

# **Place of chemotherapy in the management of brain metastases**

**Pr Antoine Carpentier, hôpital Avicenne**

# 42-yr old nurse

March 2011: Headaches

→ MRI: (16/3/2011) : 2 cerebellar lesions



→ CT scan + PET FDG: one mediastinal adenopathy



→ echo-endoscopy biopsy:

**lung adenocarcinoma**

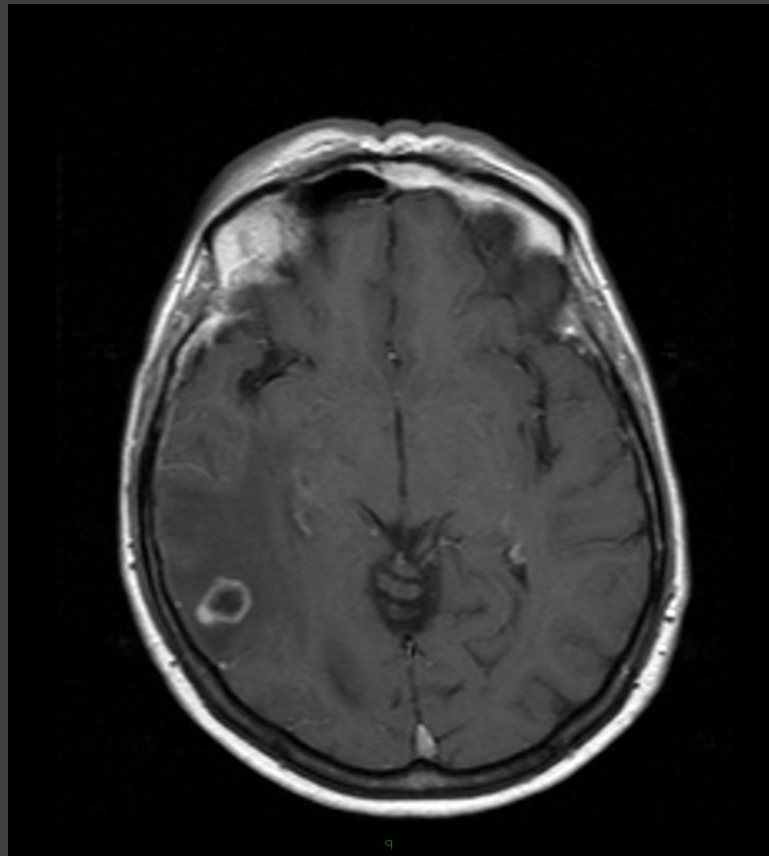
**Mutated EGFR**

⇒ **sensitivity to erlotinib/gefitinib**

# Oncological Management of brain metastases: *2 cases*

Metastase eligible for surgical  
resection or radiosurgery

#10%



Metastase non eligible for surgical  
resection or radiosurgery

#90%

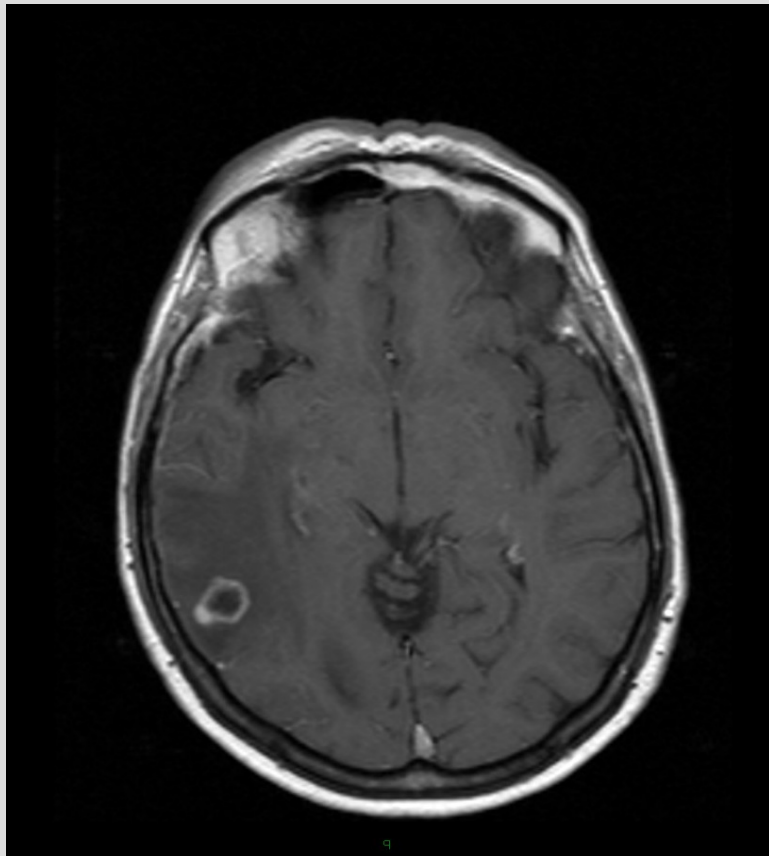


# Surgical resection or Radiosurgery ?

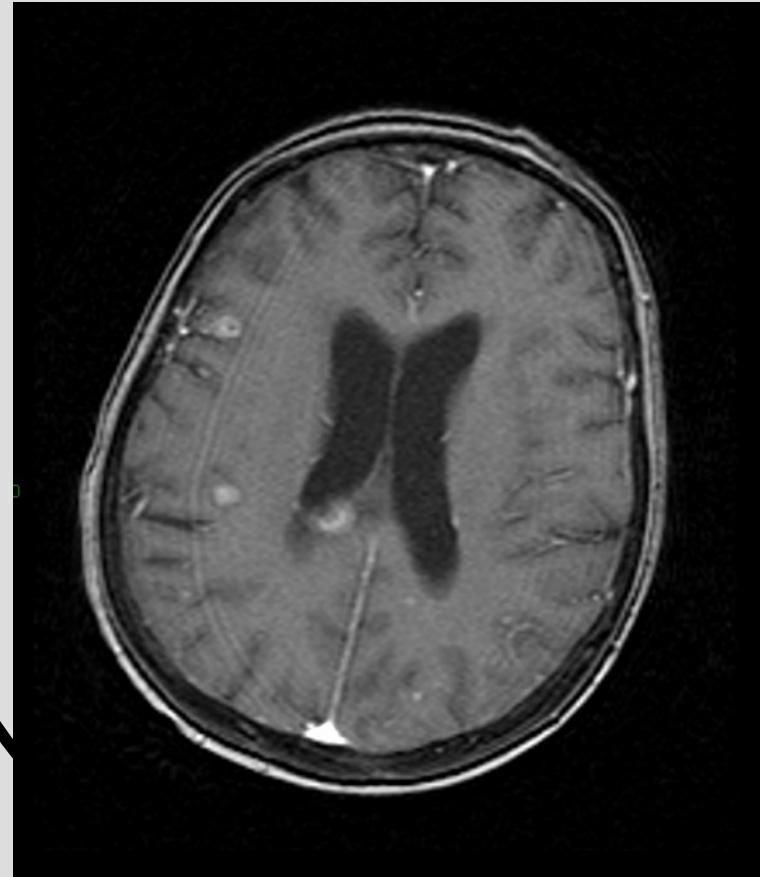
- **Surgery if**
  - size > 35mm
  - If histology required
  
- **Radiosurgery if**
  - Size < 30mm
  - Up to 3 (or 4) metastases

# Management of brain metastases: *2 cases*

Metastase eligible for surgical resection or radiosurgery



Metastase non eligible for surgical resection or radiosurgery



# Whole brain radiotherapy (WBRT)

standard protocol =  
30 Gy in 10 fractions /12 days

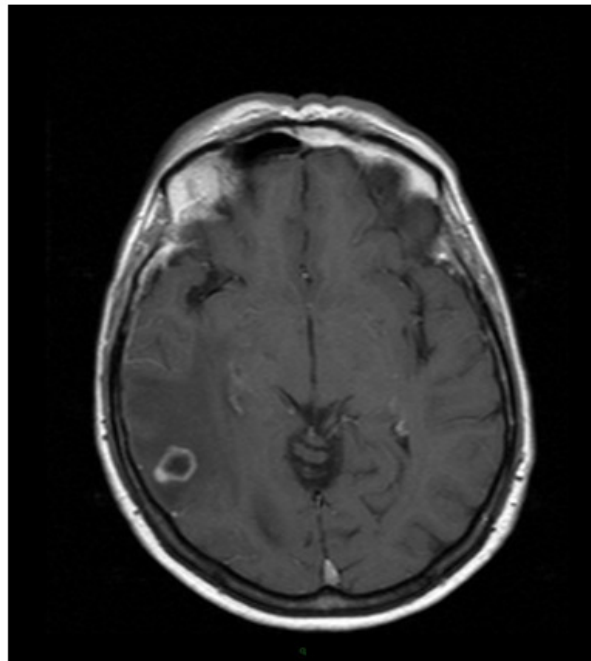
radiological response rate: # 30% in NSCLC  
# 50% in breast cancer

