarubicin [39]	497	0.2	1	9	5.6	1	Breast
Mitoxantrone [42]	444	−3.1	4	6	32.02	5	Multiple <sup>d</sup>
Paclitaxel [43, 44]	854	3	1	14	0.77	8	Lung, Melanoma
Teniposide [33, 45, 46]	657	1.5	0	13	1.03	8	Lung, melanoma, colon
					4.95	2	Breast, Melanoma
Temozolomide [25]	194	−2.8	6	2	0.118	5	NSCLC

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Mittapalli RK1, Vaidhyanathan S, Sane R, Elmquist WF

**Impact of P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) on the brain distribution of a novel BRAF inhibitor: vemurafenib (PLX4032)**

J Pharmacol Exp Ther. 2012 Jul;342(1):33-40

# Indirect Evidence for BM Tissue Penetration

Bartsch R, Berghoff AS, Preusser M.

Breast cancer brain metastases responding to primary systemic therapy with T-DM1.

J Neurooncol. 2014 Jan;116(1):205-6

Torres S, Maralani P, Verma S.

Activity of T-DM1 in HER-2 positive central nervous system breast cancer metastases.

BMJ Case Rep. 2014 Aug 14;2014

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<b>Surgical tissue</b>	<b>pros</b>	<b>cons</b>
	Simultaneous blood concentration	Invasive
	Availability	Single measurement
		Blood contamination



## **Indications for Surgery**

### **BM are still being resected**

- Lesions > 3 cm in diameter
- Single lesion, well accessible ( no morbidity to be expected)
- Lesions within posterior fossa with mass effect / large edema
- In case of multiple (up to 3 lesions) with different size:
  - microsurgical removal of one large ( > 3 cm ) lesion with/without mass effect
  - subsequent RS for the remaining lesions or WBRT

# Possible projects for Neurosurgery

- Identification of target proteins in tissue of brain metastases
- Quantification of therapeutic substances within metastases
- Target binding of new drugs in tumor tissue

(can be Cx, small molecule, antibody etc.)

# **Identification of target proteins in tissue of brain metastases**

- Tissue sampling according to protocol within a prospective study
- SOP for all centers for handling of specimen in OR and shipping
- IRB
- Central processing of specimen
- Central path review

