Cerebel trial
Any impact on the clinical practice?

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CNS metastases in HER2+ BC

- The proportion of patients with HER2+ advanced breast cancer who have CNS metastases is high

- In the registHER study, a prospective observational study of 1,012 patients with newly diagnosed HER2-positive MBC, **37.3 %** of patients developed BM at a median follow-up of 29 months.

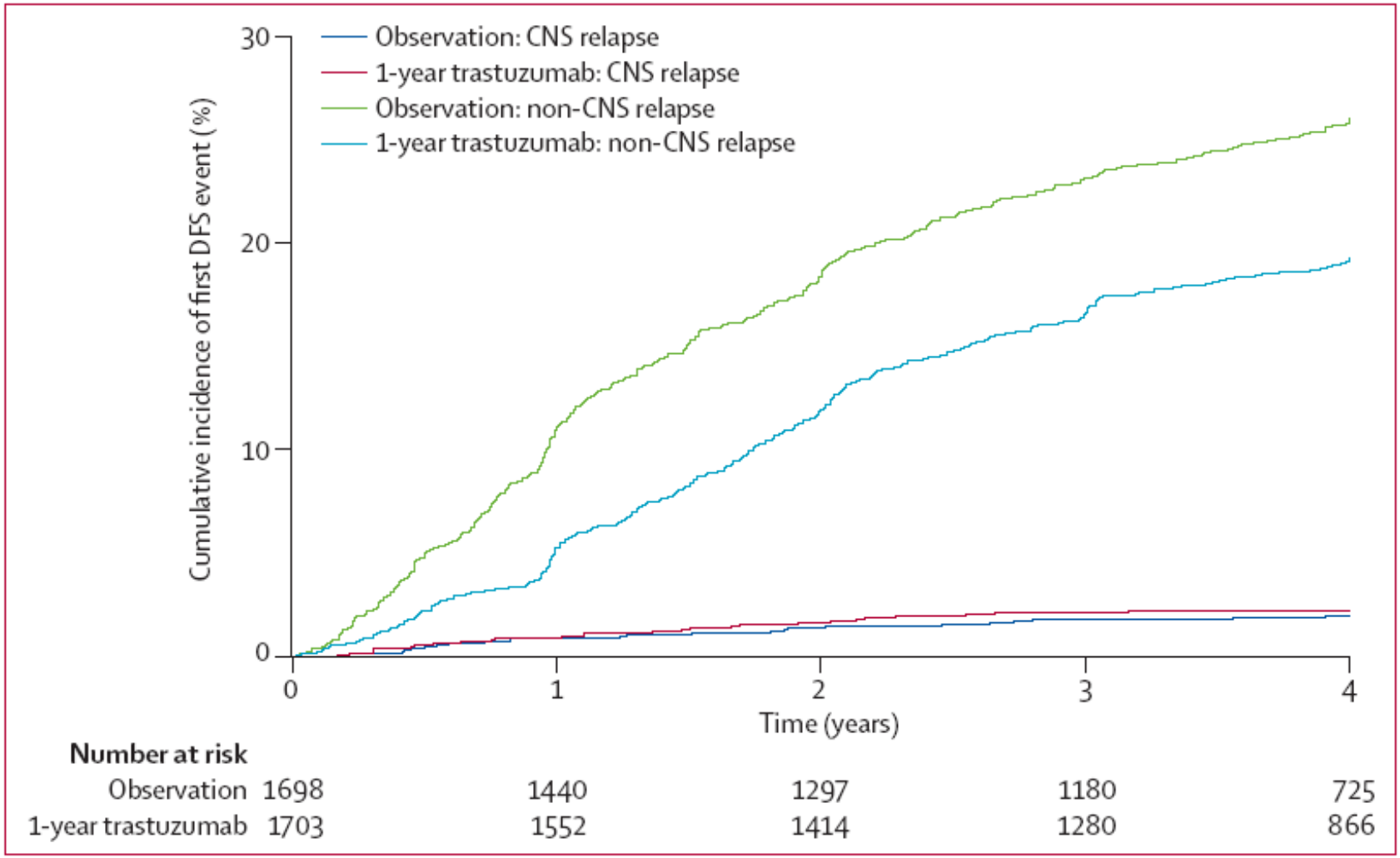
- Retrospective studies in patients treated with trastuzumab have reported similar rates, generally ranging from **25 to 48 %**
  - *biology-linked tropism*
  - *poor CNS penetration of trastuzumab through the intact blood–brain barrier*
  - *both*