## Management of brain metastases:

*2 cases*

Metastase eligible for surgical resection or radiosurgery

#10%



Metastase non eligible for surgical resection or radiosurgery

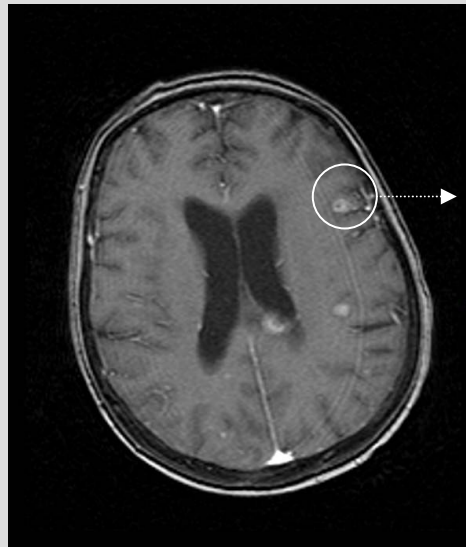
#90%



**La chimiothérapie peut elle être une alternative?**

# accès de la molécule à la métastase:

« La BHE est le problème »



**BHE est elle vraiment fonctionnelle?**



# Structure of Blood Brain Barrier

1. Endothelium
  - a. tight intercellular junctions
  - b. relative lack of vesicular transport
2. Pericytes with smooth muscle- like properties
3. Astroglial process ( >95% of the luminal vessel surface)

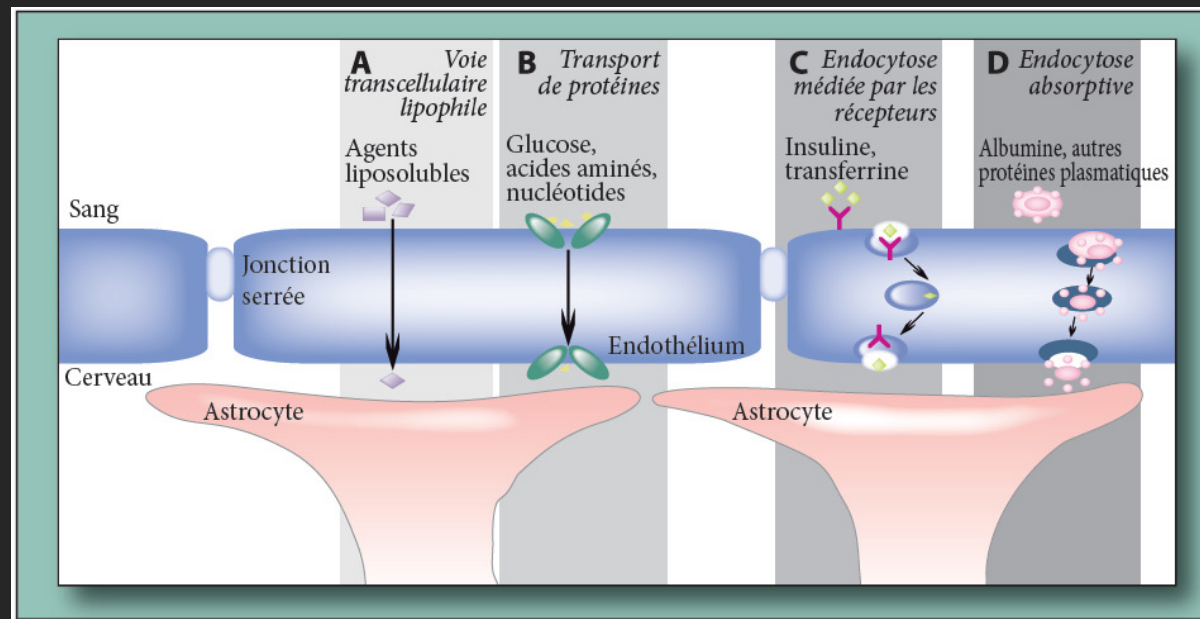
# BBB composition

## Protein components:

- Claudin & Occludin heterodimer (no occludin → Breakdown of BBB)
- Junction Adhesion Molecules (Ig superfamily) : cell-to-cell adhesion and leukocyte transmigration through BBB
- Accessory proteins (ZO-1, ZO-2, ZO-3, cingulin, MAGUKS )

# Transports

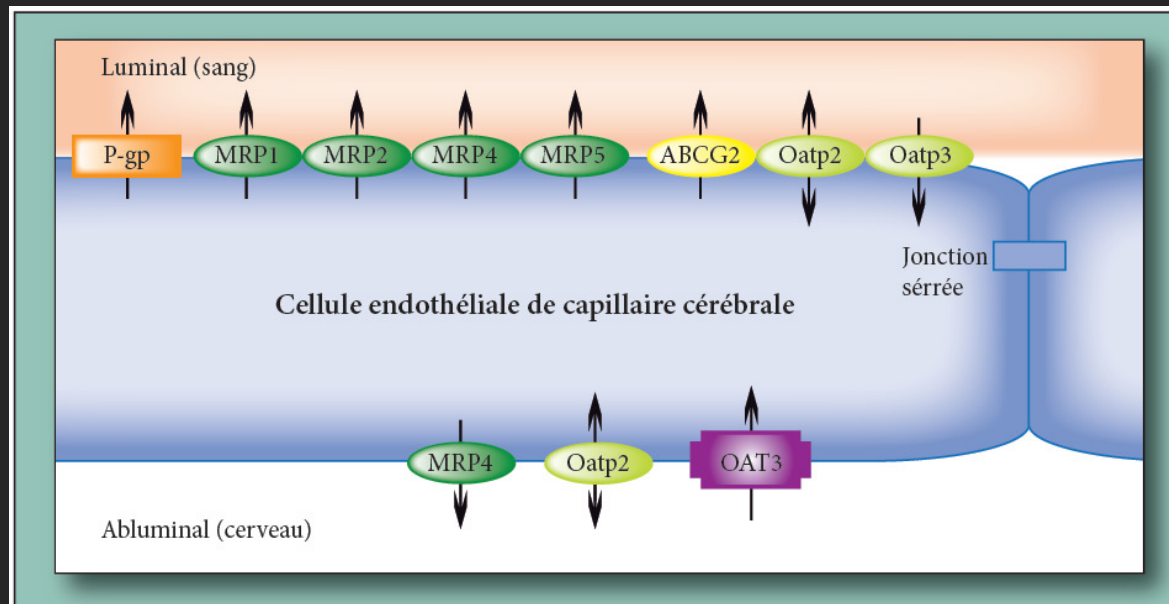
- Diffusion : pour les petits composés (< 400 Da), apolaires et lipophiles
- Transports actifs : composés polaires et hydrophiles



