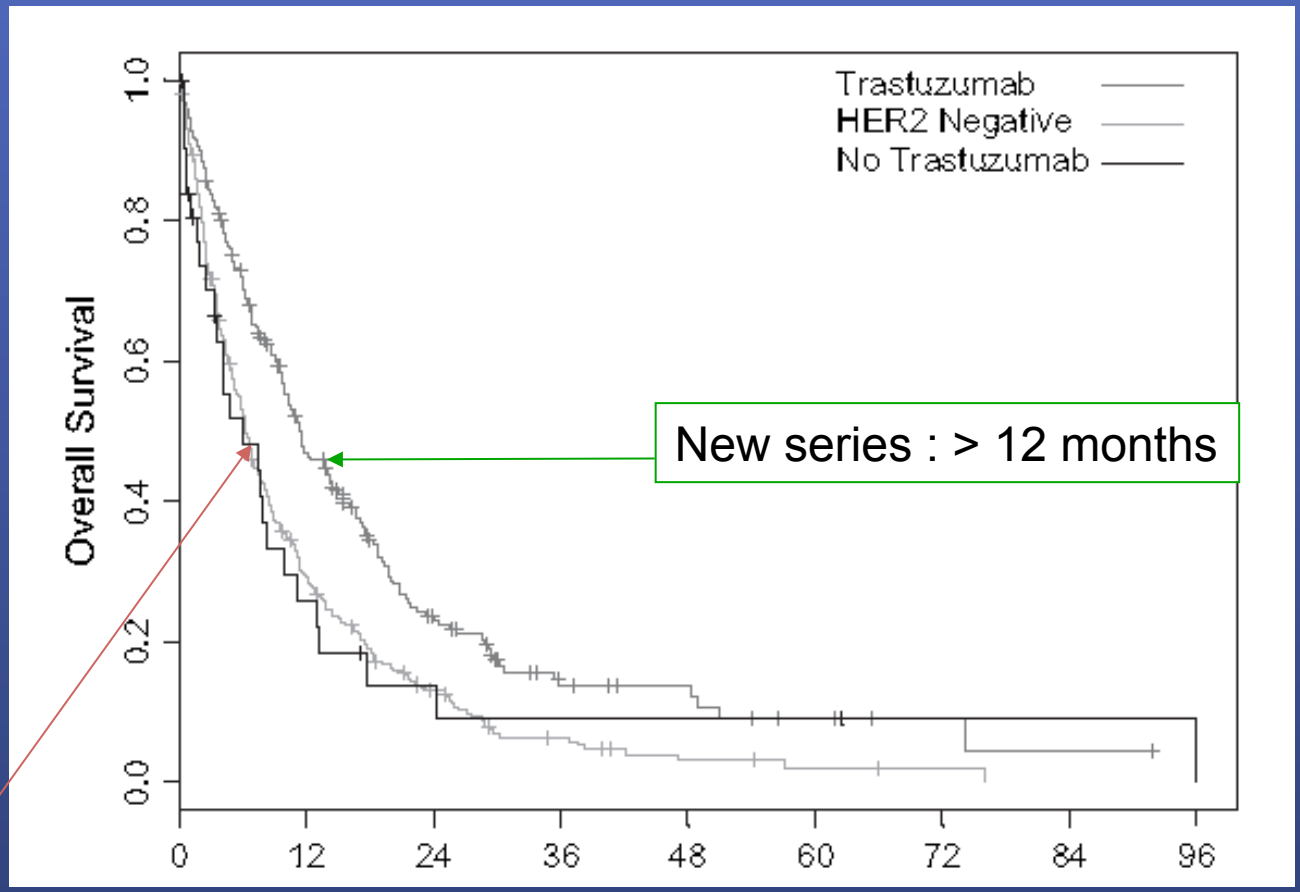
Brain metastases in HER2+ BC
Landscape trial:
toward a change of paradigm

