Putting drugs at work against brain metastases in HER2 positive BC: Results of the Landscape trial

Dr. Thomas Bachelot,

on behalf of UNICANCER collaborative group

Disclosure

Board and reserach funding:

- Roche
- Novartis
- GSK

To be discussed

Rational of upfront medical treatment for BM

Final analysis of the Landscape study

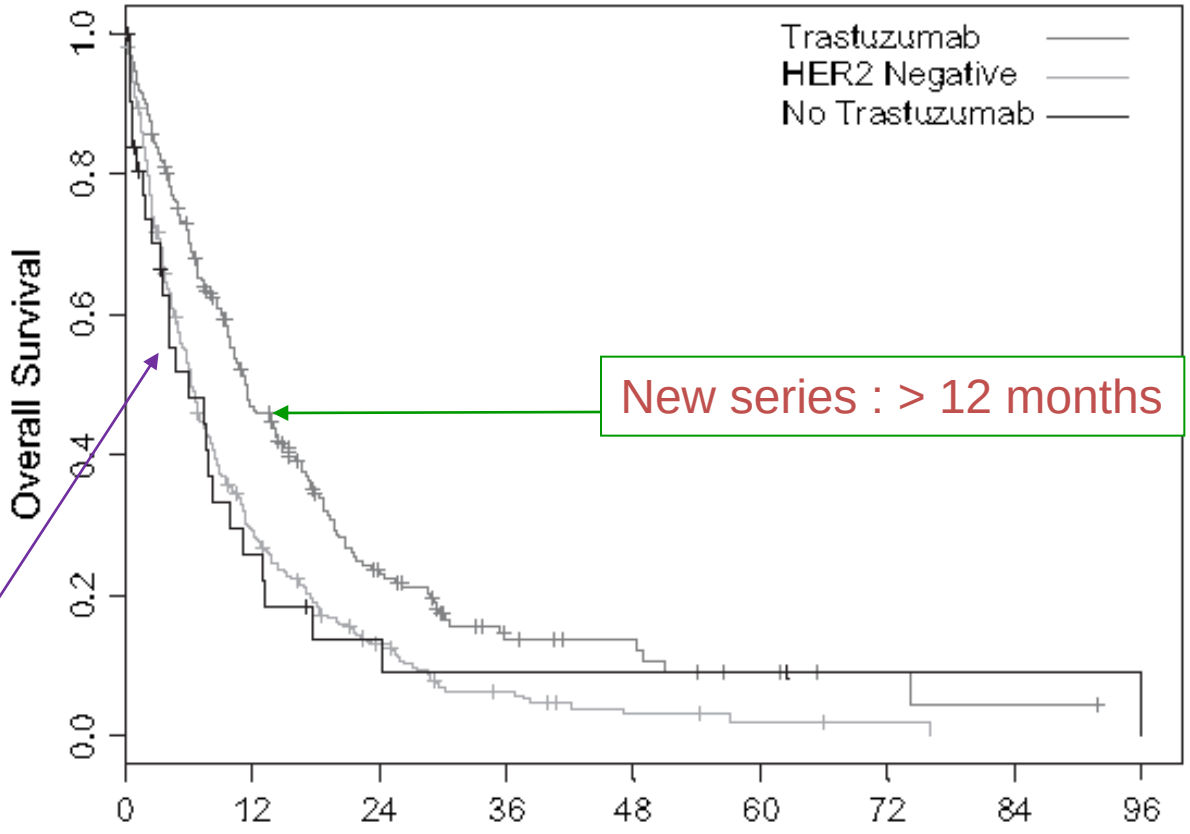
First analysis: ASCO 2011

Final analysis: Accepted for publication, Lancet Oncol 2012

Brain metastases are an important issue in the management of HER2+ metastatic breast cancer patients

- Incidence up to 30 to 40 %
- Strong contribution to morbidity and mortality
- Few therapeutic options beside whole brain radiation therapy (WBR) when multiple localizations