- transporteurs d'efflux

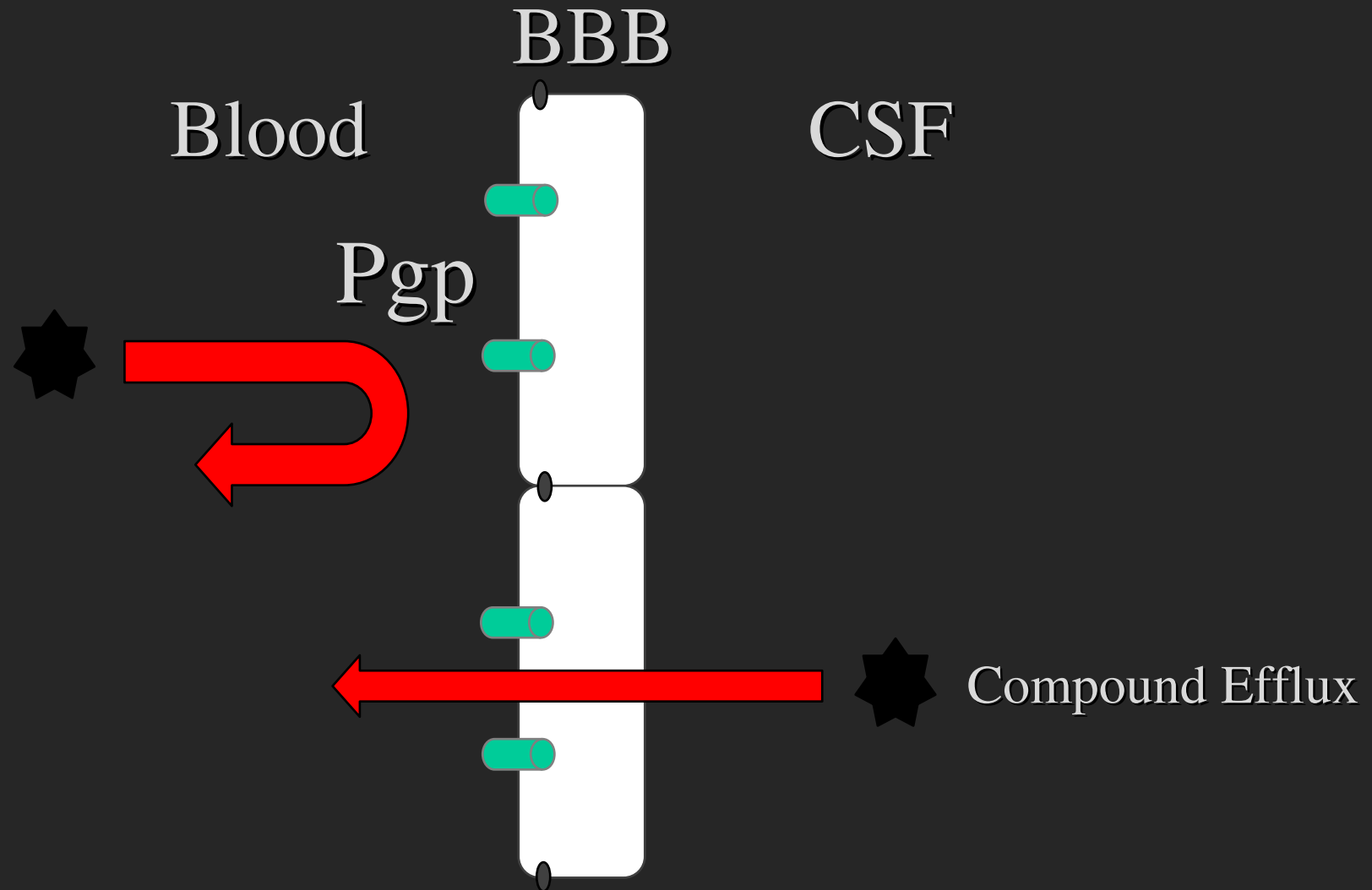
# Les transporteurs d'efflux

- La P-glycoprotéine (P-gp) encore appelée ABCB1, MDR1
- Multidrug Resistance-associated Proteins (MRP)
  - de la famille ABCC (MRP1 à MRP9)
- Breast Cancer Resistance Protein (BRCP), encore appelée ABCG2
- Les transporteurs d'anions (OAT) et de cations (OCT) organiques



# Les transporteurs d'efflux

→ Unidirectional Drug Transport at the BBB



# Transporteurs et spécificités de substrats

## ***Les transporteurs d'efflux composant la BHE et les agents chimiothérapeutiques***

<b>Transporteur</b>	<b>Nom HUGO</b>	<b>Substrats</b>
P-glycoprotéine <i>gène MDR1</i>	ABCB1	Doxorubicine, daunorubicine, docetaxel, épirubicine, idarubicine, vinblastine, étoposide
MRP1	ABCC1	Etoposide, teniposide, daunorubicine, doxorubicine, épirubicine, melphalan, vincristine, vinblastine
MRP2	ABCC2	Similaire au MRP1
MRP3	ABCC3	Similaire au MRP1
MRP4	ABCC4	Méthotrexate, 6-mercaptopurine, thioguanine
MRP5	ABCC5	6-mercaptopurine, thioguanine
MRP6	ABCC6	Actinomycine D, cisplatine, daunorubicine, doxorubicine, étoposide
BCRP	ABCG2	Mitoxantrone, méthotrexate, SN-38, topotecan, imatinib, erlotinib, gefitinib

# Principales chimiothérapies passant la BHE

## Alkylants

- Nitrosourées (BCNU, CCNU) 15-30%
- Témazolomide 20-30%
- Procarbazine

- Sels de Platine (Carboplatine, CisPlat) <5%

## Autres

- *Poison Fuseau mitotique (vincristine) 1%*
- *Inhib Topo 2 (Etoposide) 1-5%*
- *Capecitabine (Xeloda)*

# TKI and the blood-brain-barrier

CSF studies (mainly in tumoral meningitis) (Jackman 2006; Masuda 2011)

- CSF levels < 10% serum levels
- Erlotinib > Gefitinib?
- Pulsatile high dose regimen? (Grommes 2011)

PET studies in 2 pts: Erlotinib accumulation in brain metastases  
(Weber, 2011)