# Window-of-Opportunity Study

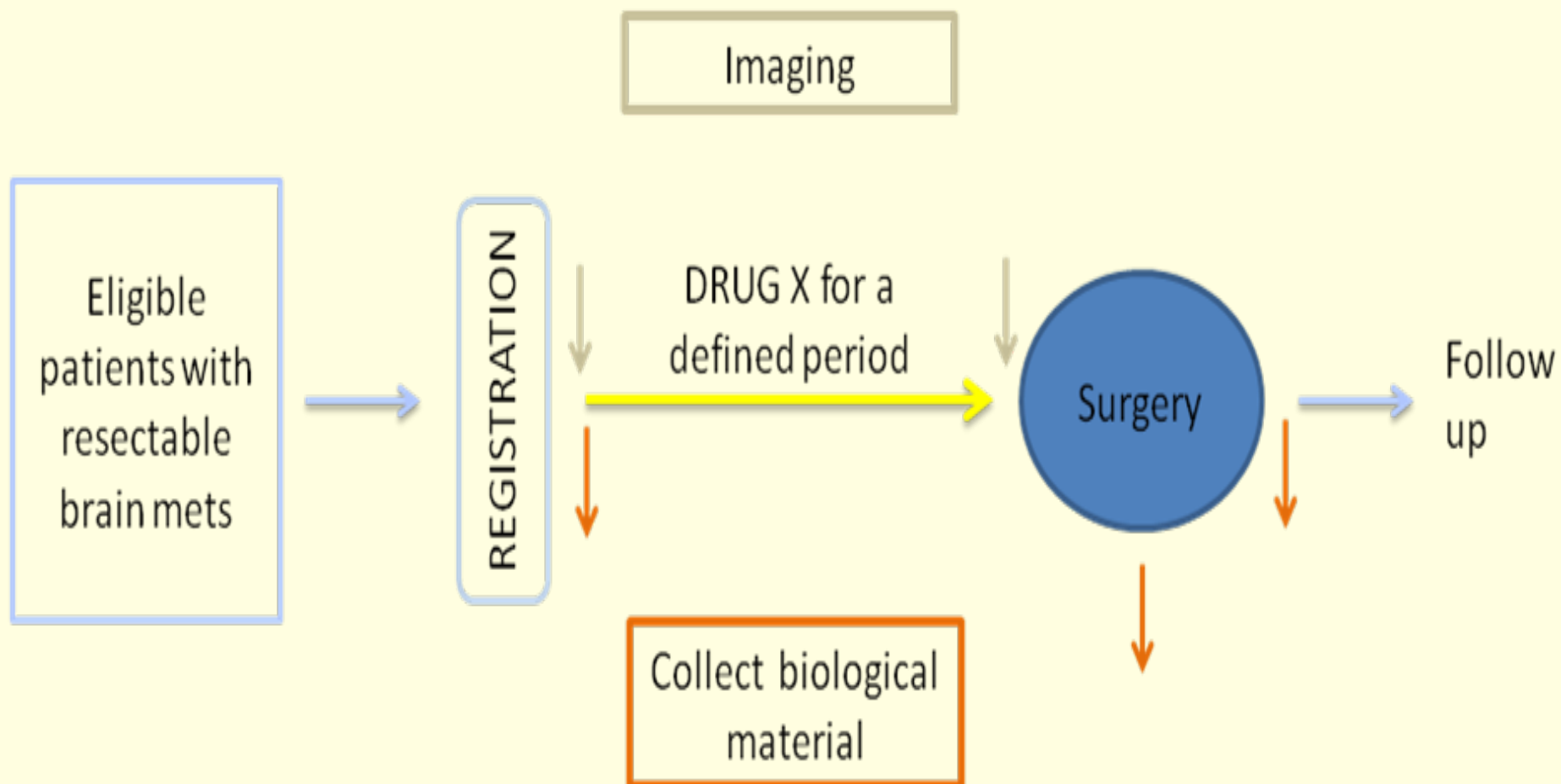
**Quantification of therapeutic substances within metastases /  
Target binding of new drugs in tumor tissue**

- Drug should be in use for cancer therapy
- Phase I studies already completed
- Toxicity known and reasonable low

# Window-of-Opportunity Study

## Quantification of therapeutic substances within metastases / Target binding of new drugs in tumor tissue

- No side effects which could be relevant for surgery (significant immediate or early bone marrow toxicity, embolic or bleeding disorders)
- Serum half life ( tissue half life) known to find most appropriate timing of drug delivery in relation to tissue sampling



# Window-of-Opportunity Study

## Elements of Protocol

- Tissue and blood/serum sampling according to protocol within a prospective study, calculation of serum level to estimate influence of intravasal drug
- intra-OP pharmacokinetics if applicable

# Window-of-Opportunity Study

## Elements of Protocol

- Central processing of specimen and central path review
- Pharmacological advice and „mentoring“ of the project