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



New series : > 12 months

Old series : 6 month

VIENNA 2012 ESMO congress

www.esmo2012.org

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

Whole Brain radiotherapy: few prospective study

Study	Pt population/ Treatment	N	ORR % (at 2-3 mo)	TTP (mo)	Median OS
Suh et al, ASTRO 2008 (ENRICH Trial, control arm)	MBC WBRT	183	27%		7.5 months
	HER2+ MBC WBRT	68	37%	> 6 mo	HR=0,66
Cassier et al. Cancer 2008	MBC WBRT+Chemo	25	76%	5.2 mo	6.5 months
Lin et al ASCO 2010	HER2+ MBC WBRT+Lapa	35	70% (57% 2-D)		
Chargari et al IJROBP 2010	HER2+ MBC WBRT+ Trastu	31	74%		18 months

Whole Brain radiotherapy: Neurocognitive toxicity

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

***Chang, Lancet Oncol* 2009; 10: 1037–44**

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%**

Lapatinib (L) and capecitabine (C)

- **Have been approved for trastuzumab resistant HER2+ MBC**
  - **Objective response rate: 23% (95% CI: 16-29)**
  - **Median time to progression: 6.2 months**
- **Have shown notable activity in patients with progressive BM after WBR**
  - **CNS volumetric response rate: 20% (95% CI: 3-33.7)**
  - **Median time to progression: 3.65 months (95% CI: 2.4-4.4)**

Cameron et al. Breast Cancer Res Treat. 2008; 112: 533-43
Lin et al. Clin Cancer Res 2009; 15: 1452-59

Brain metastasis from breast cancer: Upfront systemic therapy

Brain metastases are an important issue in the management of HER2+ MBC

Upfront systemic treatment of patients with BM allows:

=> *Concomitant treatment of extra CNS disease*

=> *Delay WBR and associated toxicities*

LANDSCAPE PROTOCOL

Designed in 2007 after the publication at ASCO of L+C activity in patients with progressive BM after WBR

Objective :

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

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**

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® system)**

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)

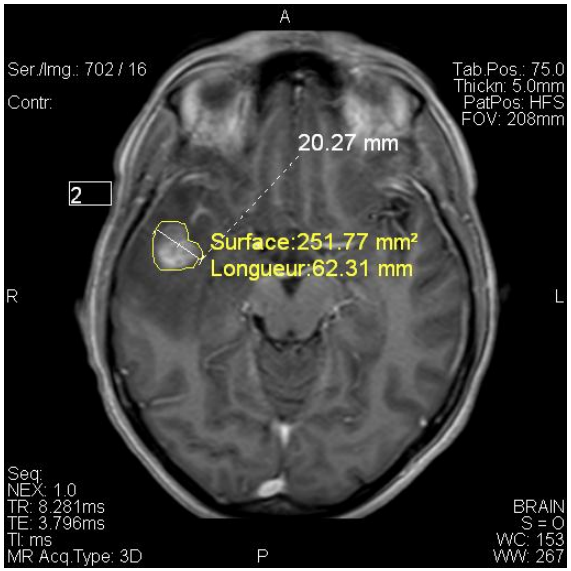
Efficacy assessment

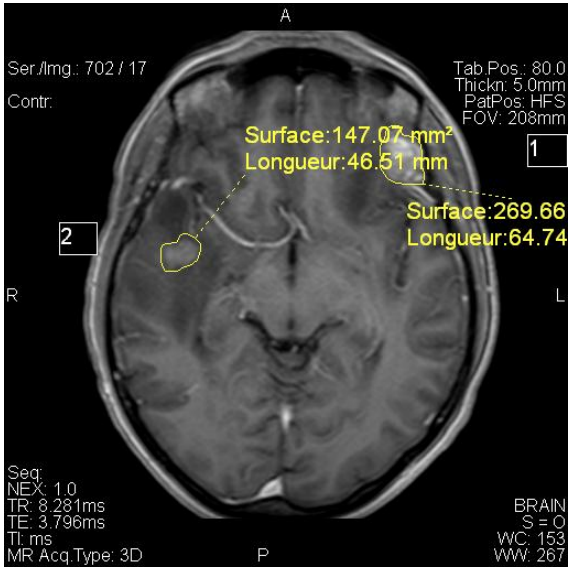
Centrally and blinded volumetric assessment of CNS lesions