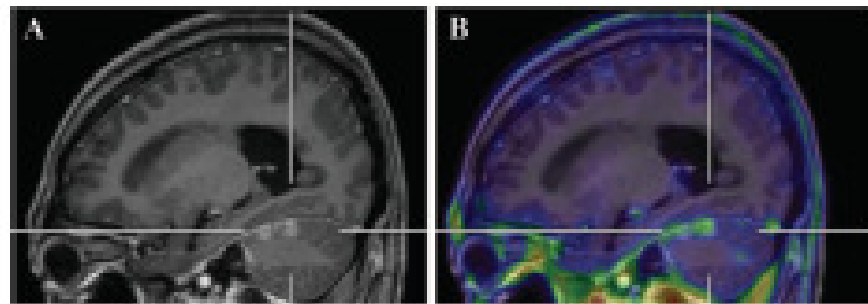


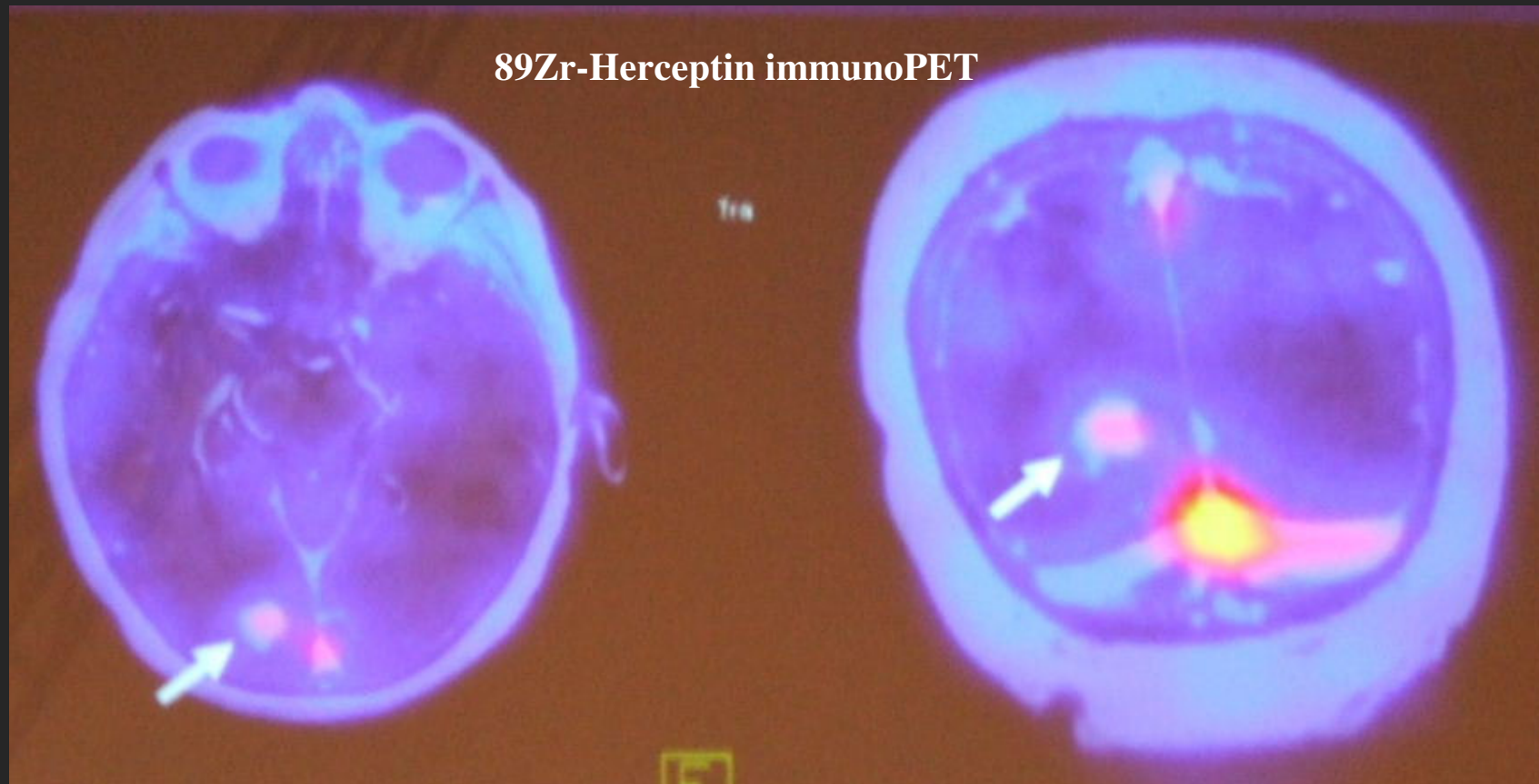
FIGURE 3. Gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) (A) coregistered with [<sup>11</sup>C]-erlotinib positron emission tomography (PET) (sum image, 5–60 minutes after tracer administration) (B) of a 32-year-old woman diagnosed with non-small cell lung cancer and brain metastases harboring an exon 19 mutation. The selected MRI image shows



# Alterations of the BBB

- Tumor itself
- Radiation
- high blood pressure
- Trauma, Ischemia, Inflammation, Infection

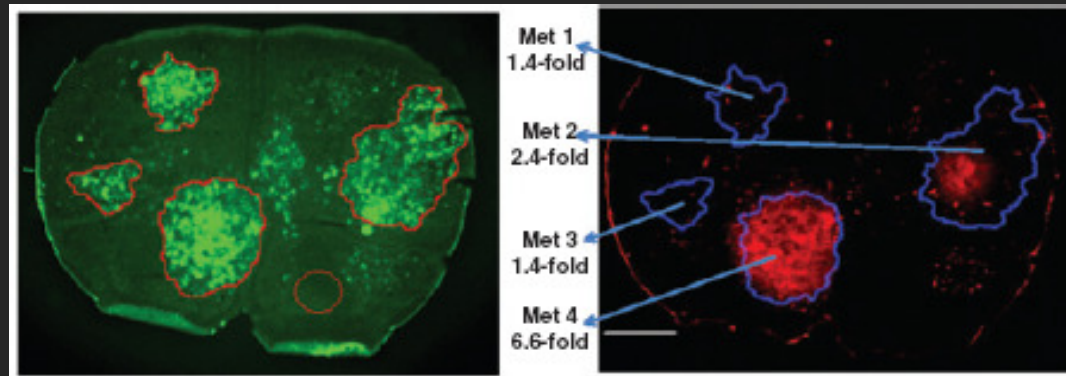
# Métastases cérébrales HER2+



# Heterogeneous Blood-Tumor Barrier Permeability Determines Drug Efficacy in Experimental Brain Metastases of Breast Cancer

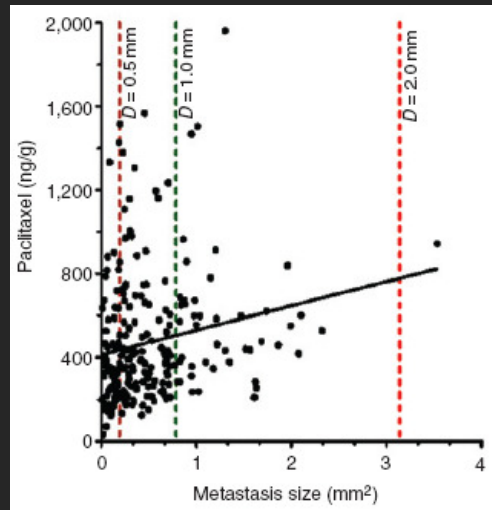
Paul R. Lockman<sup>1</sup>, Rajendar K. Mittapalli<sup>1</sup>, Kunal S. Taskar<sup>1</sup>, Vinay Rudraraju<sup>1</sup>, Brunilde Gril<sup>2</sup>, Kaci A. Bohn<sup>1</sup>, Chris E. Adkins<sup>1</sup>, Amanda Roberts<sup>1</sup>, Helen R. Thorsheim<sup>1</sup>, Julie A. Gaasch<sup>3</sup>, Suyun Huang<sup>4</sup>, Diane Palmieri<sup>2</sup>, Patricia S. Steeg<sup>2</sup>, and Quentin R. Smith<sup>1</sup>

Clin K Res 2010

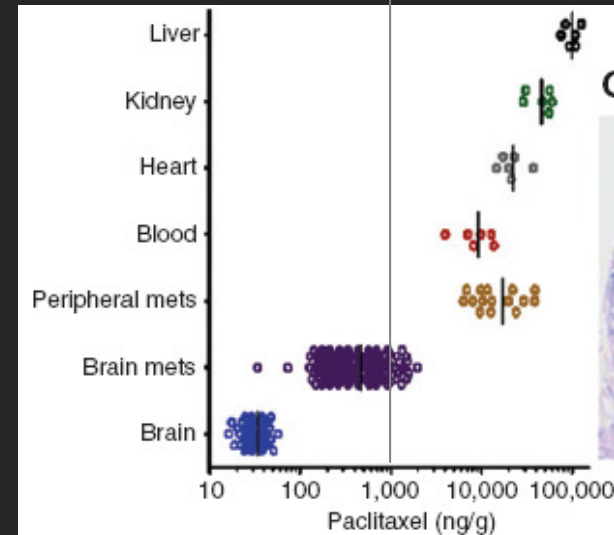


GFP-transfected 231-BR

Texas Red dextran



<sup>14</sup>C-paclitaxel concentration versus lesion size of individual metastases