CNS as first relapse site

	CNS Relapse %	
	1y-Trastuzumab	**Control**
NSABP-B31	3.2	4.0
NCCTC N9831	1.49	0.5
HERA	2.0	2.0

A meta-analysis of these trials showed that the risk of developing brain metastases higher for patients given trastuzumab (**relative risk 1.57**, 95% CI 1.03–2.37).

CNS as first relapse site in HERA



Pestalozzi, Lancet Oncol 2013

Low incidence of brain relapse

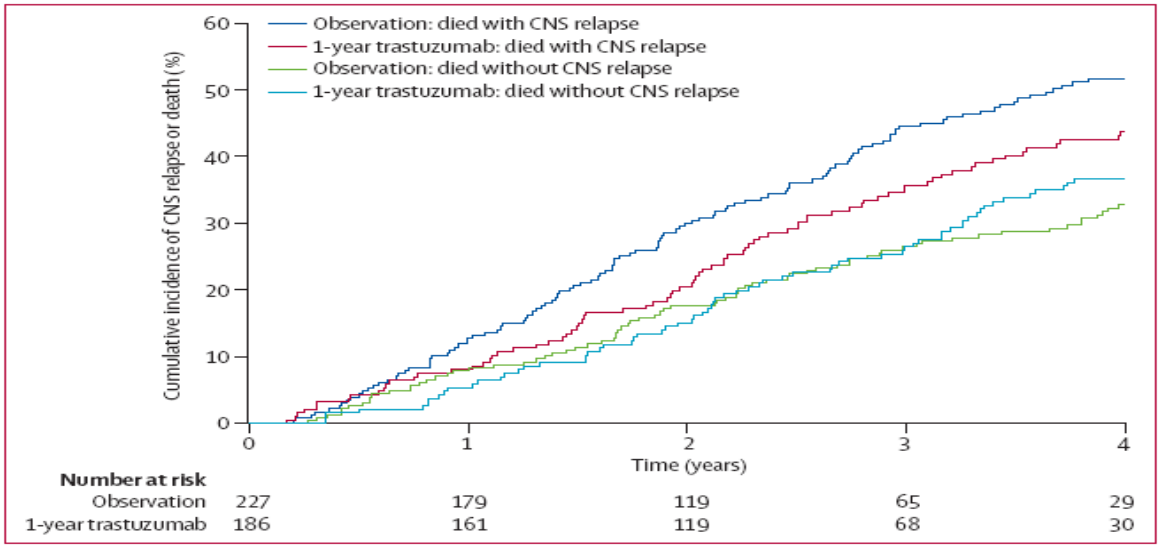
- CNS surveillance in asymptomatic patients with HER2+ early breast cancer is not justified.

- The feasibility of a CNS prophylaxis trial is dubious in view of the few events.
  - In the phase 3 TEACH trial (adjuvant lapatinib versus placebo - primary outcome DFS),13 **(<1%)** of 1571 patients in the lapatinib group and 21 **(1%)** of 1576 patients in the placebo group had a first event in the CNS.

