NEGRAR 7 OTTOBRE 2014

12° INCONTRO ONCOLOGICO DEL TRIVENETO

OSPEDALE
"SACRO CUORE - DON CALABRIA"
Via Don A. Sempreboni, 5 - 37024 Negrar (VR)
Tel. 045.601.31.11 - Fax 045.750.04.80

Terapia sistemica: quando e quale?

Stefania Gori

U.O.C. Oncologia Medica

Ospedale Classificato " Sacro Cuore- Don Calabria"

Presidio Ospedaliero, Negrar (VR)

Brain metastases in HER2+ breast cancer

Goals of treatment

Neurologic symptoms control

↑ Quality of Life

↑ Survival

Il trattamento delle metastasi cerebrali può avvalersi di:

- una terapia sintomatica
- un trattamento locale (radioterapia, chirurgia)
- una terapia sistemica antitumorale

variamente integrati tra loro nella singola paziente in base a:
prognosi,
numero di metastasi cerebrali, sede e dimensioni, situazione della malattia extra-cranica,
PS.

Gori S, Foglietta J. Metastasi del sistema nervoso centrale. In: La Medicina Oncologica;pagg 807-819. Labianca R e Cascinu S ed. LSWR Milano 2013

Terapia sintomatica delle crisi epilettiche

Glioma a basso grado ed altri tipi di tumori cerebrali primitivi o metastasi cerebrali, ad eccezione del glioblastoma

LEVETIRACETAM: 500 mg os x 2/die (250 mg os x 2/die la prima sett)
SE NECESSARIO AUMENTARE a 750-1500 mg os x 2/die
(finestra terapeutica 5-25 mg/L)

Attenzione a irritabilità o cambiamenti dell'umore

Se continuano crisi epilettiche:
AGGIUNGERE **ACIDO VALPROICO** 500-1.000 mg os x 2/die (20 mg/Kg);
SE NECESSARIO aumentare a 1.500 mg os x 2/die (finestra terapeutica: 50-100 mg/L)

Mod. da Vecht CJ et al, Oncologist 2014

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: American Society of Clinical Oncology Clinical Practice Guideline

Naren Ramakrishna, Sarah Temin, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Sharon H. Giordano, Ana M. Gonzalez-Angulo, Jeffrey J. Kirshner, Ian Krop, Jennifer Levinson, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Eric P. Winer, and Nancy U. Lin

Ramakrishna N et al, JCO 2014;32:2100-08

Results

No studies or existing guidelines met the systematic review criteria; therefore, ASCO conducted a formal expert consensus–based process.

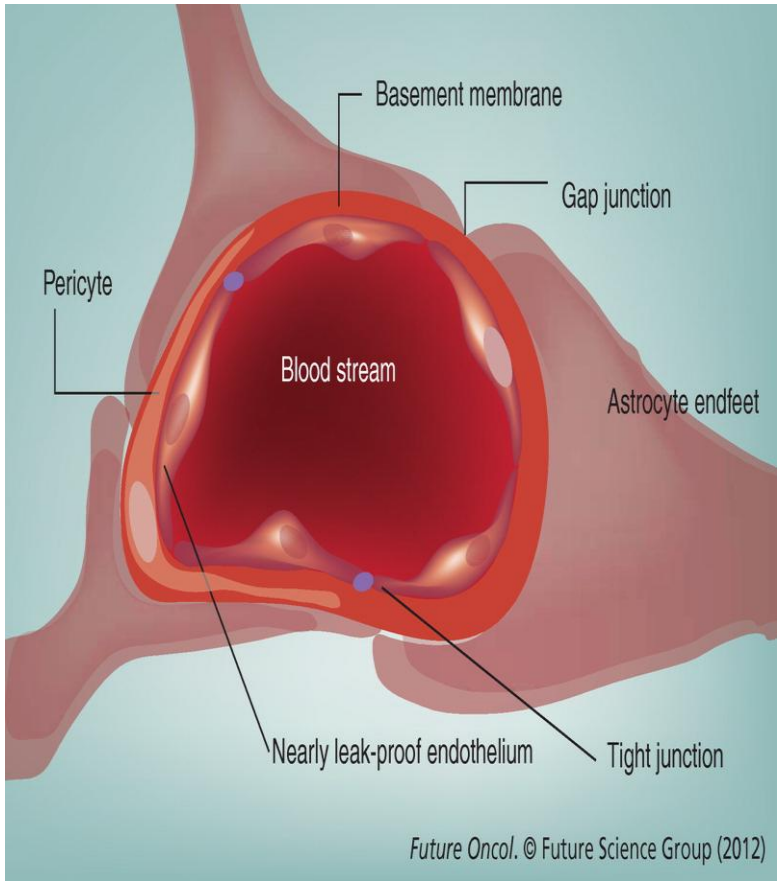
Systemic therapy in brain metastases from HER2+ BC