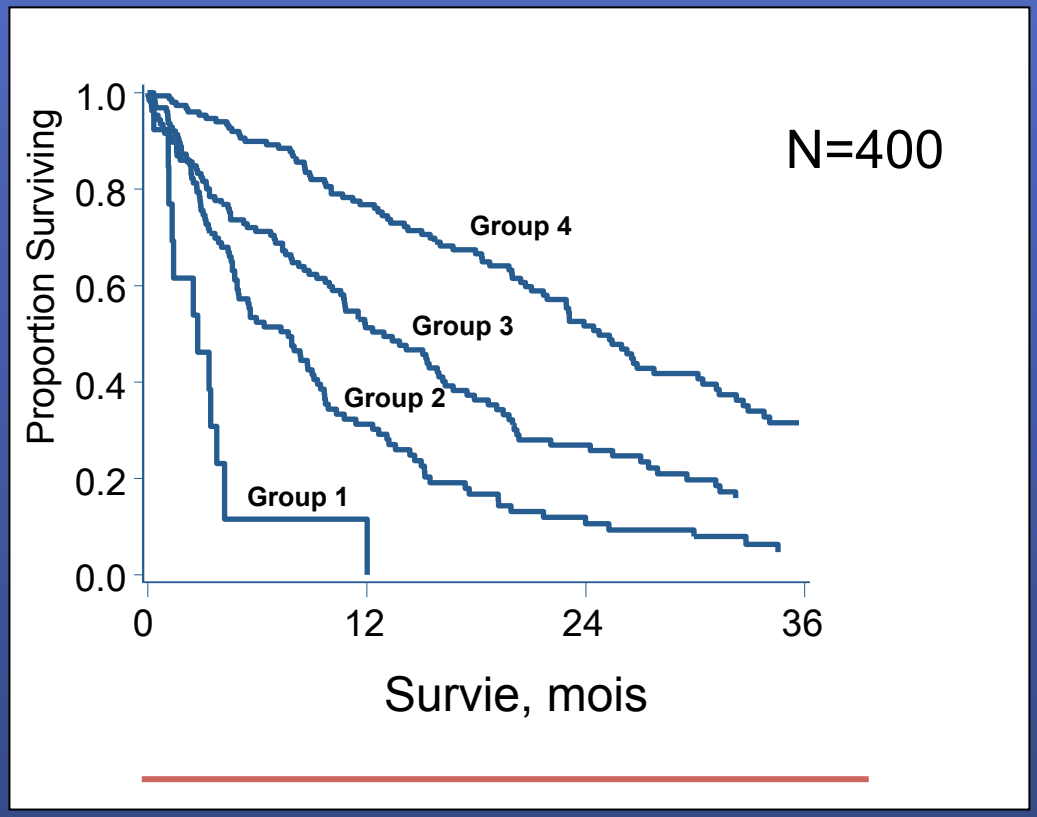
Dr Thomas Bachelot
Centre Léon Bérard, Lyon

Better prognosis of patient with HER2+ve MBC and brain metastasis



Dawood et al. Annals of Oncology 19: 1242–1248, 2008

Better prognosis of patient with HER2+ve MBC and brain metastasis



Survival after BM in MBC subgroups

Example:
48 years old
KPS 90, ER+/HER2+,

Brain mets →
Group 4 →
Median survival : 25 mo

Factor	0.0	0.5	1.0	1.5	2.0
KPS	≤ 50	60	70-80	90-100	-
Tumor Subtype	Basal	-	Luminal A	HER2+ and ER-	HER2+ and ER+
Age	≥ 60	< 60	-	-	-

Sperduto et al, IJROBP 2011

Current guidelines'

NCCN National Comprehensive Cancer Network®
NCCN Guidelines™ Version 2.2011
Multiple (>3) Metastatic Lesions → **WBRT**

NCCN National Comprehensive Cancer Network®
NCCN Guidelines™ Version 2.2011
Limited (1-3) Metastatic Lesions

Disseminated disease
Poor systemic options → **WBRT**

Newly dx'd or stable systemic dz,
Or reasonable systemic options

- unresectable → **WBRT and/or SRS**
- resectable → **Surg or SRS and/or WBRT**

Results of Whole Brain Radiotherapy (WBRT)

Study	Pt population/ Treatment	N	Response criteria	ORR % (at 2-3 mo)	TTP (mo)
Suh et al, ASTRO 2008	MBC WBRT	183 (WBRT arm)	2-D	**27%**	
Suh et al, Unpublished	HER2+ MBC WBRT	~1/3 of pt population above	2-D	**37%**	**> 6 mo**
Cassier et al. Cancer 2008	MBC WBRT+Chemo	25	2-D	**76%**	**5.2 mo**
Lin et al ASCO 2010	HER2+ MBC WBRT+Lapa	35 (28 measurable)	Volumetric	**70%** **(57% 2-D)**	
Chargari et al IJROBP 2010	HER2+ MBC WBRT+ Trastu	31	WHO	**74%**	

Adapted from Nancy Lin, ASCO 2011

WBRT and Neurocognitive function (NCF)….