Risk of subsequent brain metastases

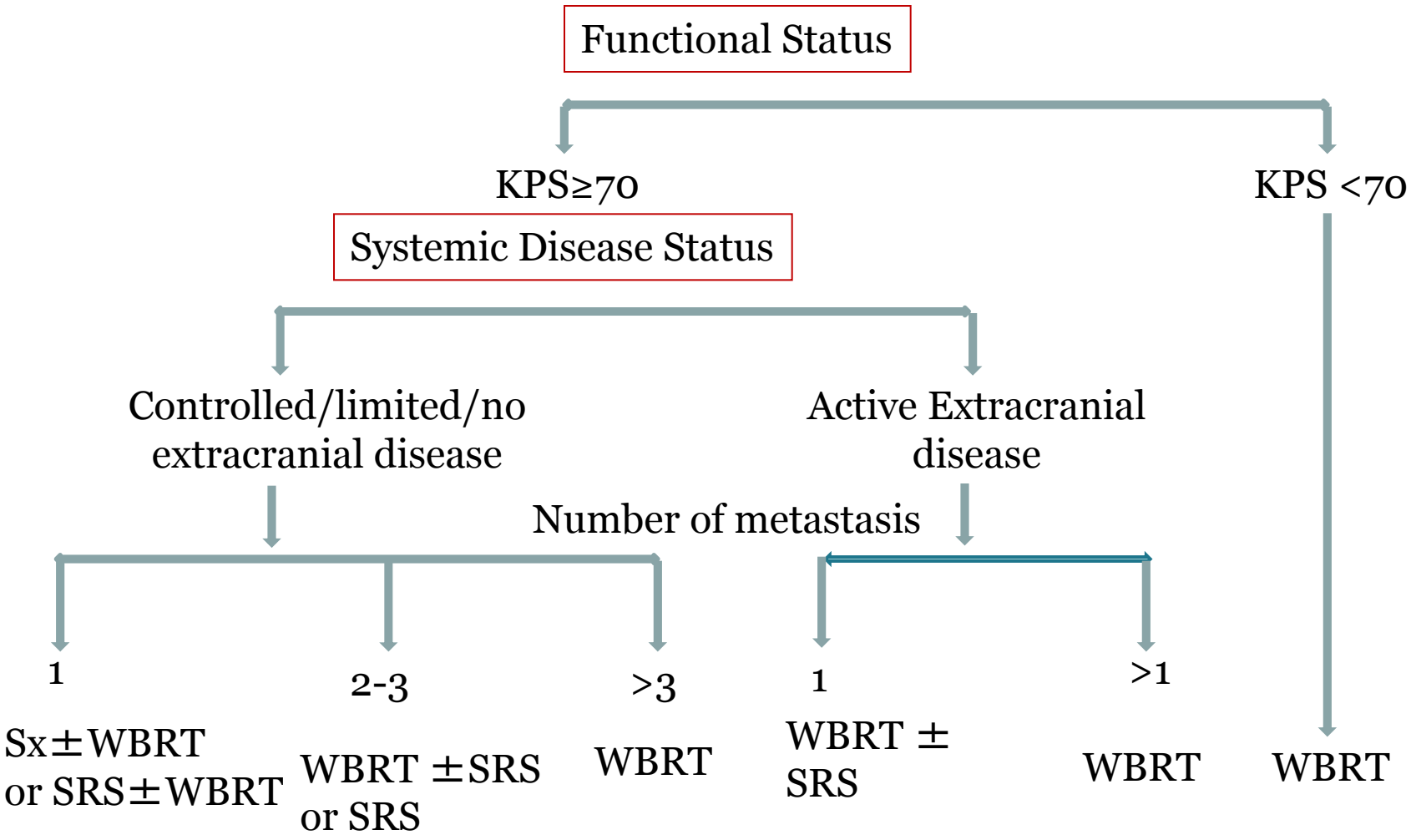
	1-year trastuzumab group	Observation group	Overall
Cohort of 3401 enrolled patients			
Number of patients	1703	1698	3401
CNS relapse as first DFS event	37 (2%)	32 (2%)	69 (2%)
Time to CNS relapse (years)	1·31 (0·53–2·03)	1·25 (0·53–2·13)	1·26 (0·53–2·03)
Other first DFS event	326 (19%)	421 (25%)	747 (22%)
Cohort of 413 patients who had died and for whom forms were returned			
Number of patients	186	227	413
Died with CNS relapse	88 (47%)	129 (57%)	217 (53%)
Time to CNS relapse (years)	2·11 (1·34–2·99)	1·89 (1·15–2·92)	2·02 (1·19–2·93)
Died without CNS relapse	98 (53%)	98 (43%)	196 (47%)

Data are n, n (%), or median (IQR). DFS=disease-free survival.