HER2 STATUS concordance between primitive tumor and brain metastases

	PRIMARY T (= n)	CNS METASTASES (= n)	CONCORDANCE
FUCHS I.B. *JCO 2002; 20: 4130-3*	13 HER2 + 16 HER2 -	13 HER2 + 15 HER2 - 1 HER2 +	100% Global Concordance 97%
LEAR-KAUL K.C. *ARCH. PATHOL. LAB. MED. 2003; 127:1451-7*	10*	10*	100%
IBRAHIM N.K. *ASCO 2006; 24 (suppl. 18) # 656*			88%
TOMASEVIC Z. *ASCO 2010 # 1117*	2 HER2 + 8 HER2 -	4 HER2 + 6 HER2 - 2 HER2 + (25% HER2- → HER2 +)	NR

* FISH amplified

CNS blood brain barrier



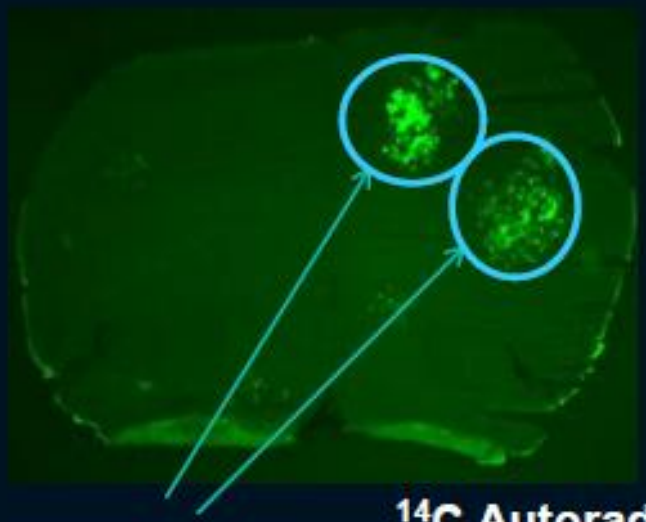
- The blood brain barrier (BBB) is permeable to substances with a diameter of < 20 nm[1]
  - **Trastuzumab** (~145 kDa) has limited ability to cross the BBB
  - **Lapatinib** (~1 kDa) has a higher potential to cross the BBB
- Studies show:
  - Trastuzumab levels in CSF 300-420 fold lower than in serum[2]
  - In animals, lapatinib levels 7-9 fold higher in brain tumour tissue compared to healthy brain tissue[3]
  - In animals, lapatinib inhibits formation of large brain metastases by HER2+ brain-seeking breast cancer calls[4]
- Whole brain radiotherapy may increase the permeability of the blood brain barrier

BBB=blood brain barrier; CSF=cerebrospinal fluid

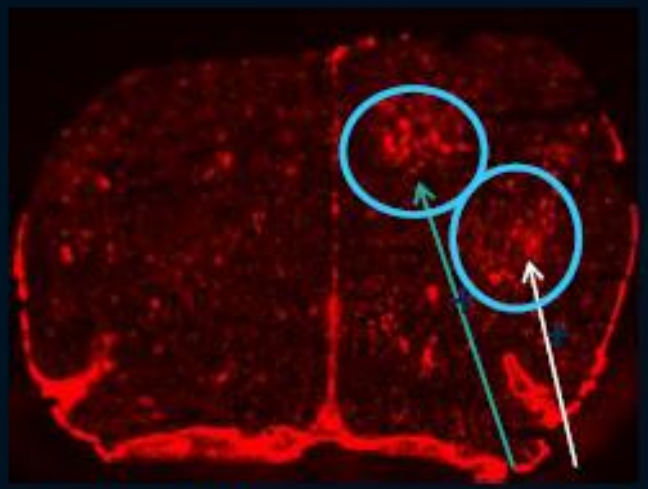
1. Azim HA & Azim HA. Future Oncol 2012;8:135-44.
2. Stemmler HJ & Heinemann V. The Oncologist 2008;13:739–50.
3. Taskar KS et al. Pharm Res 2012; 29:770-81.
4. Gril, et al. JNCI 2008; 100:1092-103.