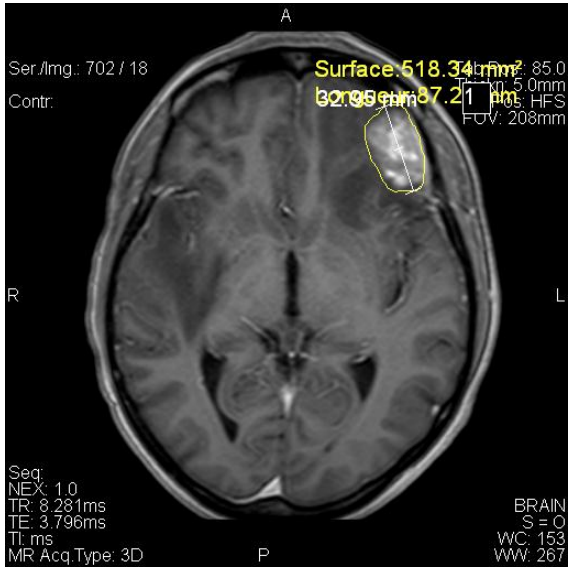
Whole brain, T1 Gado.; axial view, 5mm thickness

All target lesions contoured across all slices,

Tumor volume = ∑(outlined surfaces * slice thickness)







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 24, 2012**
- **Median follow-up: 21.2 months (range: 2.2-27.6)**

  One patient still on treatment

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)

Patient Characteristics (n=45)

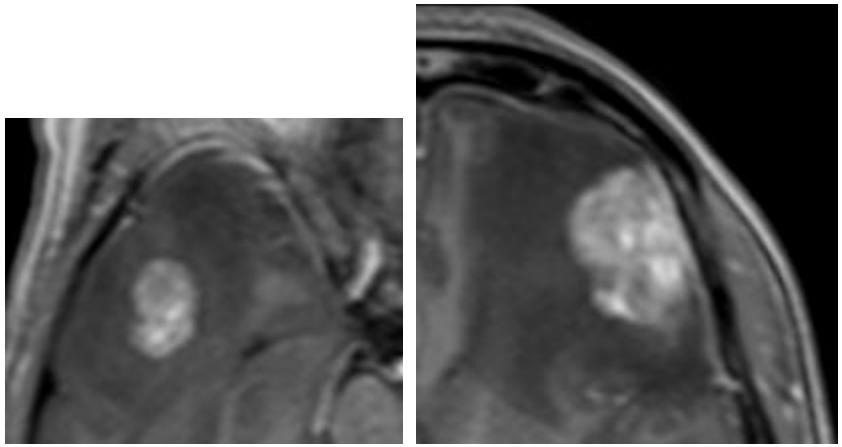
Median disease free interval, mo. (range)	34.2 (0-205)
Median time from metastatic relapse to inclusion, mo. (range)	9.7 (0-114)
Disease extension, CNS	
Median number of CNS lesions (range)	3 (1- >25)
1 CNS lesion, n (%)	6 (13.3)
Patients with NSS at inclusion, n (%)	25 (55.6)
Disease extension, extra-CNS, 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)

Primary Endpoint: CNS volumetric response

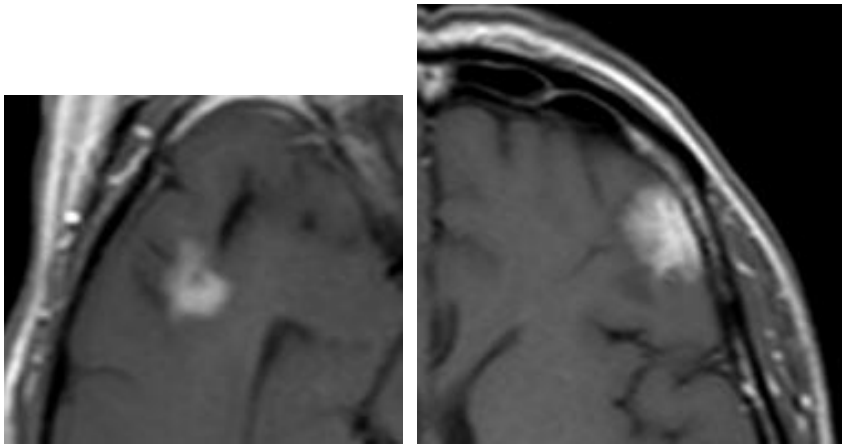
CNS Volumetric change	n = 44	%
CNS objective response	29	66% (95% CI: 50.1-79.5)
≥ 80% Reduction	*9*	*20%*
50- <80% Reduction	*20*	*46%*
20- <50% Reduction	6	14%
> 0- <20% Reduction	2	5%
Progression*	7	16%