Pestalozzi, Lancet Oncol 2013

Local Management of Brain Metastasis



Leyland-Jones. JCO 2009

Result of 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%**	

WBRT Side effects

Acute Toxicity	Late toxicity
Generally mild and self limited	More than 6-12 months after therapy
Cerebral edema may be induced or worsened	Leukoencephalopathy and brain atrophy, leading to neurocognitive deterioration and dementia.
Preceded by at least 48 hours by corticosteroid therapy (except smaller lesions)	Radiation necrosis
	Normal pressure hydrocephalus, causing cognitive, gait and bladder dysfunction
	Neuroendocrine dysfunction, most commonly hypothyroidism
	Cerebrovascular disease

Modality	Mean probability of **neurocognitive decline** @4 mos
SRS	**23%**
SRS+WBRT	**49%**

Systemic therapies

- Trastuzumab
  - penetration across BBB may be enhanced by radiation, BM, or meningeal carcinomatosis.
  - no clinical studies directly examining the impact of trastuzumab on BM.
  - retrospective studies suggest improved outcomes in patients who continue trastuzumab after radiation

Systemic therapies

- Trastuzumab
  - Trastuzumab has been shown to enhance radiation-induced apoptosis of breast cancer cells in preclinical studies.
  - One small single-arm study of concurrent trastuzumab and WBRT demonstrated a radiographic response rate of 74 %.
  - Randomized studies of WBRT versus concurrent trastuzumab plus WBRT have not been performed.
  - the ratio of trastuzumab concentrations in serum and CSF was 420:1 prior to radiation and 76:1 after radiation

Systemic therapies

- Lapatinib
  - can cross the BBB, it is a substrate of PgP, breast cancer resistance protein 1 (BCRP1), and other drug efflux proteins.
  - preclinical studies of PgP and BCRP1 knockout mice treated with lapatinib demonstrate increased brain:plasma lapatinib concentrations (1.2–1.7) compared with wild-type mice (0.03–0.04)

Lapatinib for BM 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

Lapatinib + capecitabine for BM 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	

Lapatinib before WBRT
The Landscape trial

- Concomitant treatment of extra CNS disease
- Delay WBRT and associated toxicities

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

Median Time to WBRT: 8.3 mos – Median OS 17 mos

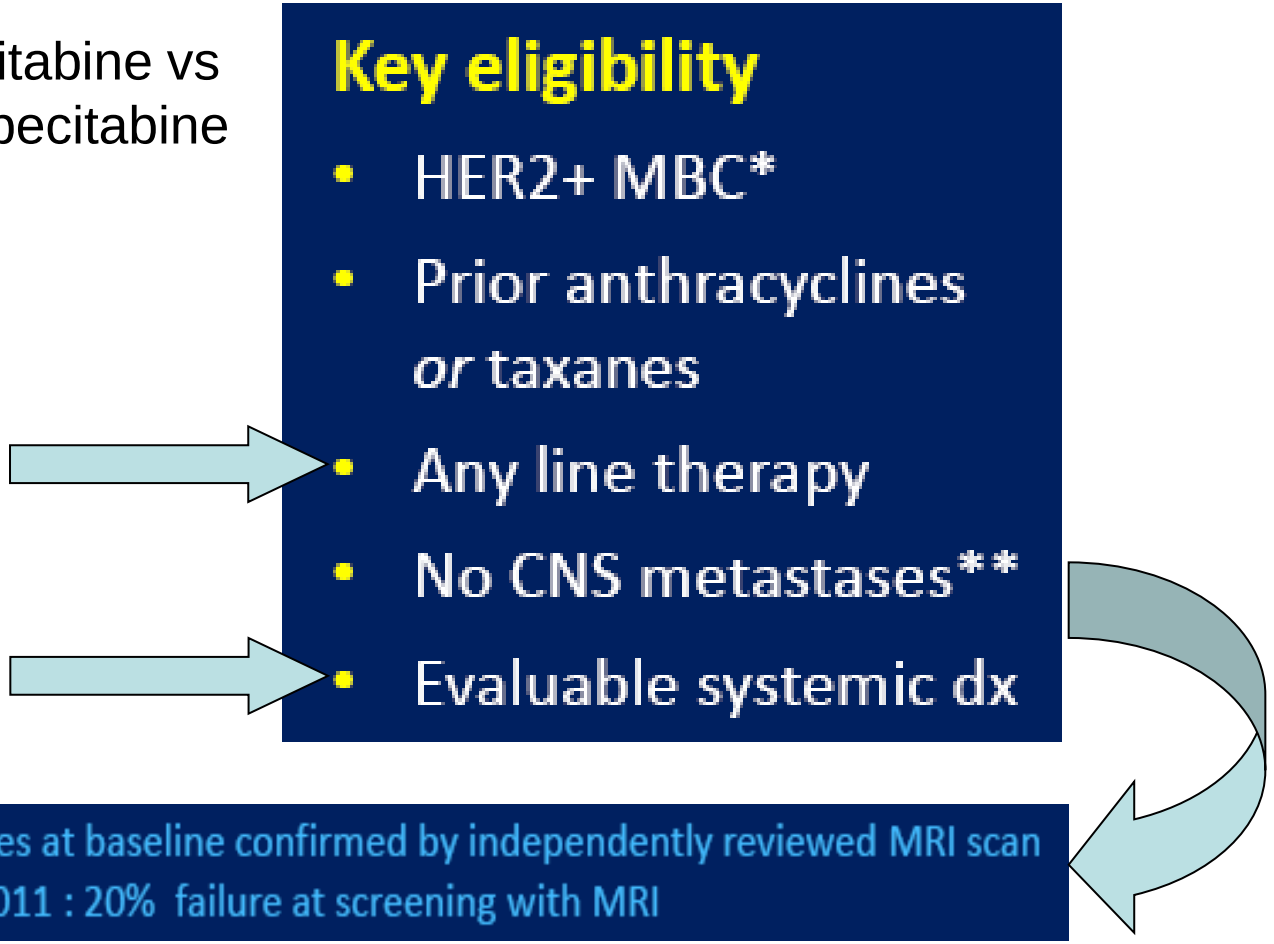
CEREBEL (EGF111438): An open-label randomised Phase III study comparing the incidence of CNS metastases in patients with HER2+ metastatic breast cancer, treated with lapatinib plus capecitabine versus trastuzumab plus capecitabine