^{14}C-Lapatinib Distribution in Brain Metastases

Green Fluorescence – GFP Tumor

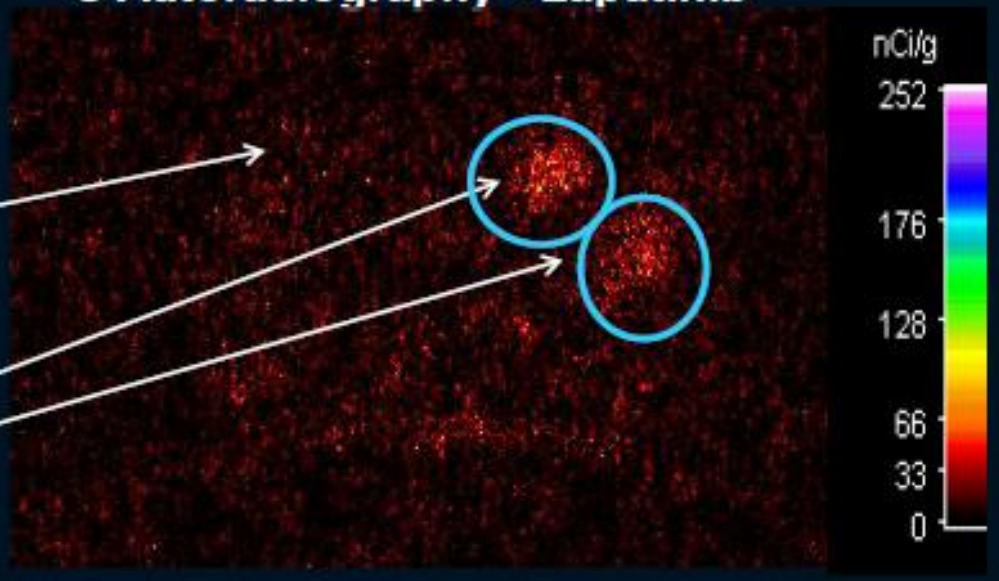


Red Fluorescence – Texas Red 3kD Dextran



Texas Red Leakage

^{14}C Autoradiography - Lapatinib



1.5 nCi/g
Normal Brain

23-26 nCi/g
Tumor

Quentin Smith
Paul Lockman
Texas Tech University

LANDSCAPE: a FNCLCC phase II study with lapatinib+capecitabine in patients with brain metastases from HER2+ MBC before WBRT

Objective :

- **Evaluate the clinical interest of L+C combination for BM in HER2+ MBC patients not previously treated with WBRT**

Treatment of patients with BM at their onset may be a way:

- *To start at once an active systemic treatment*
- *To delay WBRT and associated toxicities*

Bachelot T et al, Lancet Oncol 2013; 14:64-71

LANDSCAPE PROTOCOL

- **Enrolled 45 pts:**
  - HER2+ MBC
  - Newly diagnosed brain metastases, at least 1 cm in diameter (T1 MRI)
  - Not candidate for brain surgery
  - Any previous treatment except WBRT, 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 evaluation (including NSS) every 3 weeks**
- **Cerebral and systemic disease evaluation every 6 weeks**

NSS : Neurologic signs and symptoms

Bachelot T, Lancet Oncol 2013

Primary Endpoint:
CNS volumetric reduction

	Patients (n=44)
≥80% reduction	9 (20%)
50–<80% reduction	20 (45%)
20–<50% reduction	6 (14%)
0–<20% reduction	2 (5%)
Progression*	7 (16%)

*Two patients had progression outside of the CNS.

Table 3: Objective CNS response in assessable patients

CNS objective response =65.9%

Primary endpoint:

Centrally assessed CNS objective response (CNS-OR) defined as a ≥50% volumetric reduction of CNS lesions

in the absence of: increasing steroid use
progressive neurologic symptoms
progressive extra-CNS disease (RECIST)

Bachelot T et al, Lancet Oncol 2013; 14:64-71

Extra-CNS RECIST response

Extra-CNS-OR : 15/35 = 42.9% (95% CI: 26-61)

Extra-CNS RECIST evaluation	n = 35	
Complete response	1	(2.8%)
Partial response	14	(40%)
Stable disease	16	(45.7%)
Progression	4	(11.4%)