Modality	Mean Probability of NCF decline @ 4 months
SRS	23%
SRS+WBRT	49%

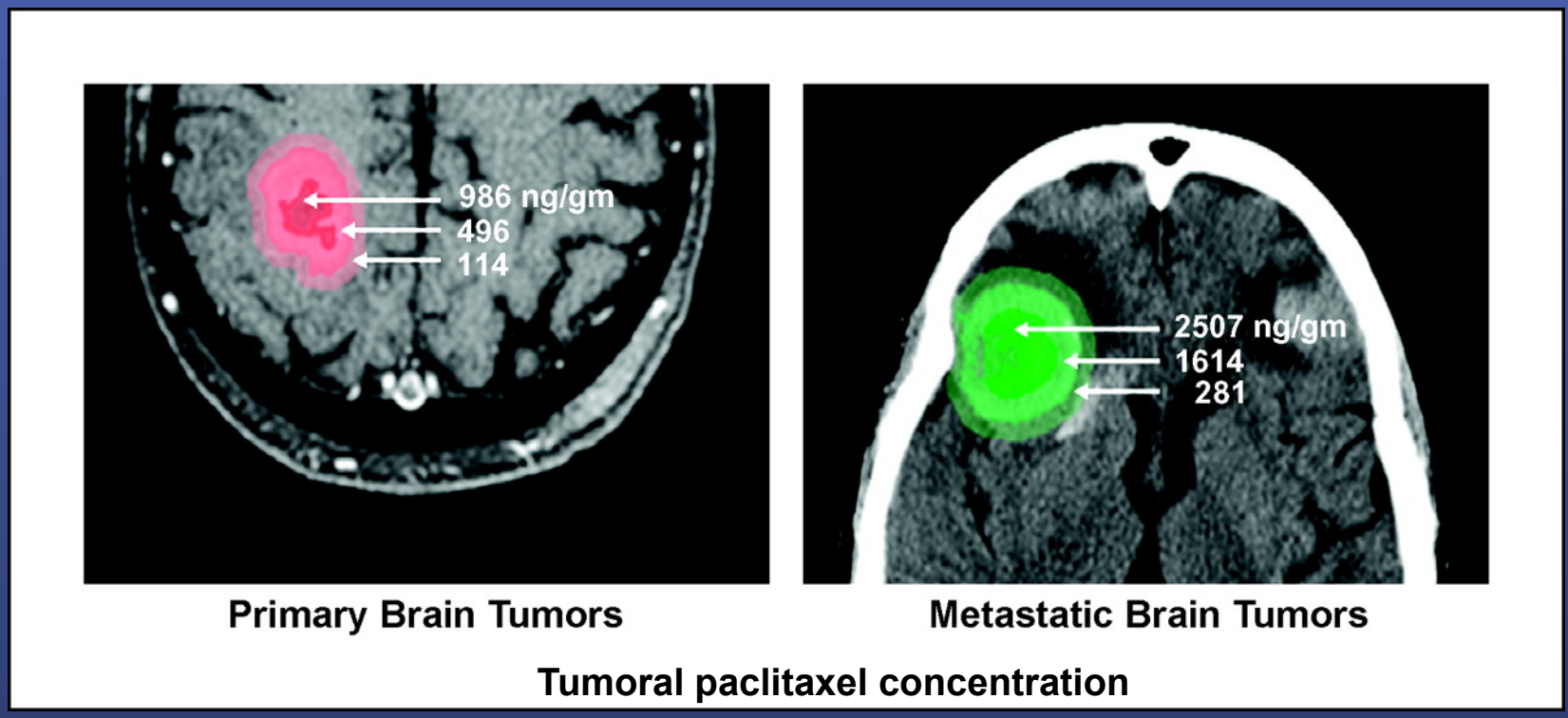
Chang, Lancet Oncol 2009; 10: 1037–44

Brain metastasis and systemic therapy

- In theory, Blood-brain barrier (BBB) isolates CNS from systemic treatment

Brain metastasis and systemic therapy

- But BBB is altered in neovasculature, particularly in the case of metastatic disease



Fine R L et al. Clin Cancer Res 2006;12:5770-5776

Brain metastasis from breast cancer: Upfront systemic therapy

Ref	Treatment	Theoretical BBB permeability	N	ORR
Rosner et al. Cancer 1986	**Endoxan + 5-FU +/- MTX**	No Limited	**87**	**53%**
Boogerd et al. Cancer 1992	**CMF CAF**	Limited Limited	**22**	**59%**
Franciosi et al. Cancer 1999	**CDDP + VP16**	Limited No	**56**	**38%**
Trudeau et al. Ann Oncol 2006	**Temozolomide**	Yes	**18** (5 with BM)	**0 %**
Rivera Cancer 2006	**Temozolomide + lapatinib**	Yes Limited	**24**	**18%**

Brain metastasis from breast cancer: Upfront systemic therapy

Ref	Treatment	Theoretical BBB permeability	N	ORR
Rosner et al. Cancer 1986	**Endoxan + 5-FU +/- MTX**	No Limited	**87**	**53%**
Boogerd et al. Cancer 1992	**CMF** **CAF**	Limited Limited	**22**	**59%**
Franciosi et al. Cancer 1999	**CDDP + VP16**	Limited No	**56**	**38%**
Trudeau et al. Ann Oncol 2006	**Temozolomide**	Yes	**18** (5 with BM)	**0 %**
Rivera Cancer 2006	**Temozolomide + lapatinib**	Yes Limited	**24**	**18%**

=> *Response is related to intrinsic drug activity against BC, not BBB permeability*

Studies of Lapatinib for HER2+ Breast Cancer Brain Metastases progressive after WBRT:

Study	N	Prior chemo	Response criteria	CNS ORR	TTP/PFS	OS
Lin et al JCO 2008	39	64% with ≥2 T+chemo	RECIST	2.6%	3.0 mo	NR
Lin et al CCR 2009	237	81% with ≥2 T+chemo	50% vol NSS, steroids, lack of non-CNS PD	6%	2.4 mo	6.4 mo
Toi et al Br J Cancer 2009	10	>80% with ≥3 prior regimens	RECIST	2 PR	NR	NR

Adapted from Nancy Lin, ASCO 2011

Studies of Lapatinib and capecitabine for HER2+ BC Brain Metastases progressive after WBRT:

Study	N	Response criteria	CNS ORR	TTP/PFS	OS
Lin et al CCR 2009	**50** *PD on lapatinib monotherapy*	50% vol	**20%**	**3.6 mo**	
Sutherland et al, Br J Ca 2010 (LEAP)	**34**	RECIST (Retrospective)	**21%**	**5.1 mo**	
Metro et al, Ann Oncol 2011	**22**	WHO (Retrospective)	**32%**	**5.1 mo**	11 mo
Lin et al, J Neurooncol 2001	**13**	50% vol	**38%**	NR	