- **Primary Objective**
  - Incidence of CNS as site of first relapse
- **Secondary Objectives**
  - PFS (time from randomisation to progression and/or death)
  - OS
  - ORR, CBR
  - Time to first CNS progression
  - Incidence of CNS progressions at any time
  - Safety

Which patients have been studied?

Lapatinib/capecitabine vs trastuzumab/capecitabine

650 pts planned



Early detection and treatment of BM

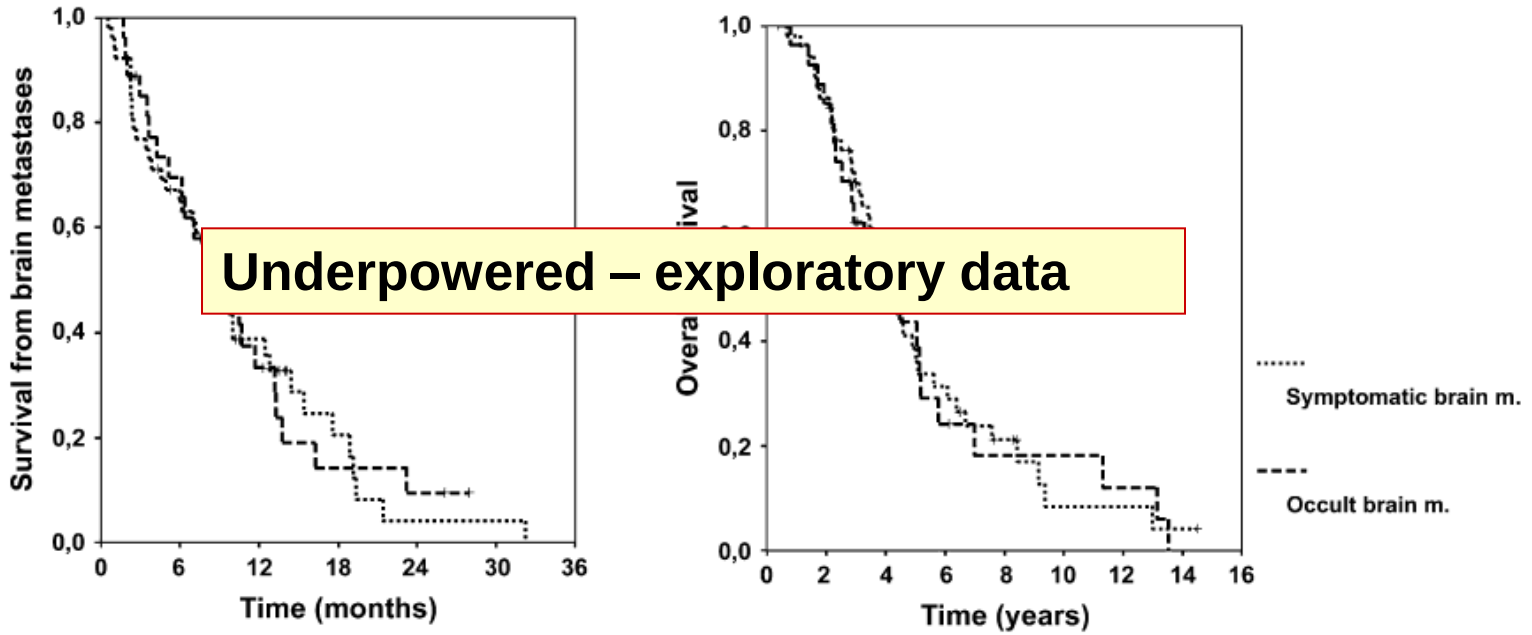
- 80 patients with HER2+ MBC without neurologic symptoms were MRI screened for occult BM q3 mos
- Occult metastases were detected *(median time 9 mos)* in **36%** of patients; 90% of them received WBRT.