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

Bachelot T, ASCO 2011, #505

Bachelot T et al, Lancet Oncol 2013; 14:64-71

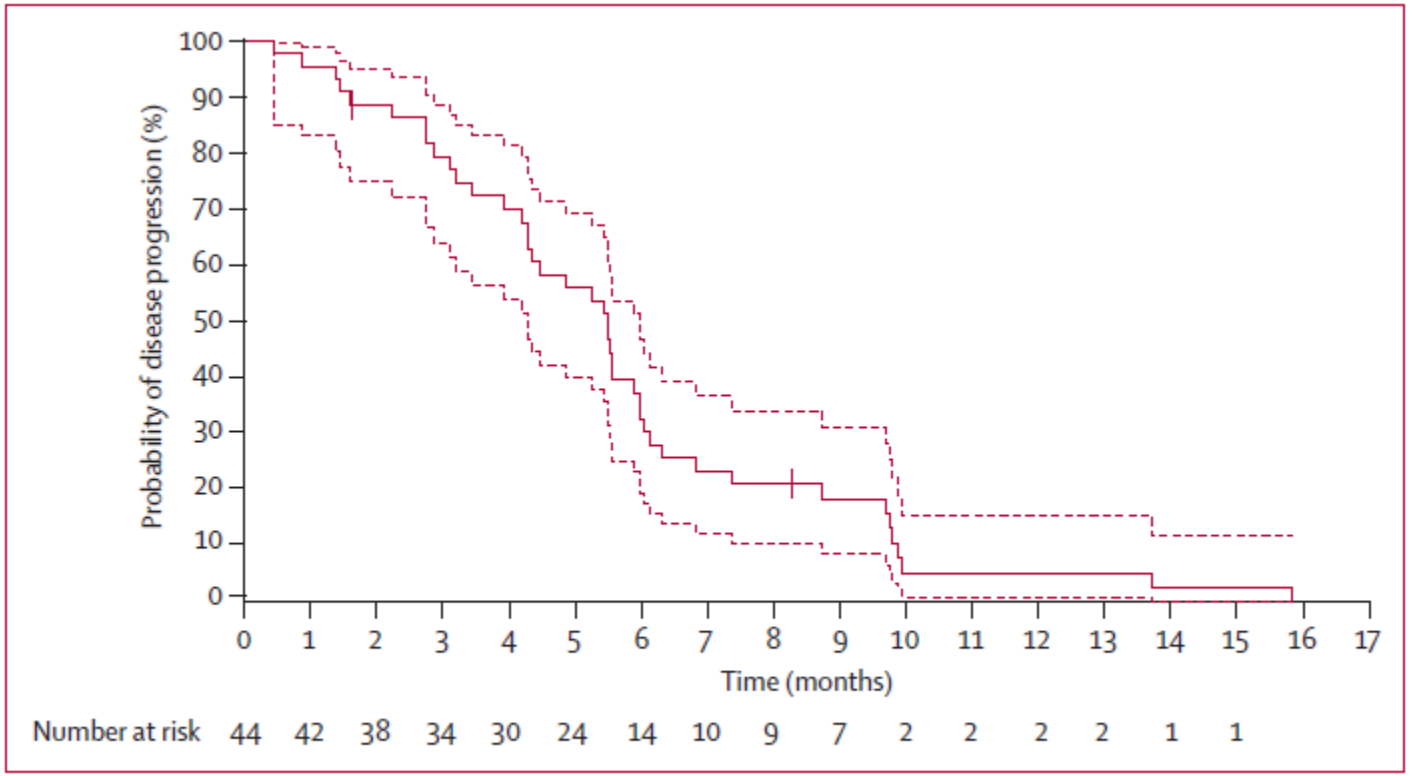


Figure 1: Time to disease progression (N=44)
Dashed lines are 95% CI.

Median time to progression: 5.5 mos

- **First progression CNS: n = 32/41 (78%); median time to CNS progression was 5.5 mos**
- **First progression extra-CNS: n = 2/41 (5%)**
- **Progression both CNS/extra-CNS: n = 5/41 (12%)**

➢ **Median time to WBRT is 8.3 months**

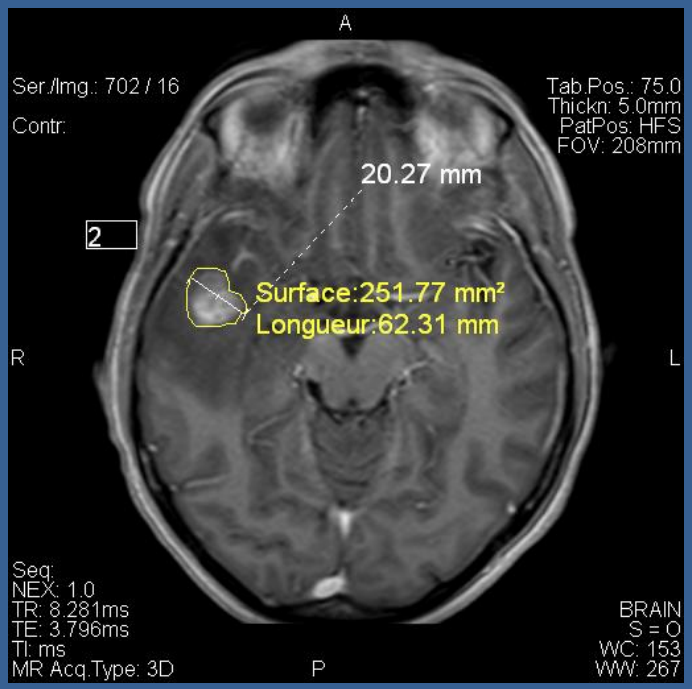
HER2+ BC and brain metastases: QUESTIONS