Adapted from Nancy Lin, ASCO 2011

LANDSCAPE PROTOCOL

Objective :

- **To assess the clinical benefit of Lapatinib and capecitabine combination for BM in HER2+ MBC patients not previously treated with WBR**

Upfront systemic treatment of patients with BM allows:

- *Concomitant treatment of extra CNS disease*
- *Delay WBR and associated toxicities*

UNICANCER R&D

LANDSCAPE PROTOCOL

- **Key Inclusion Criteria**
  - HER2+ MBC
  - Newly diagnosed brain metastases, at least 1 cm in diameter (T1 gado. MRI)
  - Not candidate for brain surgery
  - Any previous treatment except WBR, lapatinib or capecitabine
  - ECOG PS status 0-2

- **Treatment:** L: 1,250 mg/d, PO, continuous
  C: 2,000 mg/m²/d, PO, d1–14 q3weeks

- **Clinical assessment (including NSS) every 3 weeks**
- **Cerebral and systemic imaging every 6 weeks**

NSS : Neurologic signs and symptoms

UNICANCER R&D

LANDSCAPE PROTOCOL

- **Primary endpoint**
  - **Centrally assessed CNS objective response (CNS-OR) defined as a ≥50% volumetric reduction of CNS lesions[1]**
    - in the absence of: increasing steroid use
      progressive neurologic symptoms
      progressive extra-CNS disease
- **Secondary endpoints**
  - **Time to progression (CNS and extra-CNS)**
  - **Safety**
  - **Time to WBR**
  - **Prognostic and predictive value of circulating tumor cells (CTC) at baseline and day 21 (CellSearch® syste**

UNICANCER R&D

1. Lin et al. Clin Cancer Res 2009; 15: 1452-59

LANDSCAPE PROTOCOL

Statistical Considerations

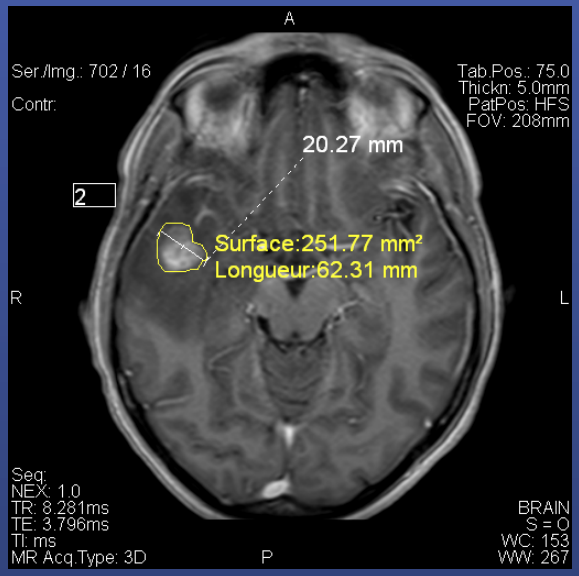
- Simon's optimal two-stage design
- Rate of interest: 20%
- Alpha: 5%, Power: 85%
  - First stage: 17 patients, if two responses:
  - Second stage: + 24 patients
  - 41 evaluable patients
- N = 45 (10% non-evaluable)

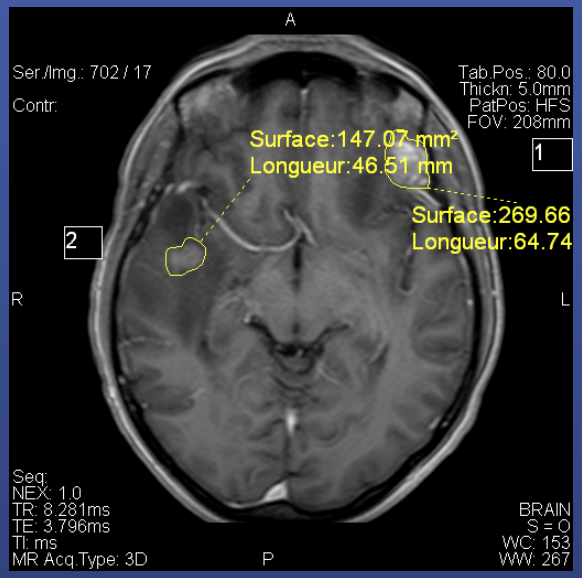
UNICANCER R&D

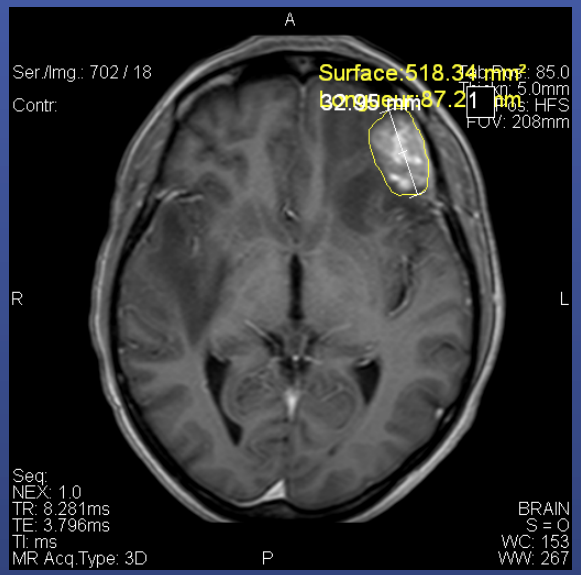
Efficacy assessment

Centrally and blinded volumetric assessment of CNS lesions

- Whole brain, T1 Gado.; axial view, 5mm thickness
- All target lesions contoured across all slices,
- Tumor volume = ∑(outlined surfaces * slice thickness)