- Compared with a separate cohort receiving **WBRT** for symptomatic BM, the use of early WBRT decreased the **rate of death from BM** (**16 vs 48 %;** P = 0.009) but had **no impact on OS** (53 vs 51 months, P = 0.944).

Cause of death	Occult BM	Symptomatic BM
Brain PD	16%	48%
Visceral PD	84%	52%

Survival of MRI screened HER2+ patients

	Screening cohort (n = 80)		
	No brain metastases (n = 51)	Occult brain metastases (n = 29)	Control group: Symptomatic brain metastases (n = 52)
Median age (y)	53	52	48
ER/PR positive	23 (46%)	13 (45%)	17 (33%)
Histopathology (Grade 3 ductal carcinoma vs. others)	17 (33%)	10 (34%)	17 (33%)
Visceral metastases	32 (63%)	28 (96.5%)	52 (100%)
Bone metastases	21 (41%)	16 (55%)	32 (61.5%)
Locoregional failure	32 (62.7%)	16 (55.1%)	16 (31%)



Underpowered – exploratory data

Niwinska, Int. J. Radiation Oncology Biol. Phys., 2010

Are Cerebel pts similar to"our pts"?

	Lapatinib + capecitabine (N=271)	Trastuzumab + capecitabine (N=269)
Stage IV at initial diagnosis	52 (19)	44 (16)
Patients who have received prior treatment for MBC, n (%)	154 (57)	148 (55)
Patients who have received prior trastuzumab, n (%)	167 (62)	159 (59)
Adjuvant	81 (30)	70 (26)
Metastatic	96 (35)	93 (35)
Age in years, median (range)	53 (27–83)	56 (31–79)
ECOG status at baseline, n (%)		
n	269	266
0/1	260 (96)	261 (98)
2	9 (3)	5 (2)
# of Involved sites		
≥3	77 (28)	78 (29)
<3	194 (72)	191 (71)

Which message from Cerebel study?

	Lapatinib + capecitabine (N=251)	Trastuzumab + capecitabine (N=250)	OR (95% CI)	p-value
CNS as first site of relapse, n (%)	8 (3)	12 (5)	0.65 (0.26, 1.63)	0.360
Incidence of CNS progression at any time, n (%)	17 (7)	15 (6)	1.14 (0.52, 2.51)	0.8646
Time to first CNS progression, median (range)	5.7 (2–17)	4.4 (2–27)	-	-