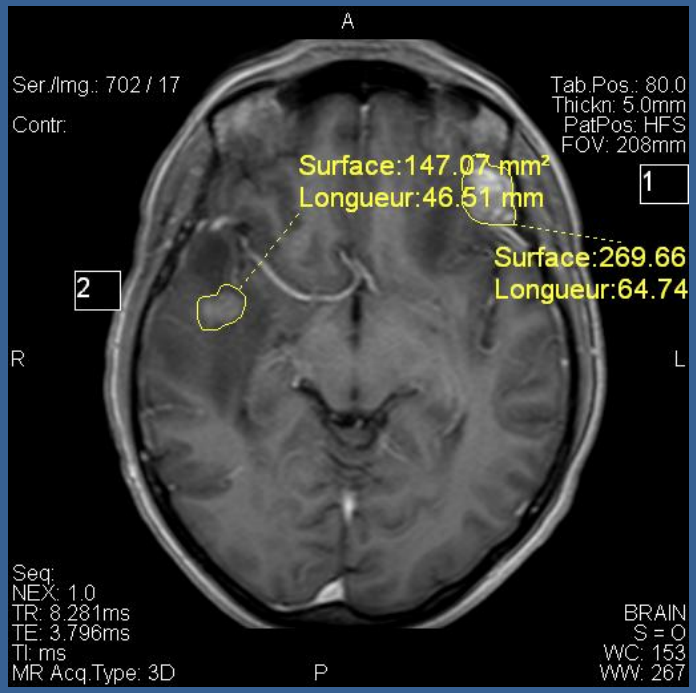
A- What response criteria in clinical practice?

Efficacy assessment

Central and blind volumetric evaluation of CNS lesions

- **MRI standardized guidelines**
- **All target lesions contoured across all slices, T1 SE axial 5mm Gado.**
- The software calculated the tumor volume of every target lesion:
  Tumor volume = ∑(outlined surfaces x slice thickness)*





*Lin NU et al. JCO 2008; 26:1993-99; Lin NU et al. Clin Cancer Res 2009; 15: 1452-59