UNICANCER R&D

- Lin et al. Clin Cancer Res 2009; 15: 1452-59

Study Status

- **45 patients included from April 2009 to August 2010**
  - →*One patient died after 3 days (metabolic complication)*
- **44 patients evaluable for efficacy**

- **Time of analysis: February 2012**
- **Median follow-up: 21.2 months**

Patient Characteristics (n=45)

Median age, years (range)	56 (35-79)
< 60 years, n (%)	26 (57.8)
ECOG PS, n (%)*	
0	17 (38.6)
1	25 (56.8)
2	2 (4.5)
Hormone receptor status, n (%)*	
ER + and/or PR+	22 (50)
ER- and PR-	22 (50)
Breast cancer GPA index[1], n(%)*	
1	0
2	0
3	22 (50)
4	22 (50)

*1 missing value

1. Sperduto et al. int J Radiat Oncol Biol Phys, April 2011; PMID: 21497451

Patient Characteristics (n=45)

Median disease free interval, mo. (range)	34.2 (0-205)
Median time from metastatic relapse to inclusion, mo. (range)	9.7 (0-114)
Disease extension, CNS	
Median number of CNS lesions (range)	3 (1- >25)
1 CNS lesion, n (%)	6 (13.3)
Patients with NSS at inclusion, n (%)	25 (55.6)
Disease extension, extra-CNS, n (%)	
No extra-CNS	7 (15.6)
Liver	22 (48.9)
Lung	16 (35.6)
3 or more	14 (31.1)
Previous trastuzumab treatment, n (%)	
No trastuzumab	3 (6.7)
Adjuvant only	11 (25)
Metastatic +/- adjuvant	31 (68.9)

UNICANCER R&D

Primary Endpoint: CNS volumetric response

CNS-OR : 29/44 = 65.9% (95% CI: 50-79)

CNS Volumetric change	n = 44 (%)	
≥ 80% Reduction	9	(20.5)
50- <80% Reduction	20	(45.5)
20- <50% Reduction	6	(13.6)
> 0- <20% Reduction	2	(4.5)
Progression*	7	(15.9)

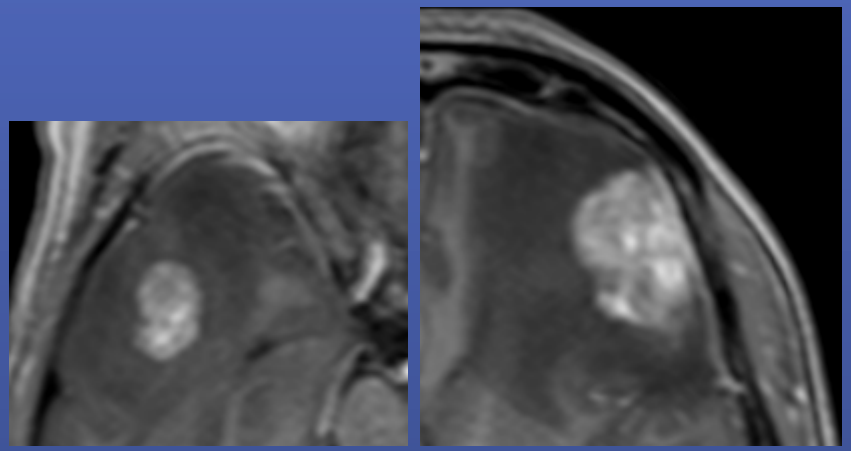
NSS improvement : 14/24 = 58.3% (95% CI: 36.6-77.9)

RECIST CNS RR: 57.2%

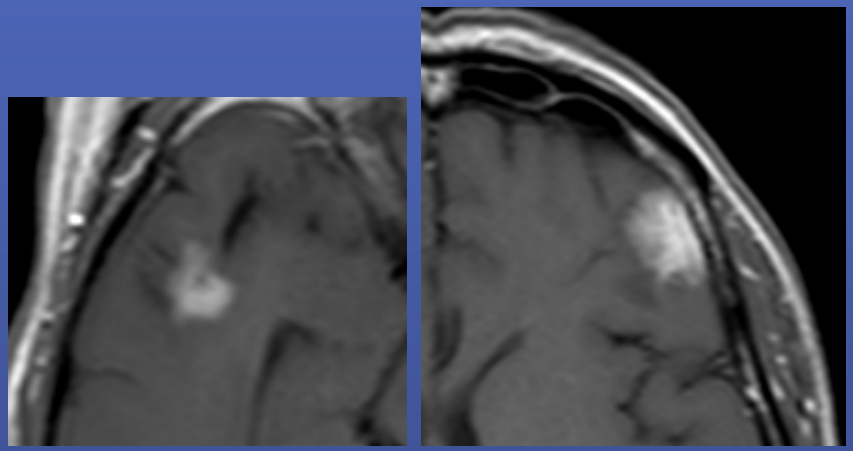
*2 patients had extra-CNS disease progression