# Window-of-Opportunity Study

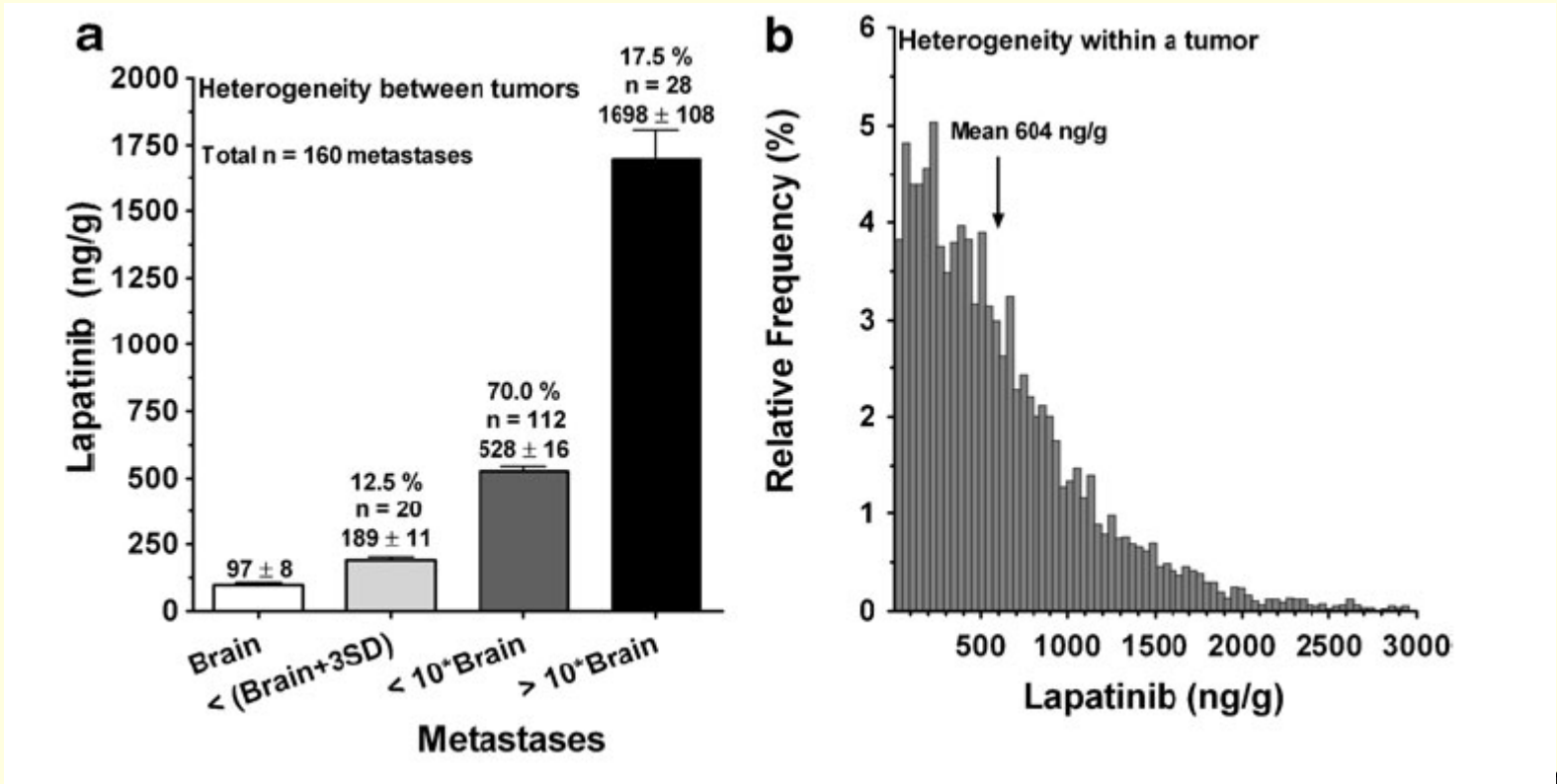
## Elements of Protocol

- SOP for all centers for handling of specimen in OR and shipping
- Oncologists on-site with specific experience with drug under investigation
- IRB and profound written information and counseling of patient prior to obtaining informed consent

# Lapatinib Distribution in HER2 Overexpressing Experimental Brain Metastases of Breast Cancer

Kunal S. Taskar • Vinay Rudraraju • Rajendar K. Mittapalli • Ramakrishna Samala • Helen R. Thorsheim • Julie Lockman • Brunilde Gril • Emily Hua • Diane Palmieri • Joseph W. Polli • Stephen Castellino • Stephen D. Rubin • Paul R. Lockman • Patricia S. Steeg • Quentin R. Smith