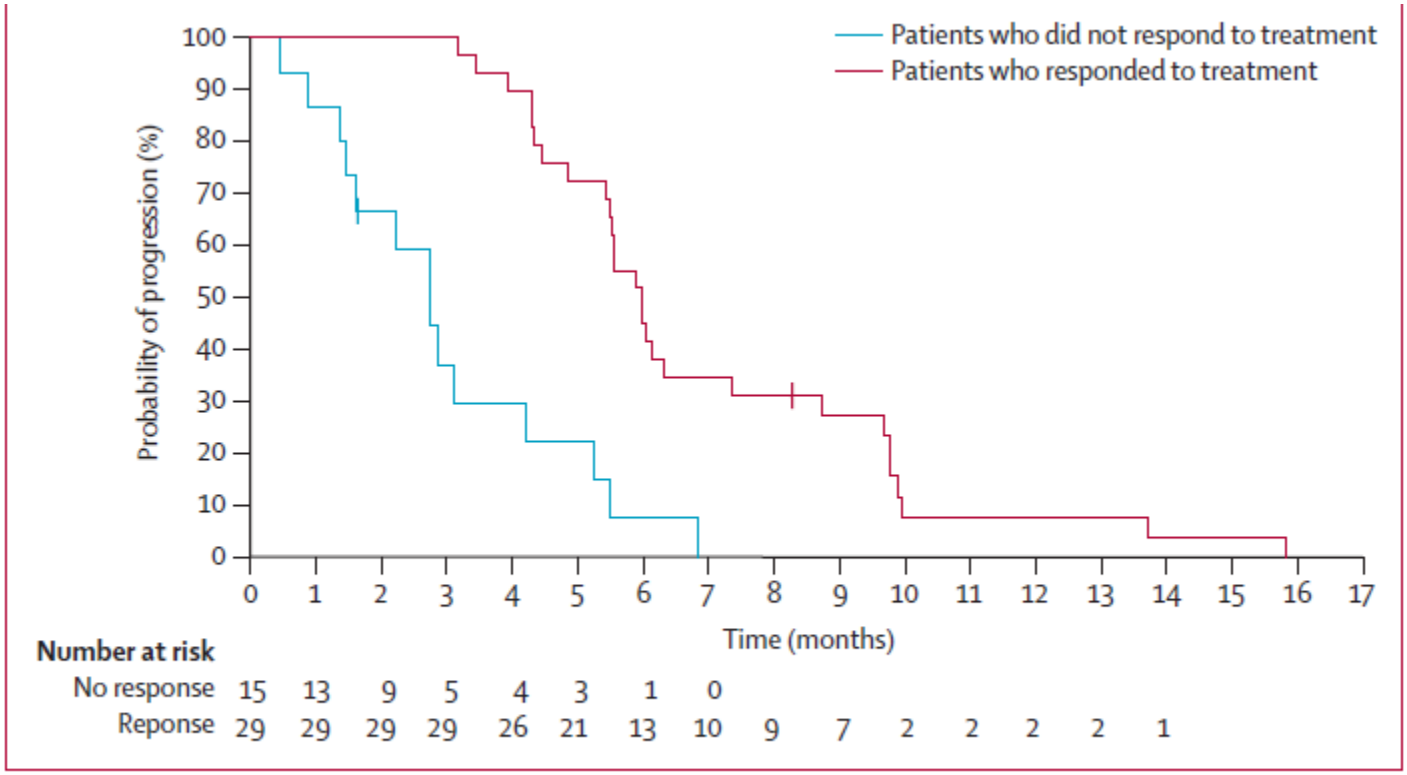


Figure 2: Time to progression, by CNS response (volumetric analysis; N=44)

Exploratory analysis:

Volumetric reduction	n (%)	Time To Progression (95% CI)	*p*
≥ 50 %	29 (67.4)	6 mo. (5.5-7.4)	*<0.0001*
< 50 %	14 (32.5)	2.8 mo. (1.4-4.2)	

HER2+ BC and brain metastases: QUESTIONS

B- There are new systemic therapies?