*2 patients had extra-CNS disease progression

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



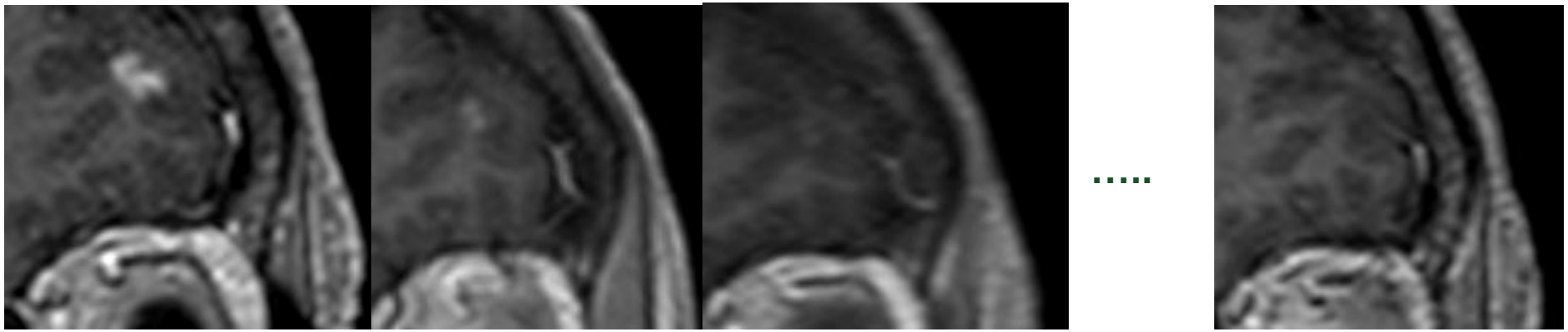
January 27, 2010

Volumetric reduction: 70%

CNS progression : June 14, 2010

WBR : July 8, 2010

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%

Progressed after 15 months (1 dose reduction)

Secondary end-point

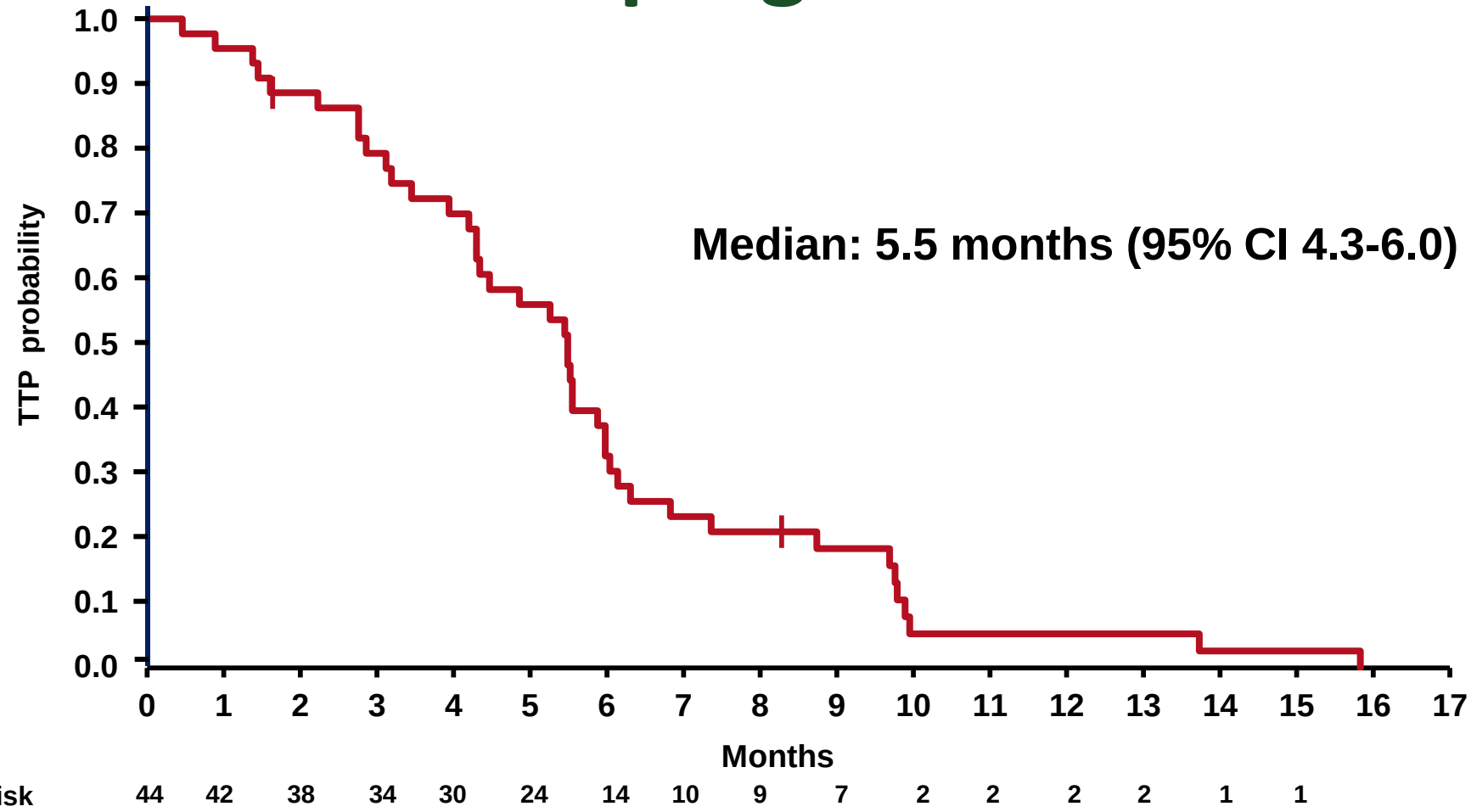
CNS-OR by RECIST (42 pts): 2CR and 22PR => ORR 57.2%