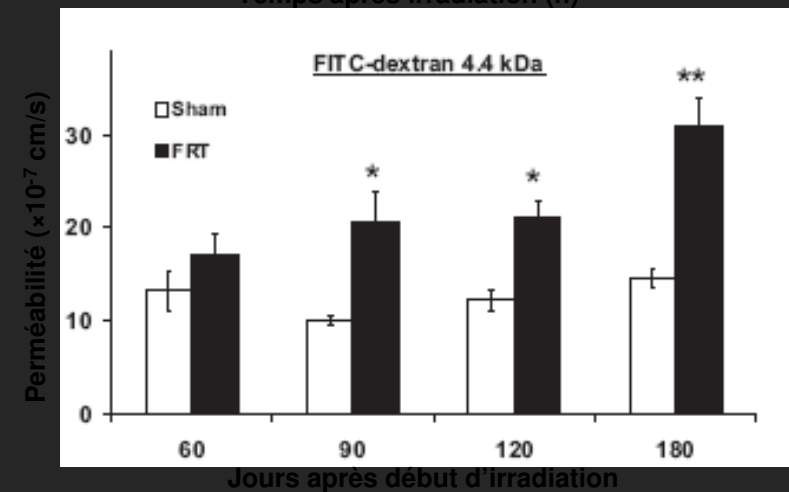
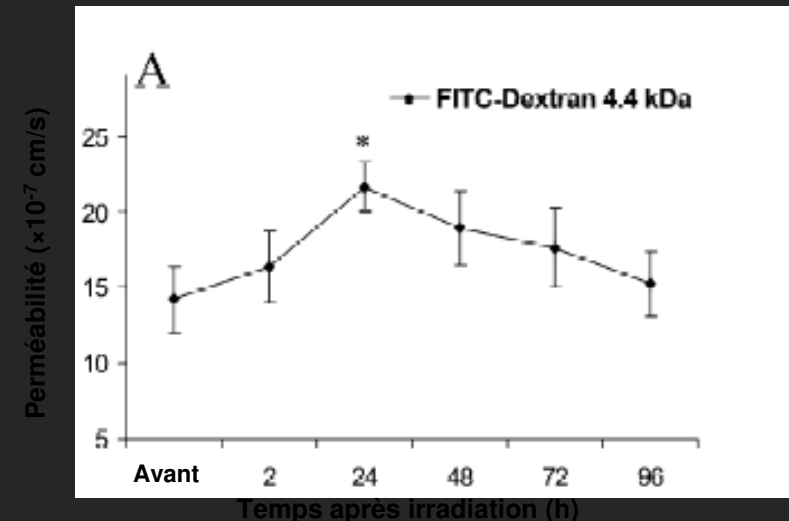


<sup>14</sup>C-paclitaxel concentration (ng/g)  
in brain and 231-BR-Her2 brain metastases

# Radiothérapie Encéphalique in toto

Augmentation de la perméabilité :

- Rapide avec une radiothérapie à simple dose  
(une fraction de 20 Gy)<sup>1</sup>
- Retardée avec une radiothérapie à dose fractionnée (une fraction de 2 Gy 5 fois/semaine durant 4 semaines)<sup>2</sup>



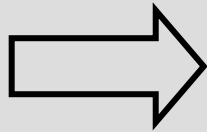
(1) Yuan et al. Brain Research, 2003

(2) Yuan et al. International Journal of Radiation Oncology, 2006

# Drug delivery through the BBB

- [intracerebral injections ]
- Pharmaceutical disruption of the BBB :
  - osmotic means (IV Mannitol)
  - vasoactive substances such as RMP-7 (bradykinin agonist)
  - blocking of active efflux transporters
  - localized exposure to ultrasound
- transport systems:
  - Carrier/ receptor-mediated transcytosis (for ex transferrin receptors)
  - nanoparticles / liposomes

# Chemotherapy and brain metastases



Non small cell Lung cancer  
No previous chemotherapy  
No previous radiotherapy

Auteurs	date	chimiothérapie	n	RR cérébrale
Thomas	1990	cisplatine	30	27%
Minotti	1998	cisplatine + téniposide	23	35%
Crino	1999	cisplatine + gemcitabine	26	41%
Franciosio	1999	cisplatine + étoposide	43	30%
Fugita	2000	cisplatine + ifosfamide + irinotecan	30	50%
Robinet	2001	cisplatine + vinorelbine	86	27%
Cortes	2003	cisplatine + Taxotère + vinorelbine/gemcitabine	25	38%
Cortot	2006	cisplatine + TMZ	50	12%
Barlesi	2011	Cisplatine+Alimta	43	42%
Bailon	2012	Carboplatine+Alimta	30	40%

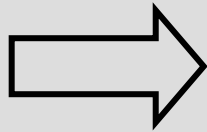
**platine + others**

**32%**



Brain metastases are chemosensitive

# Chemotherapy and brain metastases



Non small cell Lung cancer  
 No previous chemotherapy  
 No previous radiotherapy

Auteurs	date	chimiothérapie	n	RR cérébrale	RR systémique
Thomas	1990	cisplatine	30	27%	
Minotti	1998	cisplatine + téniposide	23	35%	26%
Crino	1999	cisplatine + gemcitabine	26	41%	37%
Francioso	1999	cisplatine + étoposide	43	30%	
Fugita	2000	cisplatine + ifosfamide + irinotecan	30	50%	62%
Robinet	2001	cisplatine + vinorelbine	86	27%	35%
Cortes	2003	cisplatine + Taxotère + vinorelbine/gemcitabine	25	38%	50%
Cortot	2006	cisplatine + TMZ	50	12%	12%
Barlesi	2011	Cisplatine+Alimta	43	42%	35%
<b>Cisplatine + others</b>				<b>32%</b>	<b>33%</b>



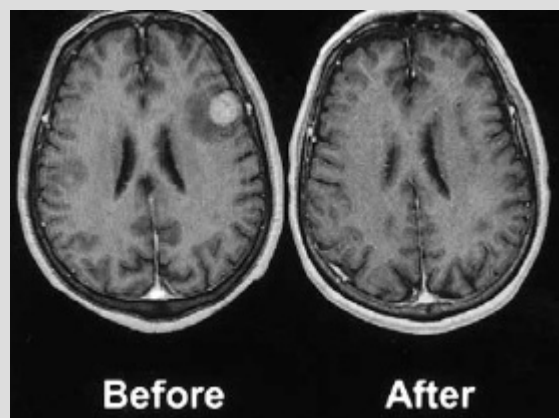
Same chemosensitivity for brain/lung lesions

# Tyrosine kinase inhibitors (TKI)

NSCLC + Brain metastases

Treatment with TKI (upfront in #50%)

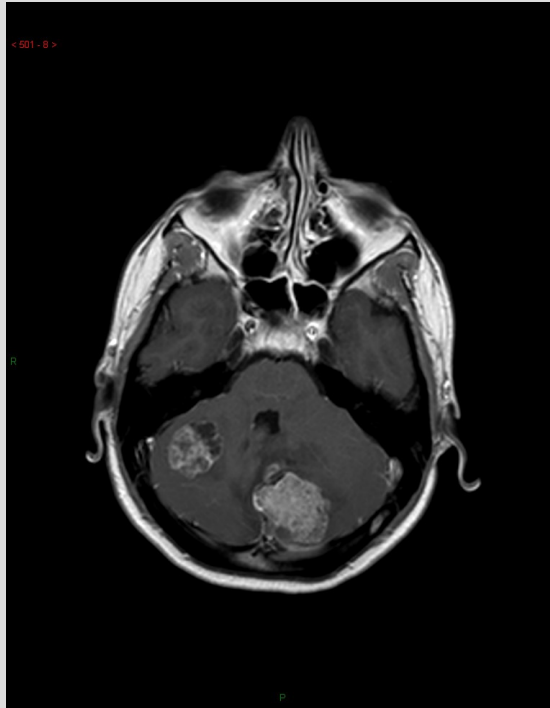
Ref		TKI	n	Brain RR	Extra neural RR
Kim	2009	Gefitinib or Erlotinib	23	74%	70%
Kim	2010 (asco)	Gefitinib	23	70%	
Porta	2011	Erlotinib	17	82%	88%



From Chiu et al, Lung Cancer 2005

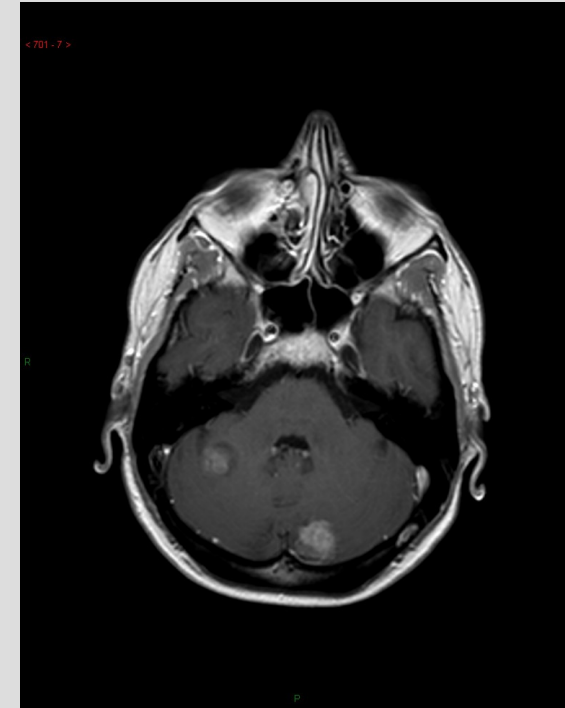


# 42-yr old nurse



7 avril 2011

Gefitinib



20 mai 2011

Courtesy of Dr A Augier, Hop Avicenne

## **LANDSCAPE (phase IIa)**

- **breast cancer expressing HER2 with brain metastases**
- **n= 45 pts**
- **previously treated with trastuzumab in 42 pts**