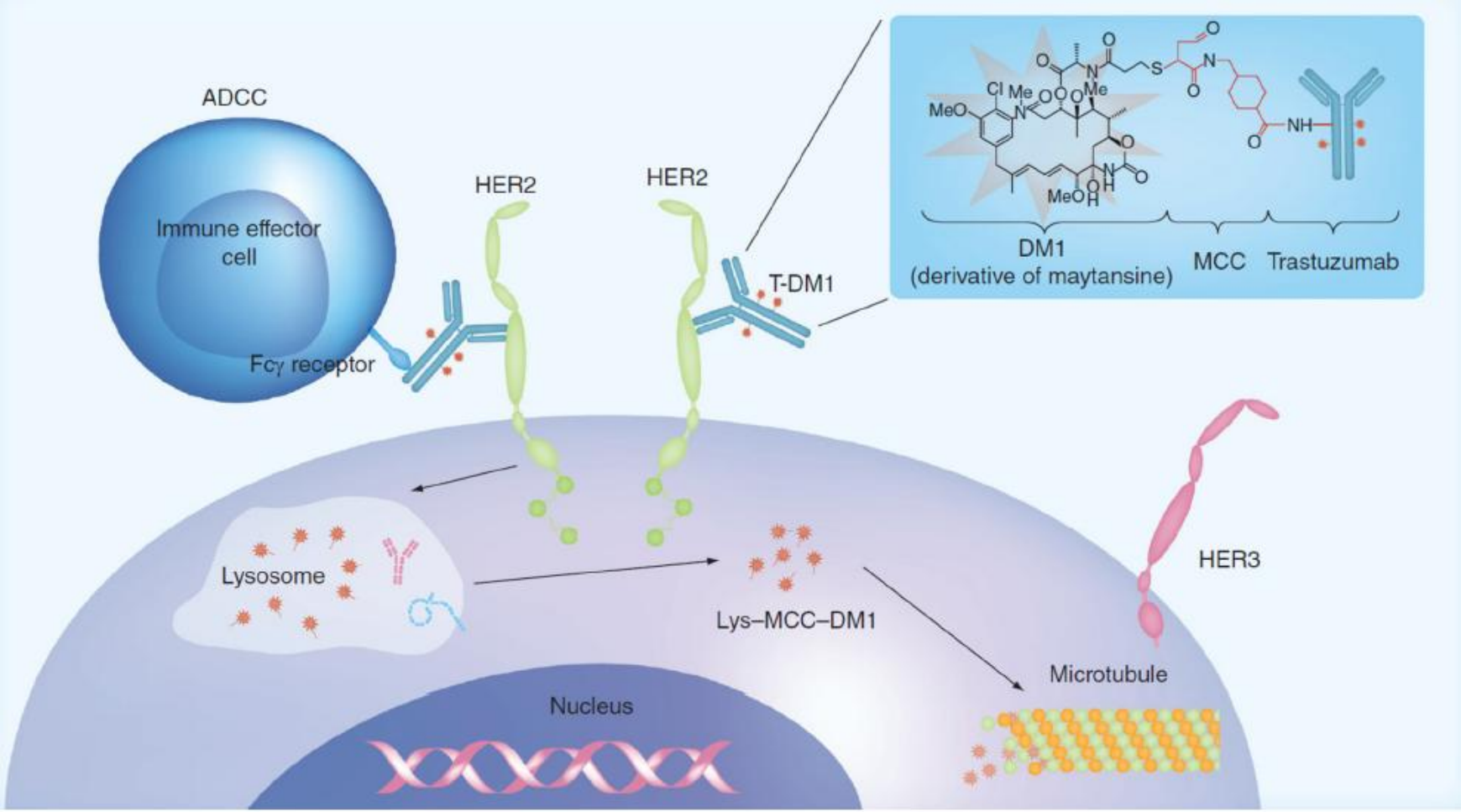


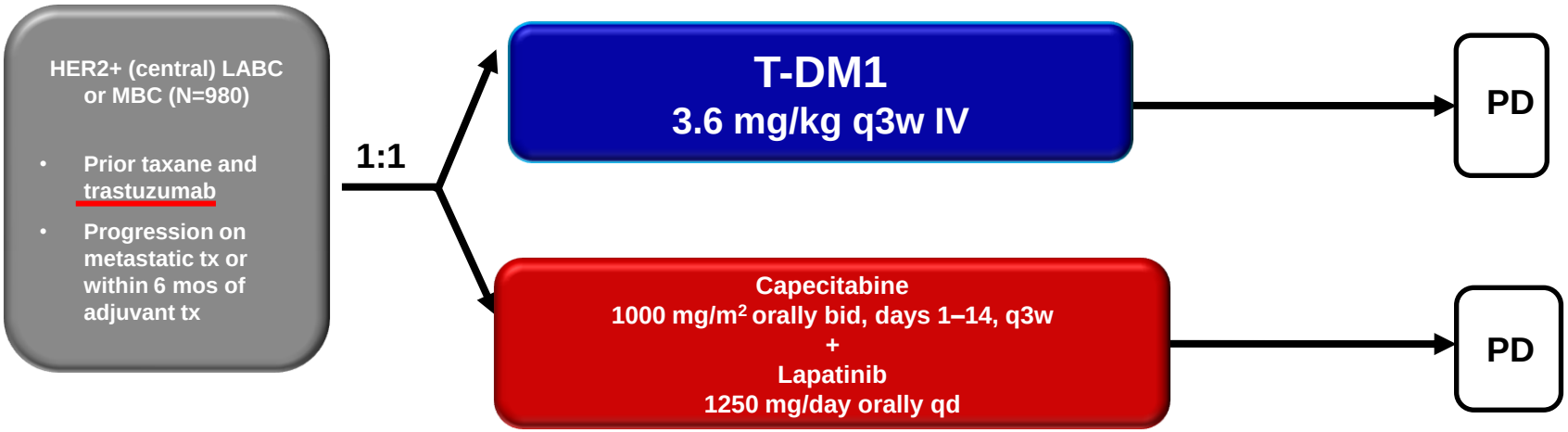
Figure 1. Structure of trastuzumab emtansine and mechanisms of action

After T-DM1 binds HER2, the HER2–T-DM1 complex undergoes internalization, followed by lysosomal degradation. This process results in the intracellular release of DM1-containing catabolites that bind to tubulin and prevent microtubule polymerization, as well as suppress microtubule dynamic instability. T-DM1 has also been shown to retain mechanisms of action of trastuzumab, including disruption of the HER3/PI3K/AKT signaling pathway and FCγ receptor-mediated engagement of immune effector cells that leads to antibody-dependent cellular cytotoxicity.

ADCC: Antibody-dependent cellular cytotoxicity; Lys: Lysine; T-DM1: Trastuzumab emtansine.