15 Stable disease (35.7%)

Neurological symptom (24 pts) : 14 improvement (58.3%)

Extra-CNS res. (34 pts) : 1CR and 14 PR => 44.1% (95% CI: 26-61)

Time to progression



At risk	44	42	38	34	30	24	14	10	9	7	2	2	2	2	1	1

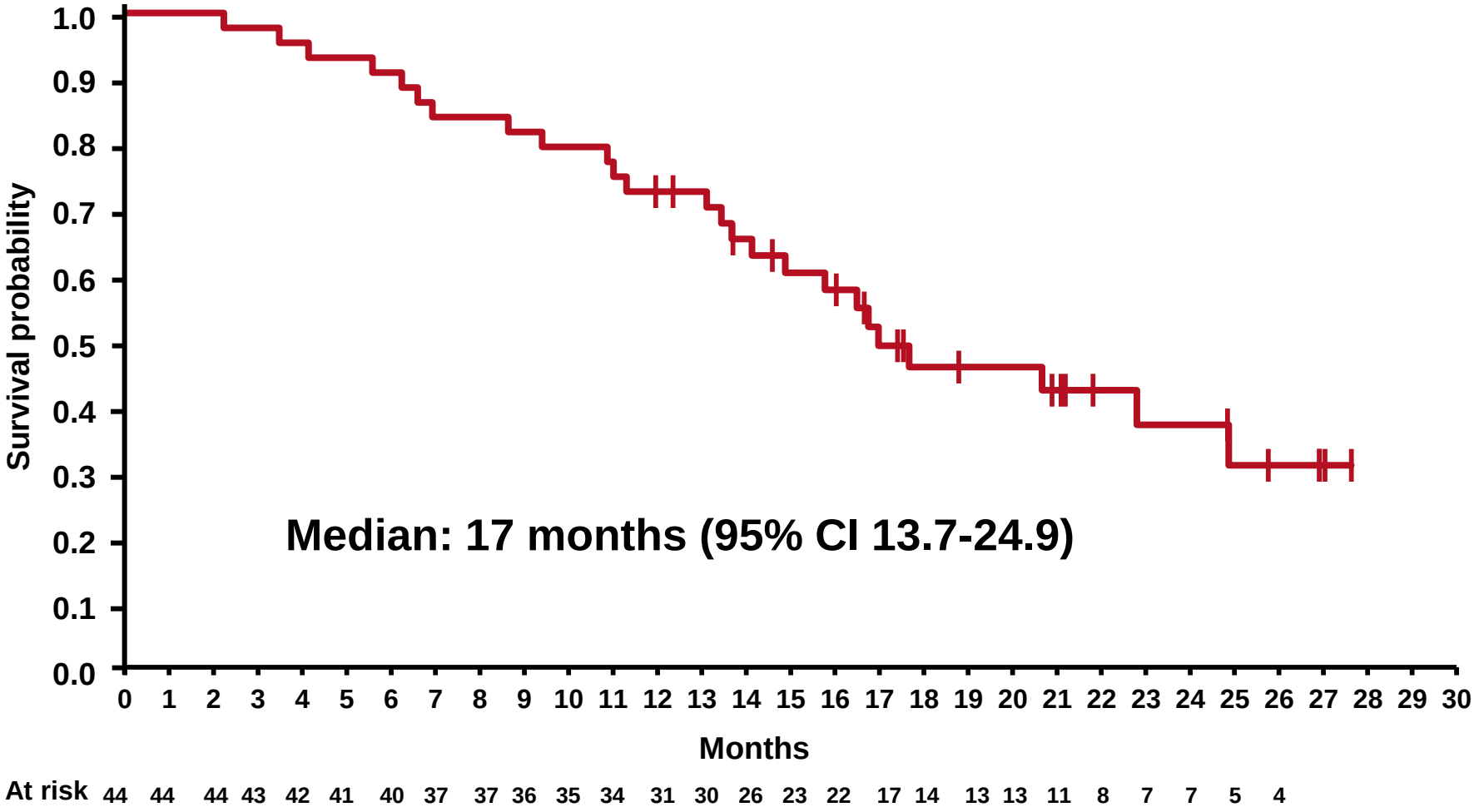
Site of first progression	n = 41	(%)
CNS	32	(78)
Extra CNS	2	(4.9)
Concomitant CNS & extra CNS	5	(12.1)