UNICANCER R&D

53-year-old patient, left breast cancer w synchronous metastases: Oct. 2008
Bone and pulmonary mets: trastuzumab + paclitaxel
Progression and multiple brain mets: October 2009



October 23, 2009



January 27, 2010

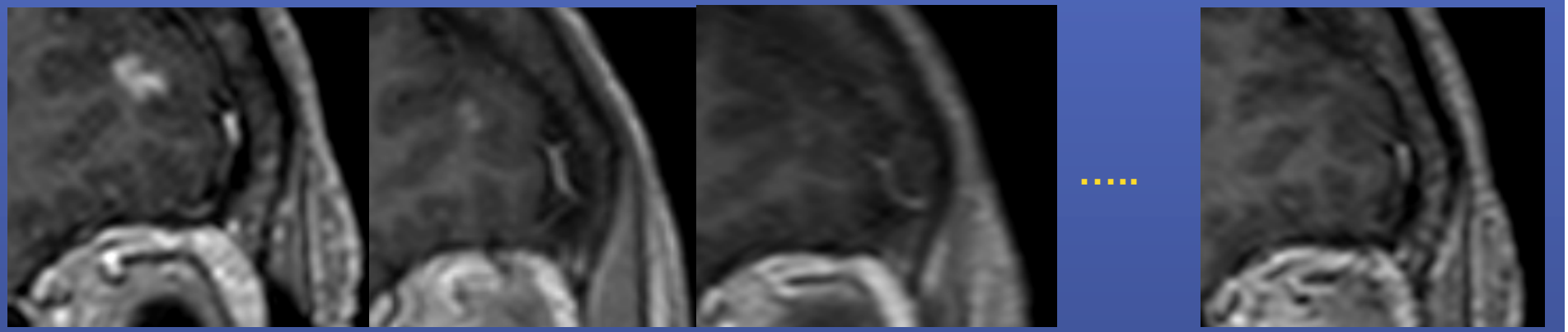
Volumetric reduction: 70%

CNS progression : June 14, 2010

WBR : July 8, 2010

UNICANCER R&D

43-year-old patient, left breast cancer pT1pN1: June 2006
Bone, liver, pulmonary mets: March 2009, trastu. + paclitaxel
Symptomatic multiple brain mets (25): June 2009



July 6, 2009 **August 20, 2009** **Oct. 1, 2009** **July 23, 2010**

Volumetric reduction: 98%

Still on treatment after 13 months (1 dose reduction)

Extra-CNS RECIST response

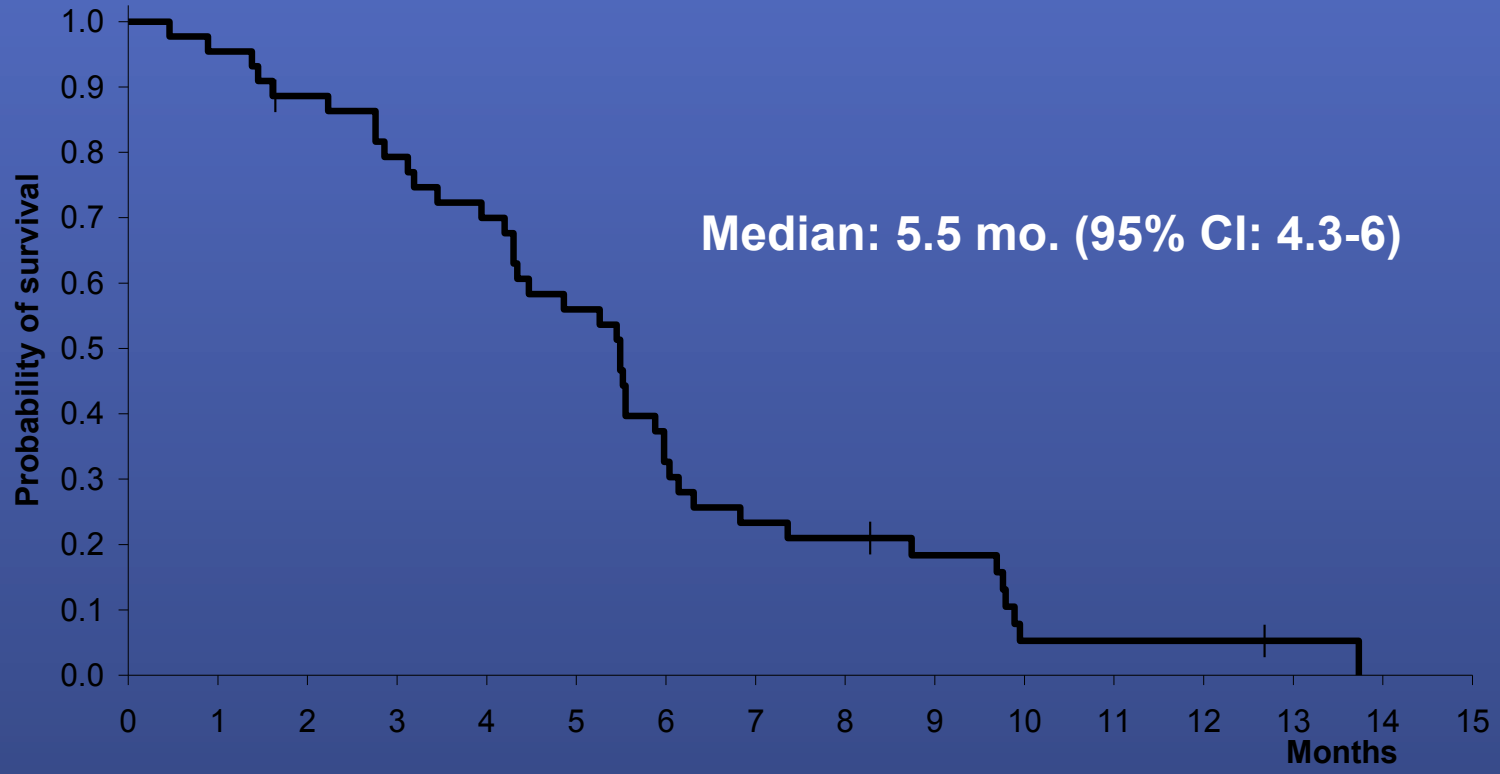
Extra-CNS-OR : 15/34 = 44.1% (95% CI: 27-62)