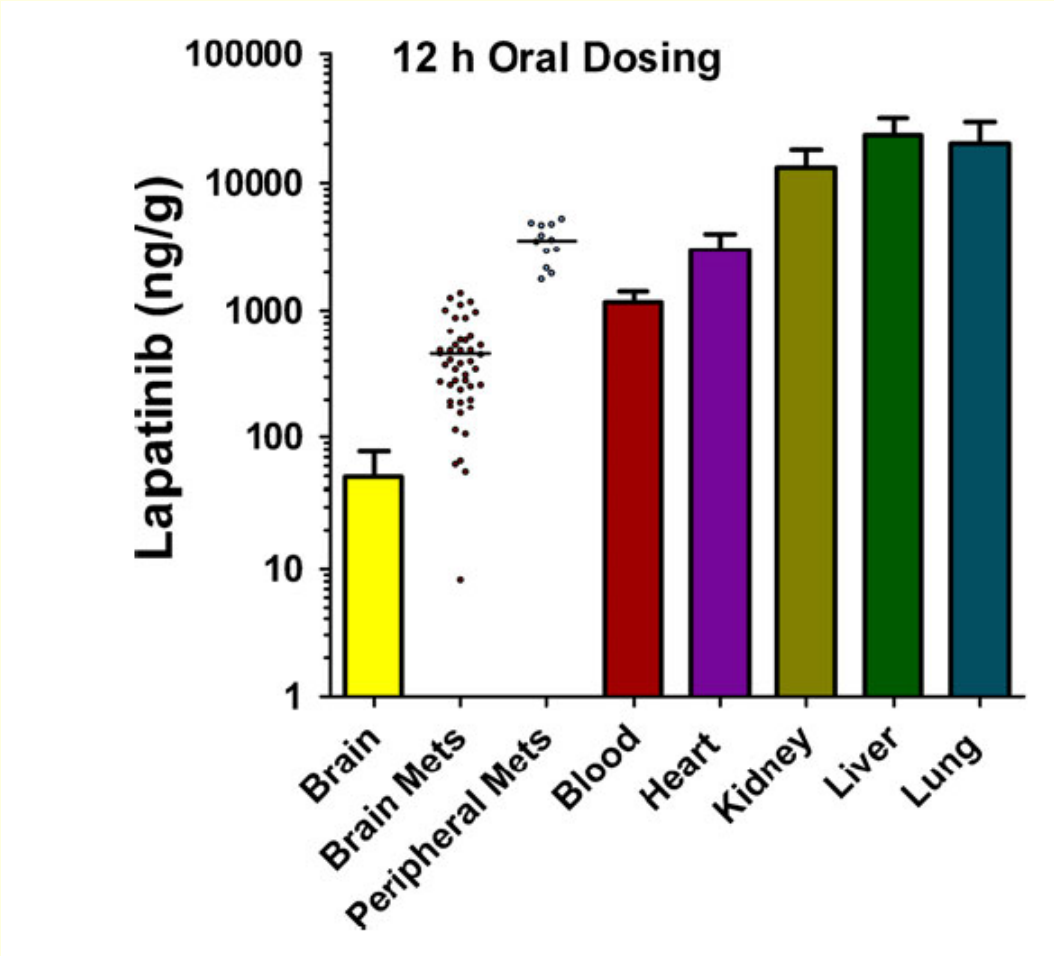
Pharm Res (2012) 29:770–781



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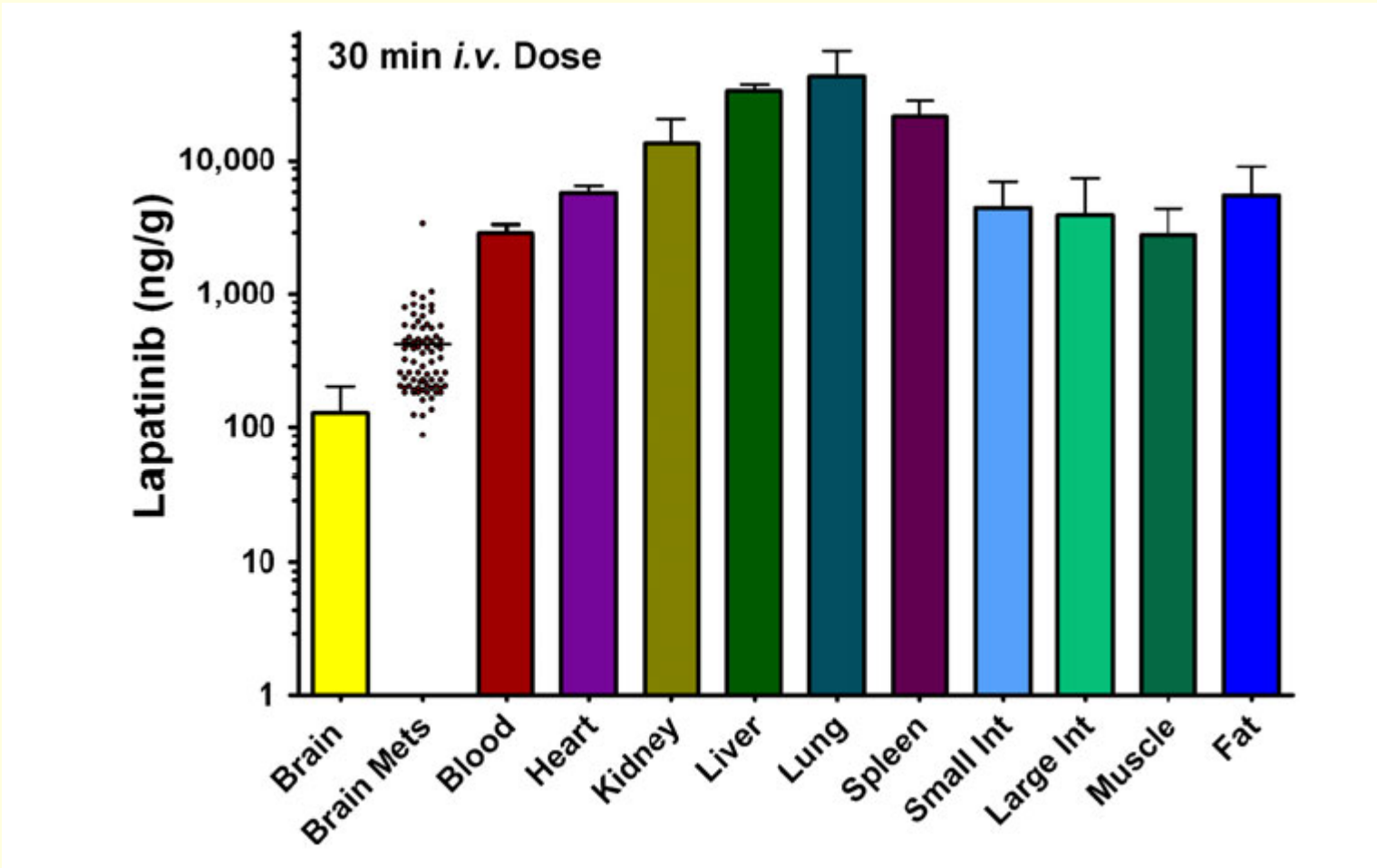