Time to WBR

- Data were available for 43 patients
- At time of analysis, 32 (74.4%) had received WBR

➢ **Median time to WBR is 7.8 mo. (95% CI: 5.4-9.1)**

Overall Survival



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

Selected subgroup analysis

CNS volumetric response

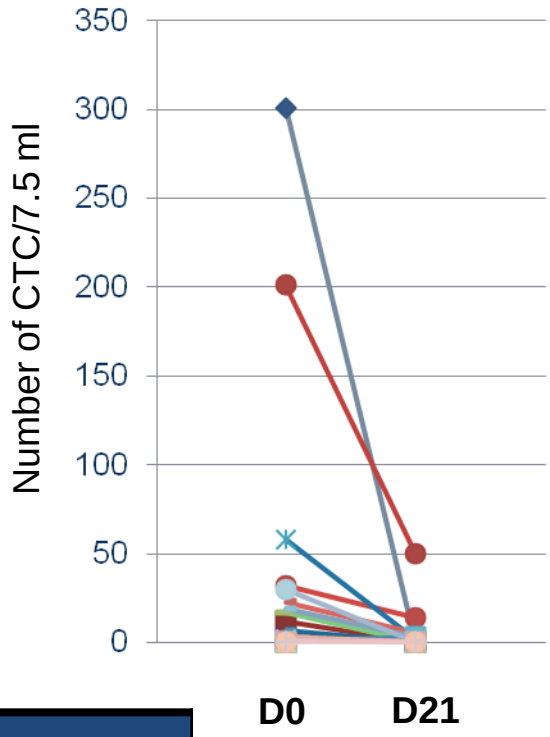
CNS-OR, n (%)	n=43 (%)
ALL	*29/43 (67.4)*
GPA index = 3	14 / 21 (68)
GPA index = 4	14 / 22 (64)
1 CNS lesions	7 / 12 (58)
≥ 2 CNS lesions	22 / 30 (73)
Patients with NSS at inclusion	16 / 24 (67)
Patients without NSS at inclusion	13 / 19 (68)
Previous metastatic trastuzumab	20 / 30 (67)
No previous metastatic trastuzumab	9 / 14 (64)

CTC analysis

CTC/7.5ml at baseline and changes under treatment

Date of sampling	≥1 (%)	*≥ 5 (%)*
Baseline (n=41)	20 (48.8)*	*9 (22)*
Day 21 (n=38)	7 (18.4)*	*3 (7.9)*