Extra-CNS RECIST evaluation	n = 34 (%)	
Complete response	1	(2.9)
Partial response	14	(41.2)
Stable disease	15	(44)
Progression	4	(11.7)

- 7 patients had no extra-CNS disease
- 3 patients had no RECIST evaluable lesions

UNICANCER R&D

Time to progression



Median: 5.5 mo. (95% CI: 4.3-6)

Patients at risk:	44	42	38	34	30	24	14	10	9	7	2	2	2	1

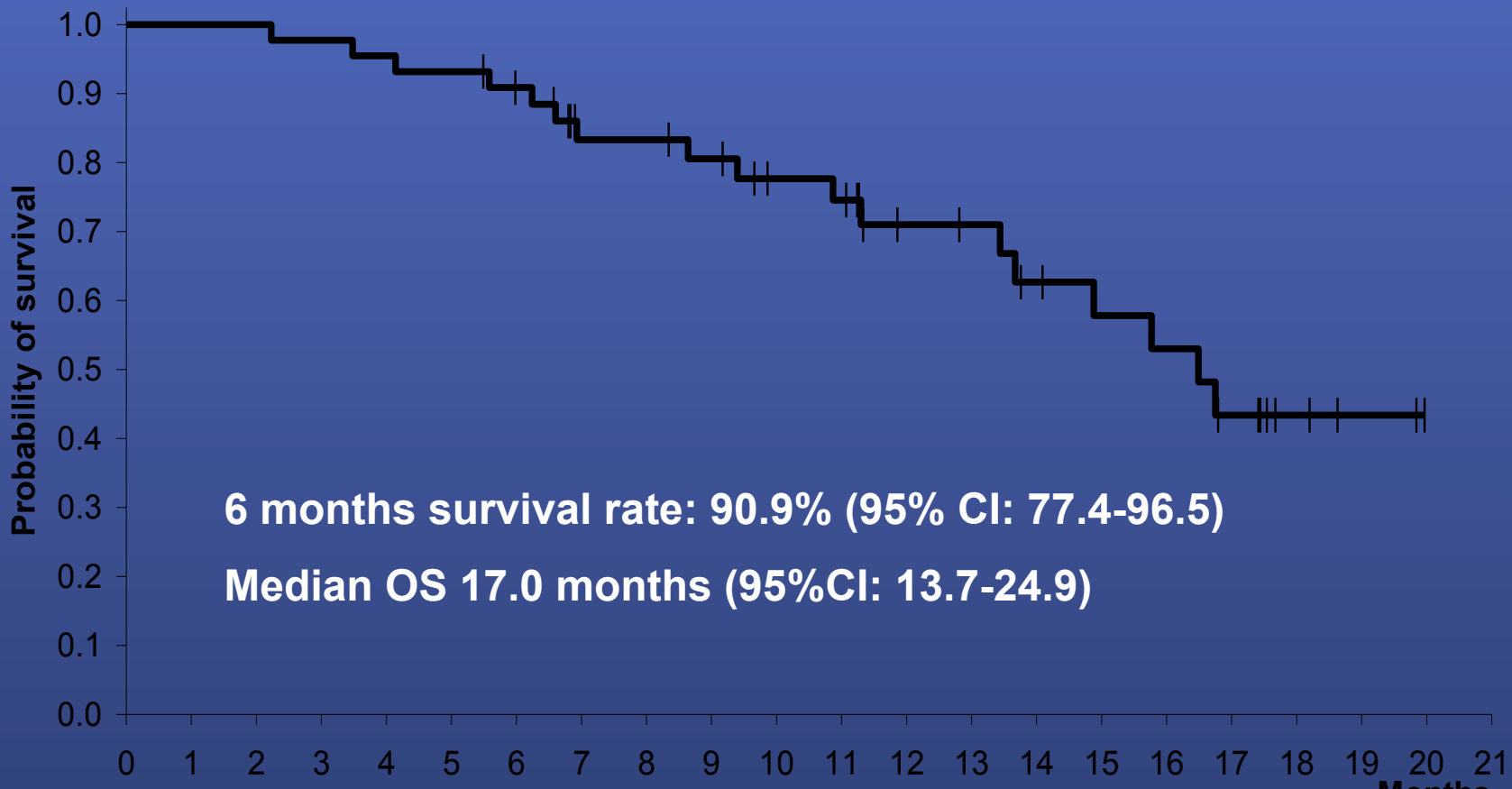
Site of first progression	n = 43 (%)	
CNS	32	(73.4)
Extra CNS	3	(7)
Concomitant CNS & extra CNS	5	(11.6)