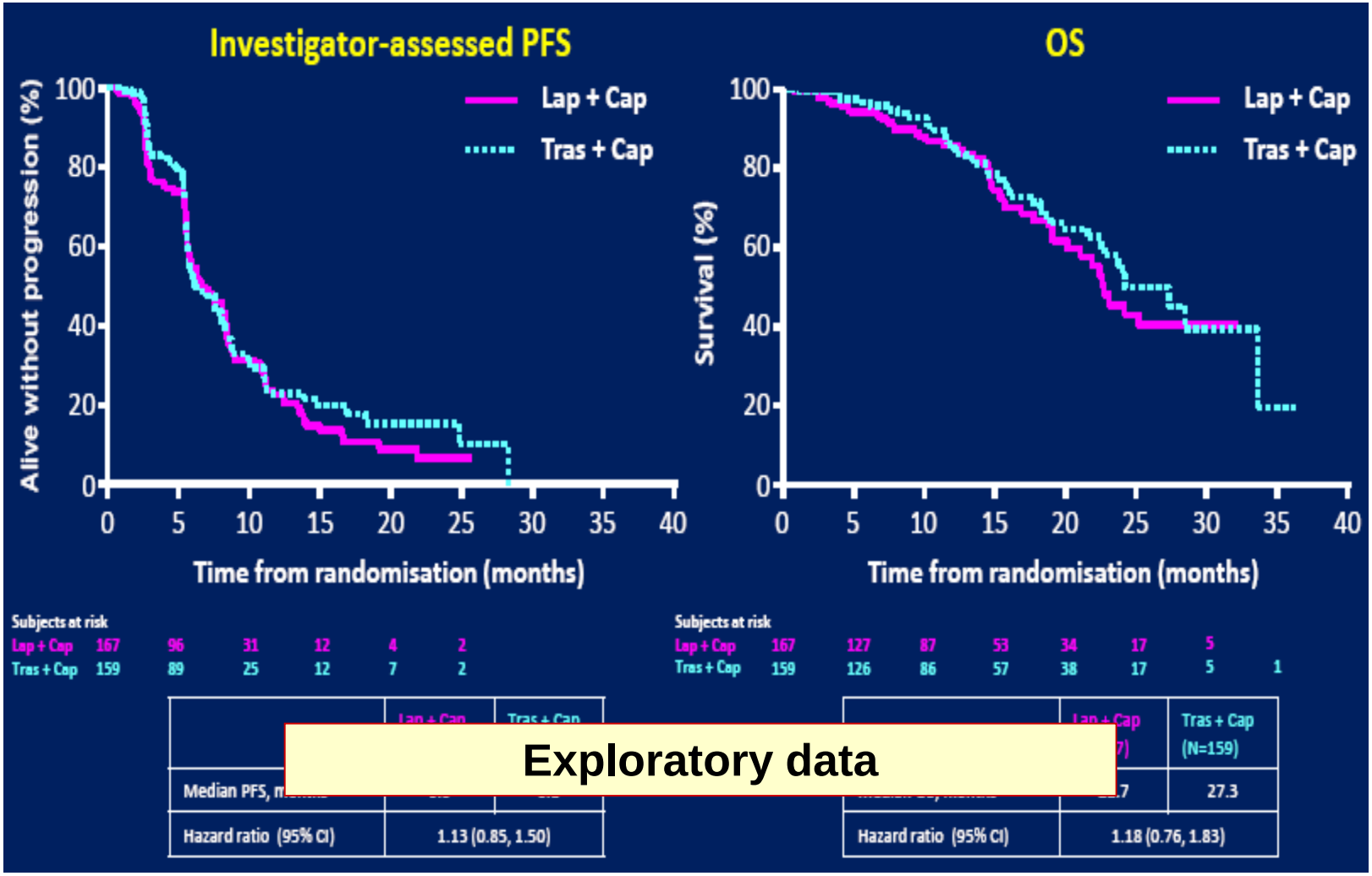
MRI detection rate of asymptomatic brain metastases in as high as 20%

Lower than expected incidence of brain metastases

In pts with MRI negative for BM, 35% less incidence of brain relapse with lapatinib *(not statistically significant) – chance?*

Treatment effect on the whole disease

Pretreated with trastuzumab



	Lap + Cap	Tras + Cap
Median PFS, m		
Hazard ratio (95% CI)	1.13 (0.85, 1.50)	

	Lap + Cap	Tras + Cap (N=159)
	7)	
	7	27.3
Hazard ratio (95% CI)	1.18 (0.76, 1.83)	

Exploratory data

What will we do tomorrow for a HER2+ BC lady without symptomatic BM?