**→ Ttt with Lapatinib + Capecitabine.**

**Cerebral Response rate ( $\geq 50\%$  reduction) = 67%**

## Original article

### Results of a phase III study of early *versus* delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Français de Pneumo-Cancérologie (GFPC) Protocol 95-1\*

NSCLC

No previous treatment

Brain met

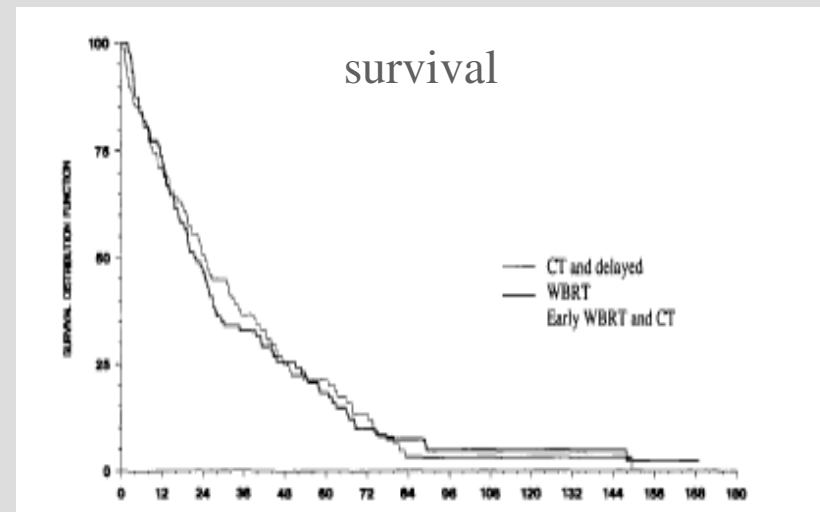
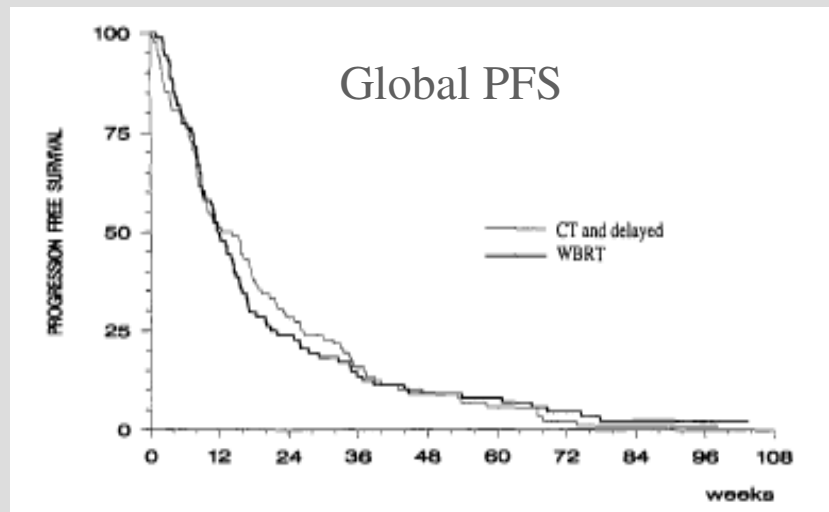
Chemotherapy alone

→ 27% brain RR

Chemotherapy + WBRT → 33% brain RR

CT: n=86

CT+RT: n=85



# Timing of WBRT still difficult to define

- no impact in NSCLC
- positive impact in SCLC, especially in a prophylactic setting

- **Role of radiosensitivity?**

- **Role of blood-brain-barrier (BBB) ?**

- macroscopic metastases, with disrupted BBB

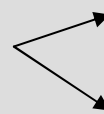
→ chemo alone? (with WBRT at relapse +++)

- microscopic metastases, with intact BBB

→ upfront WBRT ?



**Need for randomized trial ++**

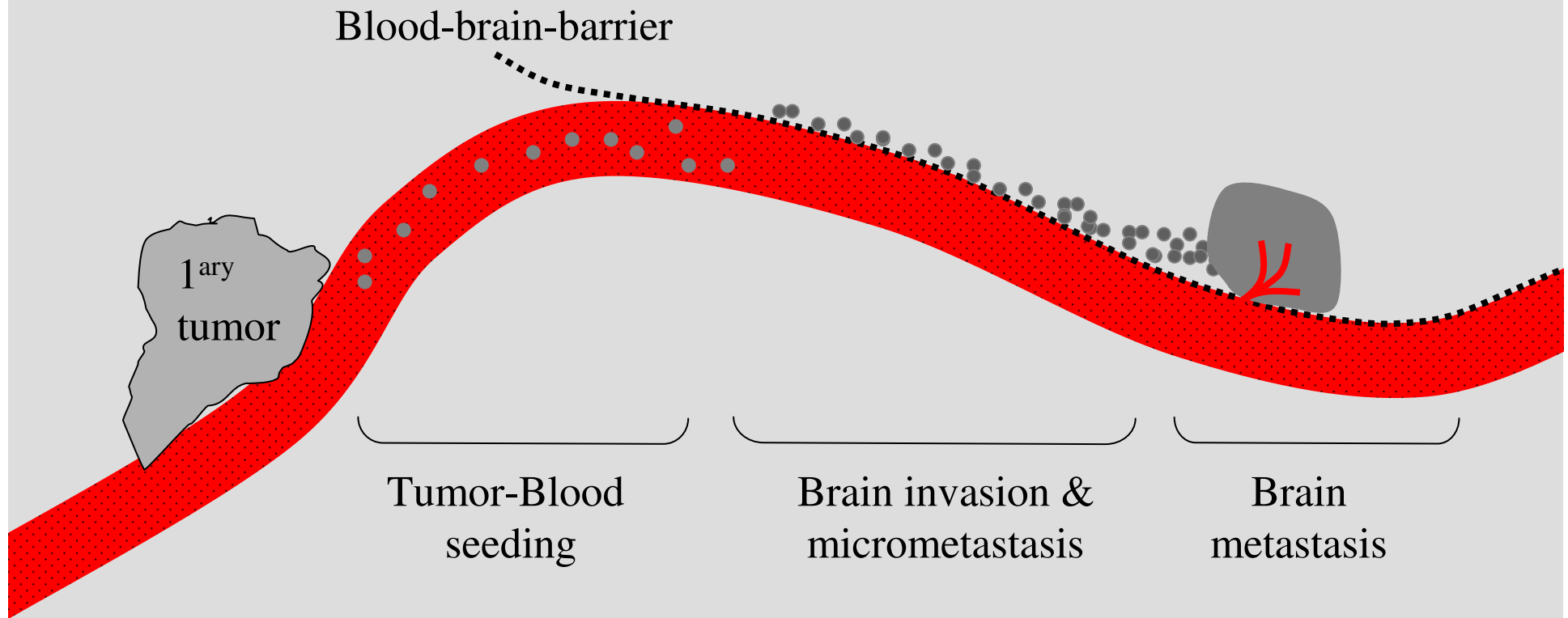


**Chemotherapy (and delayed WBRT)**

**Chemotherapy + WBRT**

**Chemotherapy  
in a prophylactic setting?**

# Brain metastasis



ORIGINAL ARTICLE

## Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D.,

breast cancer treated with trastuzumab.<sup>9-11</sup> In both trials, the incidence of isolated brain metastases as first events was higher in the trastuzumab group than in the control group (21 vs. 11 in trial B-31 and 12 vs. 4 in trial N9831).