Time to WBR

- Data were available for 43 patients
- At time of analysis, 36 (81.8%) had received WBR

➢ **Median time to WBR is 8.3 mo. (95% CI: 5.4-9.1)**

Overall Survival



Patients at risk

44	44	44	43	42	41	38	31	31	29	25	24	18	17	14	12	11	8	4	2

Adverse Events

Incidence, n (%)		n = 45	
Grade		Any	3/4
Patients with at least one SAE		14 (31.1)	
Most Common Adverse Events			
Diarrhea		38 (84.4)	9 (20)
Hand foot syndrome		34 (75.5)	9 (20)
Fatigue		22 (48.9)	6 (13.3)
Rash		11 (24.4)	2 (4.4)
Nausea		23 (51.1)	1 (2.2)
Bilirubin increase		21 (46.6)	1 (2.2)
Vomiting		16 (35.5)	1 (2.2)
Stomatitis		13 (28.9)	1 (2.2)
Dose reduction due to AE	Lapatinib		17 (37.8)
	Capecitabine		26 (57.8)
Treatment discontinuation due to AE		3 (6.7)	

No toxic death

UNICANCER R&D

CNS volumetric response

Selected subgroup analysis

CNS-OR, n (%)	n=44
ALL	*29/44 (65.9)*
GPA index = 3	14 / 20 (70)
GPA index = 4	14 / 22 (63.6)
1 or 2 CNS lesions	13 / 20 (65)
≥ 3 CNS lesions	16 / 22 (72.7)
Patients with NSS at inclusion	16 / 23 (69.6)
Patients without NSS at inclusion	13 / 20 (65)
Previous metastatic trastuzumab	20 / 29 (69)
No previous metastatic trastuzumab	9 / 14 (64.3)

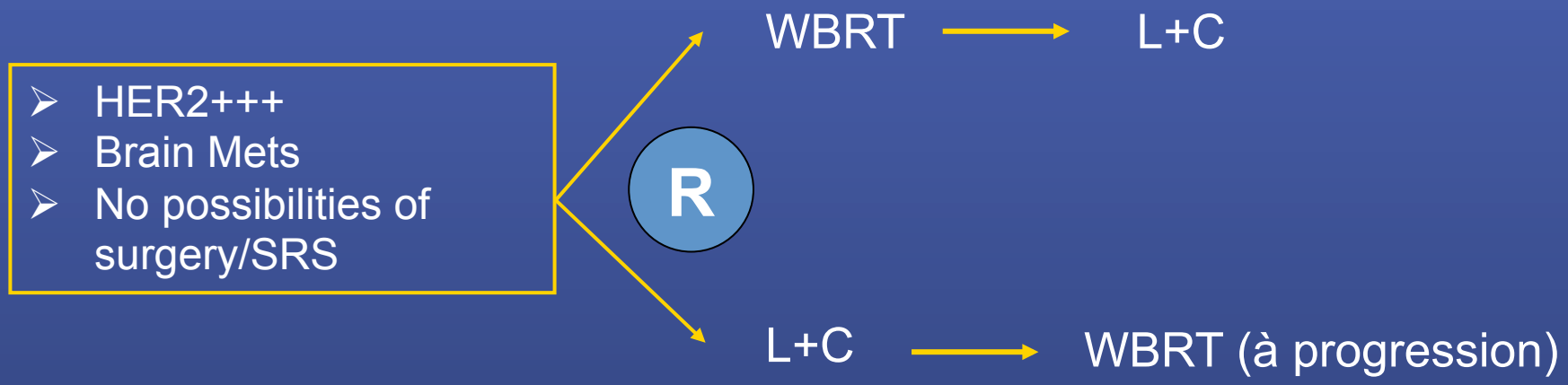
Conclusions

L+C for newly diagnosed BM in HER2+ MBC:

- **L+C is highly active for untreated BM**
  - **CNS volumetric response rate was 66%**
  - **Median TTP was 5.5 months**
- ***This approach might change the management of selected patients with BM, allowing a delayed WBRT***

Conclusions

RAID "RAdiotherapy Immediate or Delayed",
D Azria, T Bachelot



Composite primary end-point : Cognitive Toxicity and cerebral progression

UNICANCER R&D