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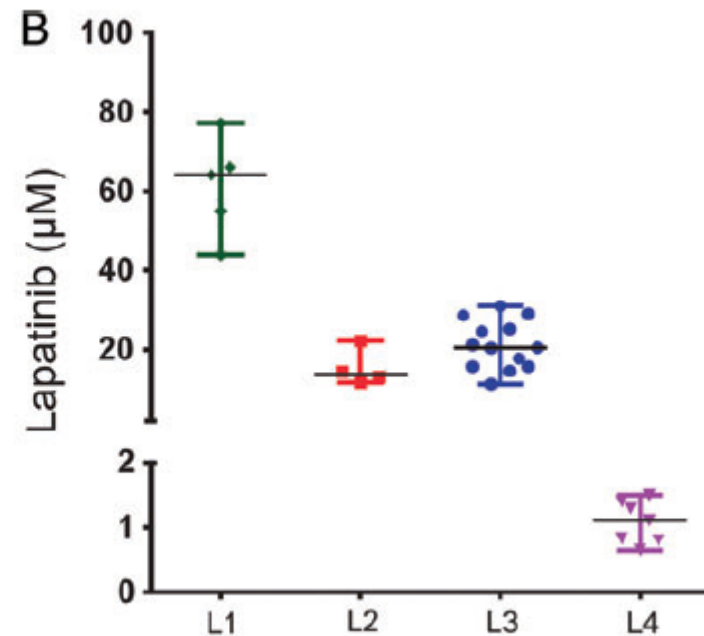
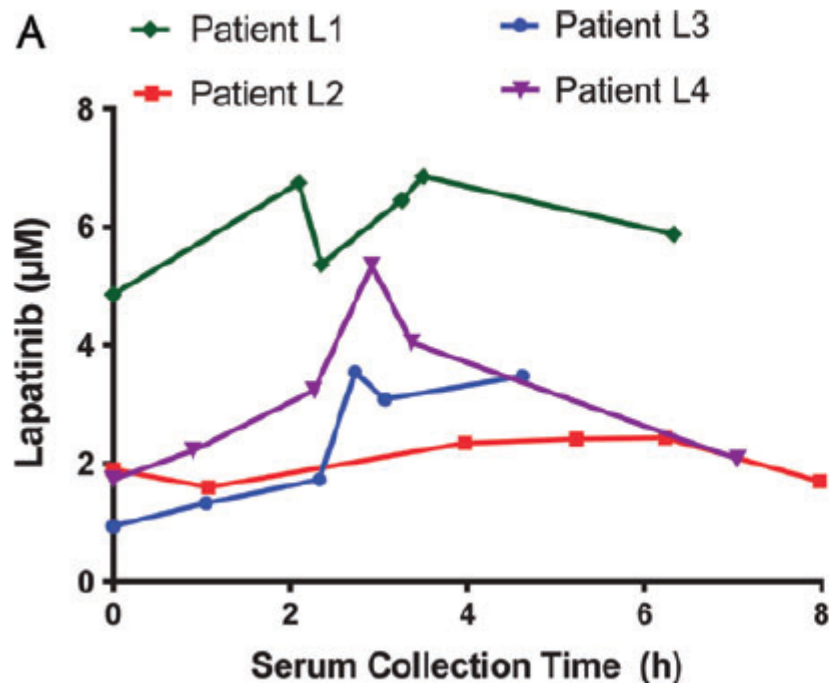


# Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study

Aki Morikawa, David M. Peereboom, Helen R. Thorsheim, Ramakrishna Samala, Rajiv Balyan, Conleth G. Murphy, Paul R. Lockman, Ahkeem Simmons, Robert J. Weil, Viviane Tabar, Patricia S. Steeg, Quentin R. Smith, and Andrew D. Seidman

**Neuro-Oncology Advance Access published July 11, 2014**

- Oral lapatinib 1250 mg/daily 2-5 days. Last dosage 2-3 h before surgery
- Serum: 1) before 2) after 1 h of drug administration, 3) at start of surgery 4) at tumor identification, 5) at tumor resection, 6) end of surgery



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**Table 3.** Lapatinib concentrations at time of BCBM resection and BCBM-to-serum ratio<sup>a</sup>

Patient	No. Preop Doses	BCBM Avg Concentration (range), $\mu\text{M}^a$	Serum 4 Concentration, <sup>b</sup> $\mu\text{M}$	BCBM/ Serum 4
L1	5	63.6 (43.9–77.2)	6.5	9.8
L2	3	14.6 (11.7–22.2)	2.4	6.0
L3	3	18.6 (11.3–31.0)	3.5	5.3
L4	2	1.0 (0.7–1.5)	5.3	0.19

<sup>a</sup>BCBM average concentrations were calculated from multiple samples of a single collected lesion.