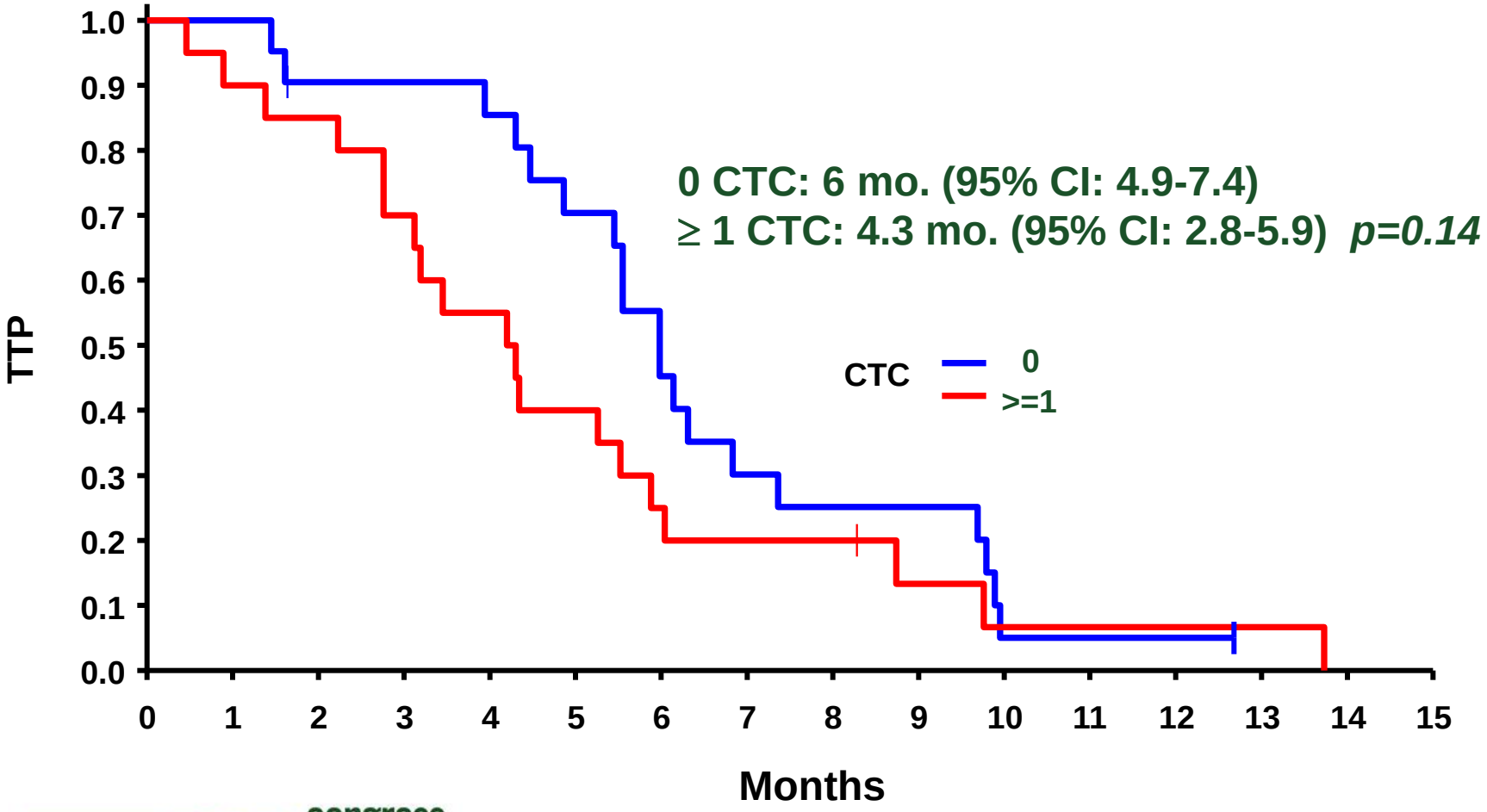
*p=0.006



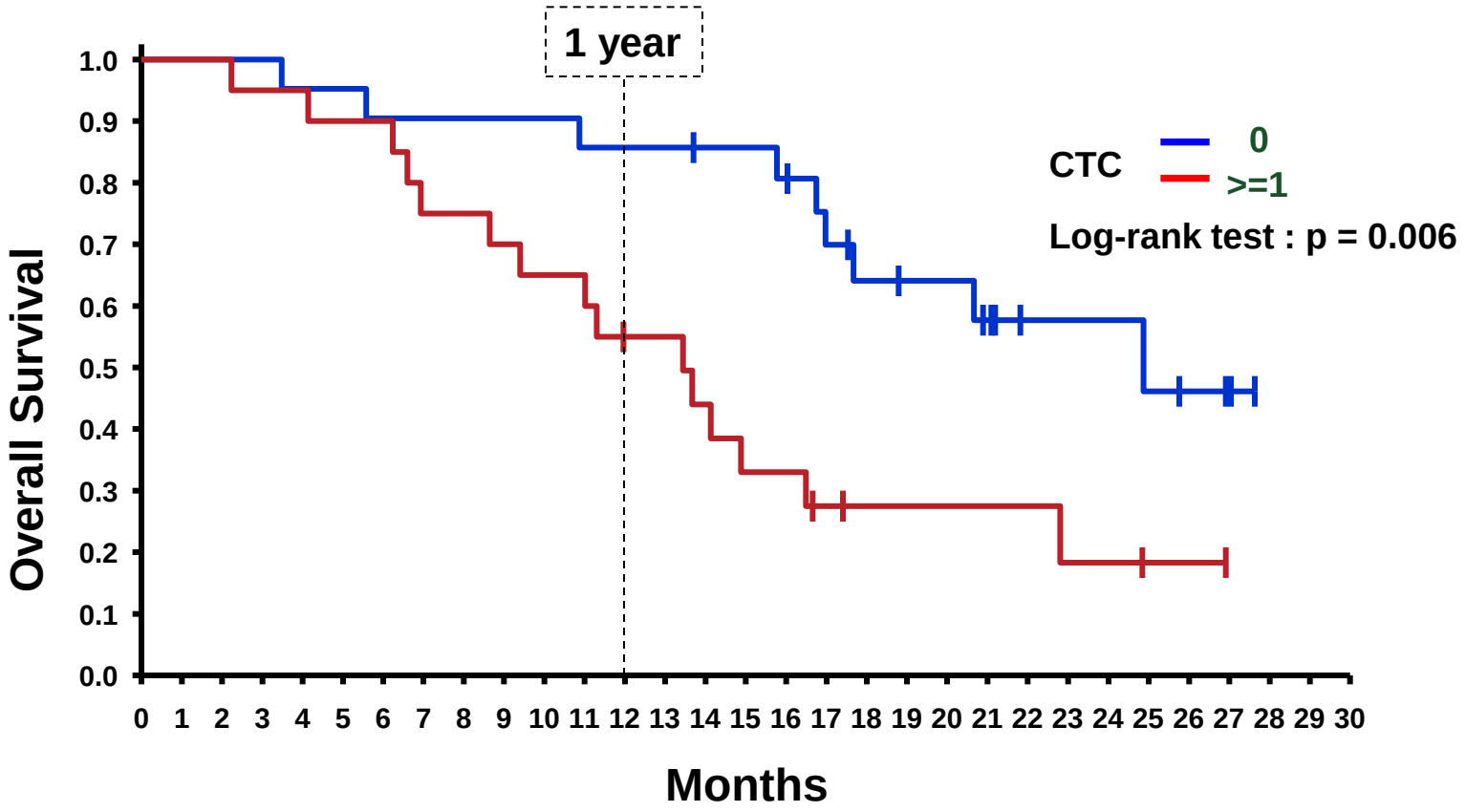
Correlation with CNS-OR, (n=40)

Date of sampling	CTC Status	CNS-OR (%)	*p*
Baseline (n=41)	0 at baseline	17 / 21 (81)	*NS*
	≥ 1 at baseline	11 / 20 (55)	
Day 21 (n=38)	0 at day 21	25 / 31 (81)	*0.03*
	≥ 1 at day 21	2 / 7 (29)	

TTP according to Baseline CTC count (0 vs. ≥ 1)



OS according to Baseline CTC count (0 vs. ≥ 1)



Conclusions

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

We shown that lapatinib+capecitabin efficacy compare favorably with published results of whole brain radiotherapy in term of RR and OS

This strategy could help delaying whole brain radiotherapy associated neurological toxicity.

This combination warrants further evaluation

Acknowledgments

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