- **CNS staging with MRI in M+?**
  - *No (but pts with visceral disease have 4 fold risk of BM). No clear advantage for treating asymptomatic pts, if extracranial disease is suboptimal treated (room for future studies with new agents)*

- **Treatment with lapatinib+capecitabine after trastuzumab failure**
  - *Yes, an option at the moment (second line only approved) (but better extracranial disease control with TDM1 – EMILIA study)*
    - PFS and OS similar to trastuzumab
    - Fewer and later CNS 1°progressions
    - Similar safety profile (capecitabine!)

- **Treatment with lapatinib+capecitabine before trastuzumab**
  - *No, better control of extracranial disease with trastuzumab (and even better with pertuzumab+trastuzumab+doce) (data on CNS PD?)*

Next future options in HER2+ mBC

Expected Patient characteristics

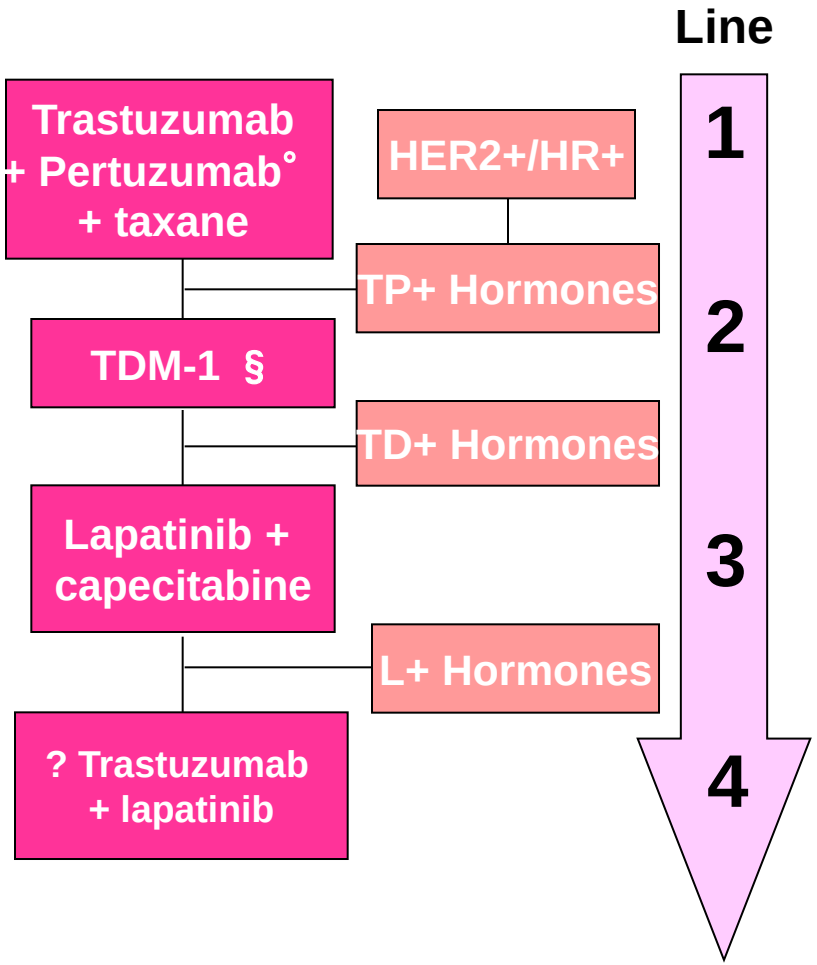
Adjuvant trastuzumab in 80-90%; DFI: < 1 yr: 5-7%

Onset as stage IV: 15-20%

Visceral (liver) disease; often symptomatic

	PFS mos	Absolut gain° (mos)	OS mos	Absolut gain° (mos)
T+P+D	18.7	6.3	n.r^	13+
TDM-1	9.6	3.2	30.9	5.8
L+C	6.2*	4.0	15.6	0.3
T+L	2.7	3.0	14	4.5

° against control arm



Fast changing sequence

^ 66% at 3 years; * 11.5 mos in pts < 3 previous lines