<sup>b</sup>Serum 4 is taken at the time the BCBM is identified.

Rodent  
mean conc 2 $\mu$ M

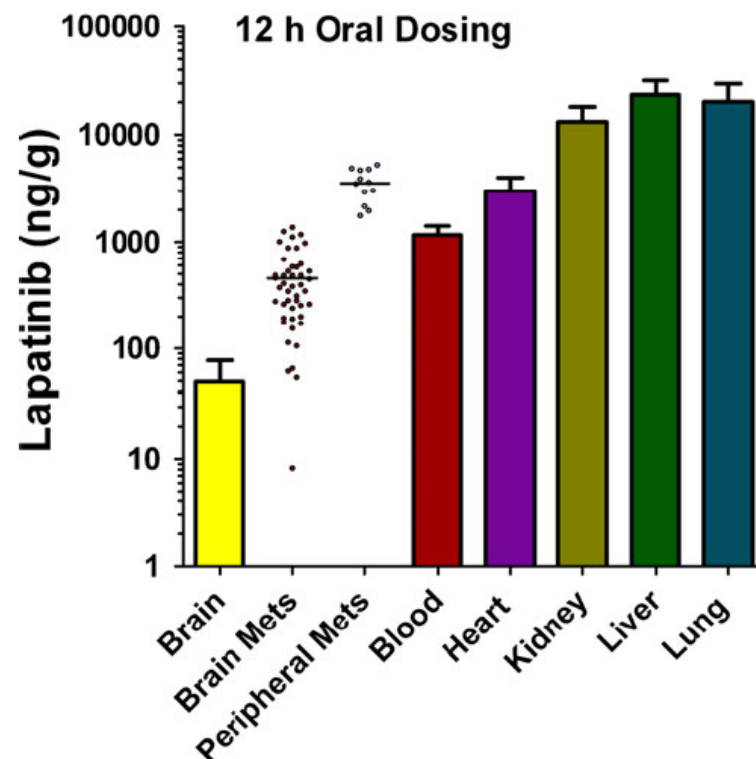
Human

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MW: 581 g/mol

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## Conclusions:

- capecitabine and lapatinib penetrate to a significant but variable degree into human BCBM
- Drug delivery to BCBM is variable and appears in some cases limiting
- Important to elucidate mechanisms which limit drug concentration



# Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study

Thomas Bachelot, Gilles Romieu, Mario Campone, Véronique Diéras, Claire Cropet, Florence Dalenc, Marta Jimenez, Emilie Le Rhun, Jean-Yves Pierga, Anthony Gonçalves, Marianne Leheurteur, Julien Domont, Maya Gutierrez, Hervé Curé, Jean-Marc Ferrero, Catherine Labbe-Devilliers

*Lancet Oncol* 2013; 14: 64–71

**Findings** Between April 15, 2009, to Aug 2, 2010, we enrolled 45 patients, 44 (98%) of whom were assessable for efficacy, with a median follow-up of 21·2 months (range 2·2–27·6). 29 patients had an objective CNS response (65·9%, 95% CI 50·1–79·5); all were partial responses. Of all 45 treated patients, 22 (49%) had grade 3 or grade 4 treatment-related adverse events, of which the most common were diarrhoea in nine (20%) patients and hand-foot syndrome in nine (20%) patients. 14 (31%) patients had at least one severe adverse event; treatment was discontinued because of toxicity in four patients. No toxic deaths occurred.

**Interpretation** The combination of lapatinib and capecitabine is active as first-line treatment of brain metastases from HER2-positive breast cancer. A phase 3 trial is warranted.

# Window-of-Opportunity Study

Promising tool

- to obtain information about inter-individual variation of drug concentrations and optimal drug dosage of new compounds for systemic treatment of BM
- to reduce risk of
  - using ineffective drugs (waste of opportunity)
  - missing effective drugs (loss of opportunity)
- for efficient and evidence-based planning of early phase II trials