Selection beyond the BBB

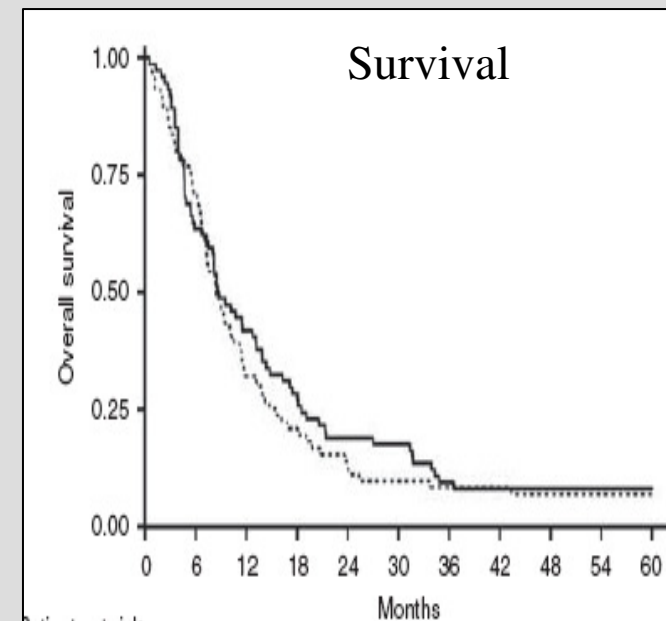
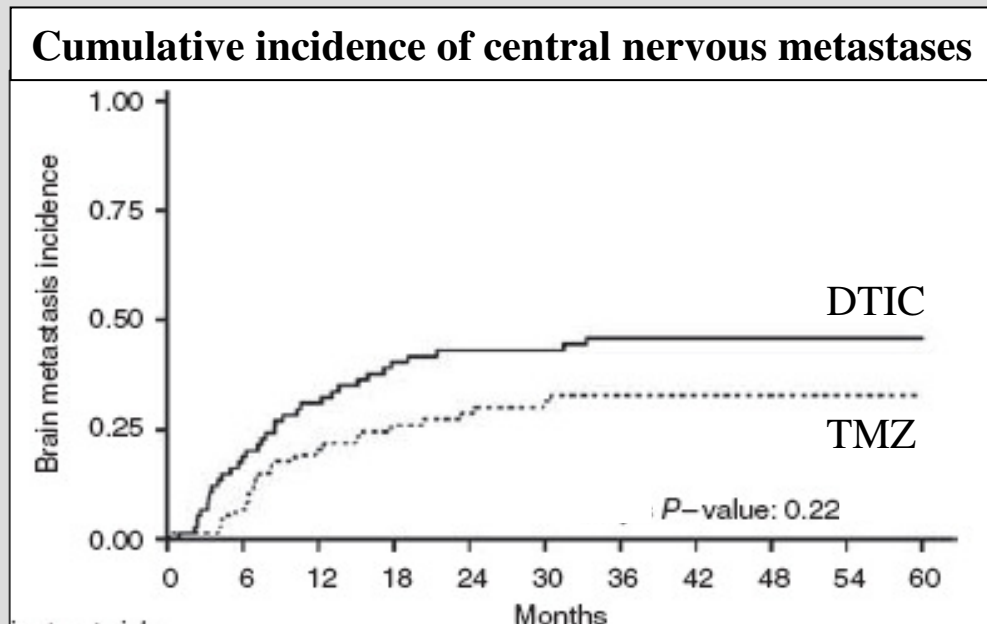
# Central nervous system failure in melanoma patients: results of a randomised, multicentre phase 3 study of temozolomide- and dacarbazine- based regimens

V Chiarion-Sileni<sup>1\*</sup>, M Guida<sup>2</sup>, L Ridolfi<sup>3</sup>, A Romanini<sup>4</sup>, P Del Bianco<sup>5</sup>, J Pigozzo<sup>1</sup>, S Brugnara<sup>6</sup>, G Colucci<sup>2</sup>, R Ridolfi<sup>3</sup> and GL De Salvo<sup>5</sup> for the Italian Melanoma Intergroup (IMI)

British Journal of Cancer (2011) 104, 1816–1821

stage IV melanoma, without evidence of CNS metastases

TMZ	+ Cisplatin + IL2	n= 74
Dacarbazine	+ Cisplatin + IL2	n= 75





# Other targets

[CANCER RESEARCH 64, 4190–4196, June 15, 2004]

## **Overexpression of ADAM9 in Non-Small Cell Lung Cancer Correlates with Brain Metastasis**

Yasushi Shintani,<sup>1,2</sup> Shigeki Higashiyama,<sup>3</sup> Mitsunori Ohta,<sup>2</sup> Hirohisa Hirabayashi,<sup>2</sup> Sakae Yamamoto,<sup>1</sup> Tatsuya Yoshimasu,<sup>4</sup> Hikaru Matsuda,<sup>2</sup> and Nariaki Matsuura<sup>1</sup>

Cancer Sci. 2004 Feb;95(2):142-8.

## **Increased expression of integrin alpha3beta1 in highly brain metastatic subclone of a human non-small cell lung cancer cell line.**

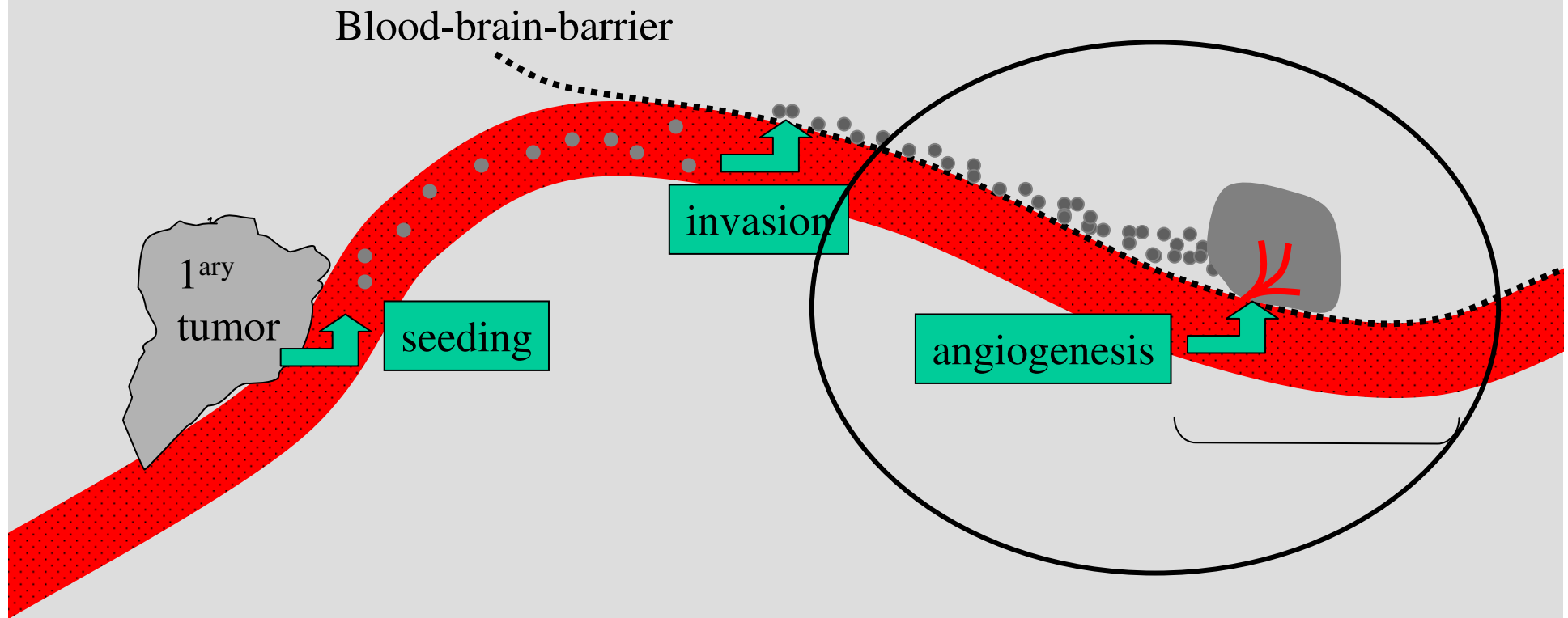
Yoshimasu T, Sakurai T, Oura S, Hirai I, Tanino H, Kokawa Y, Naito Y, Okamura Y, Ota I, Tani N, Matsuura N.

## **CCR7 signalling as an essential regulator of CNS infiltration in T-cell leukaemia**

Silvia Buonamici<sup>1,2</sup>, Thomas Trimarchi<sup>1,2</sup>, Maria Grazia Ruocco<sup>1,3</sup>, Linsey Reavie<sup>1,2</sup>, Severine Cathelin<sup>1,2</sup>, Brenton G. Mar<sup>4</sup>, Apostolos Klinakis<sup>5</sup>, Yevgeniy Lukyanov<sup>1</sup>, Jen-Chieh Tseng<sup>1</sup>, Filiz Sen<sup>1,2</sup>, Eric Gehrie<sup>6</sup>, Mengling Li<sup>7</sup>, Elizabeth Newcomb<sup>1</sup>, Jiri Zavadil<sup>1</sup>, Daniel Meruelo<sup>1</sup>, Martin Lipp<sup>8</sup>, Sherif Ibrahim<sup>1</sup>, Argiris Efstratiadis<sup>5</sup>, David Zagzag<sup>1</sup>, Jonathan S. Bromberg<sup>6</sup>, Michael L. Dustin<sup>1,3</sup> & Iannis Aifantis<sup>1,2</sup>

Nature, 2009

# Brain metastasis



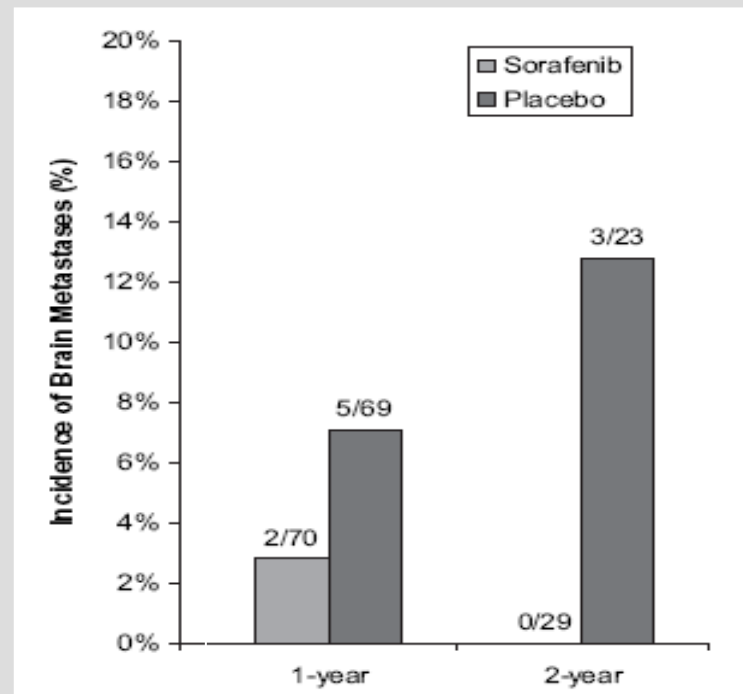
## Incidence of brain metastases in renal cell carcinoma treated with sorafenib

C. Massard<sup>1</sup>, J. Zonierek<sup>2</sup>, M. Gross-Goupil<sup>1</sup>, K. Fizazi<sup>1</sup>, C. Szczylik<sup>2</sup> & B. Escudier<sup>1\*</sup>

*Annals of Oncology* 21: 1027–1031, 2010

### Retrospective analysis of TARGET (phase III):

- renal carcinoma without CNS metastases
- second-line treatment with Sorafenib (anti-VEGF, PDGF, Raf)



# In summary

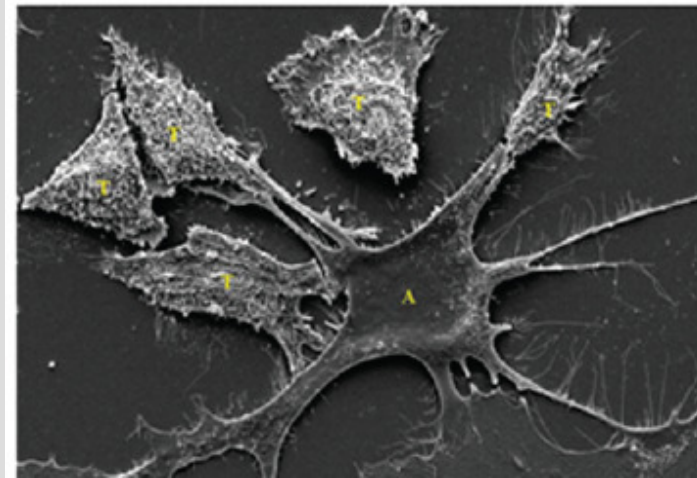
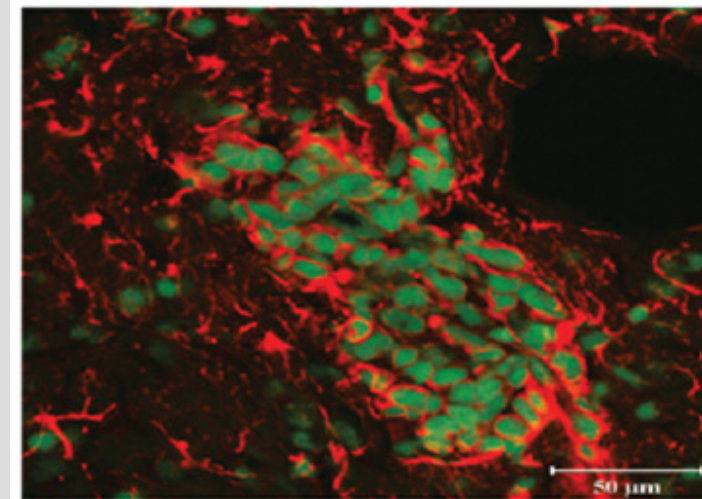
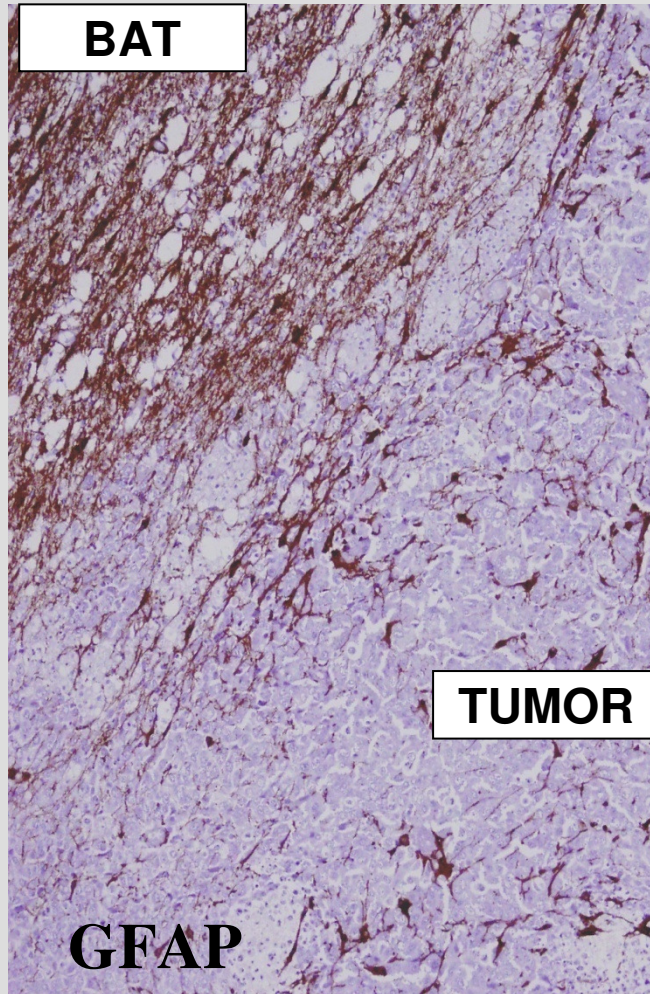
**- Macroscopic Brain metastases are chemosensitive**

**→ Respective place of Chemo/RT to be reconsidered**

**- Prophylaxis of brain met by chemotherapy/targeted therapy?**

**(especially in lung cancer, breast cancer, melanoma)**

# A role for astrocytes ?



# A role for astrocytes ?