EMILIA: T-DM1 after disease progression

- **EMILIA Study Design**



- **Primary endpoints:** PFS by independent review, OS, and safety

Outcome	T-DM1	Lap +Cap	HR (95%CI); p value
Median PFS	9.6 mo	6.4 mo	0.65 (0.55-0.77); p <.001
Median OS	30.9 mo	25.1 mo	0.68 (0.55-0.85); p <.001

- **Rate of grade 3-4 AEs** lower with T-DM1 vs Lapatinib+Capecitabine (41% vs 57%)

Verma S, NEJM 2012; 367:1783-91

EMILIA: SNC metastases Retrospective analysis

CNS metastases

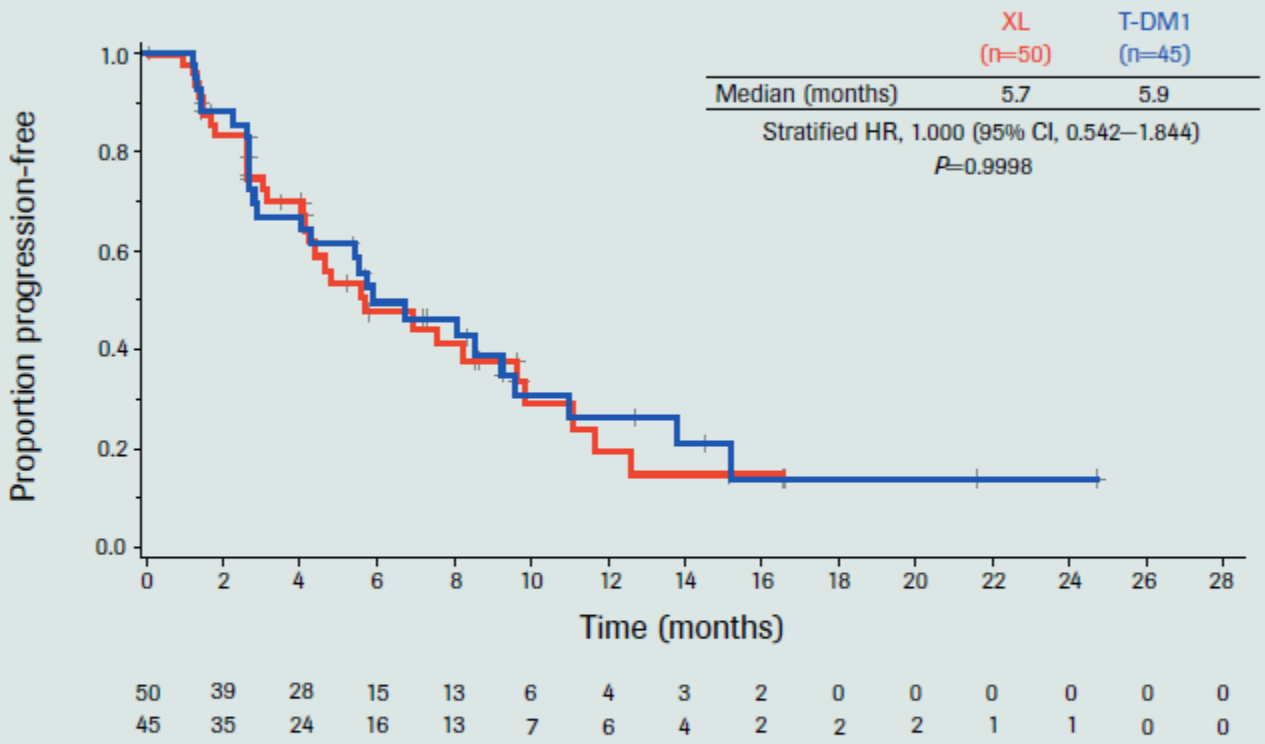
- All patients underwent brain magnetic resonance imaging (MRI) or computed tomography (CT) at screening, and follow-up scans were performed as clinically indicated (but were not mandated per protocol)
- Patients with asymptomatic CNS metastases who were treated with radiotherapy were eligible to enroll 14 days after the last dose of radiotherapy
- Patients with CNS metastases who were untreated, symptomatic, or required therapy to control symptoms ≤2 months prior to randomization were excluded from EMILIA, as were patients with CNS-only disease

Retrospective analysis of patients with CNS metastases

- Patients with CNS metastases at baseline or who developed CNS metastases on study were identified retrospectively using tumor assessment data from the independent review committee (IRC)
  - This analysis was exploratory and not prespecified in the protocol
- Kaplan–Meier methodology was used to estimate median PFS and OS

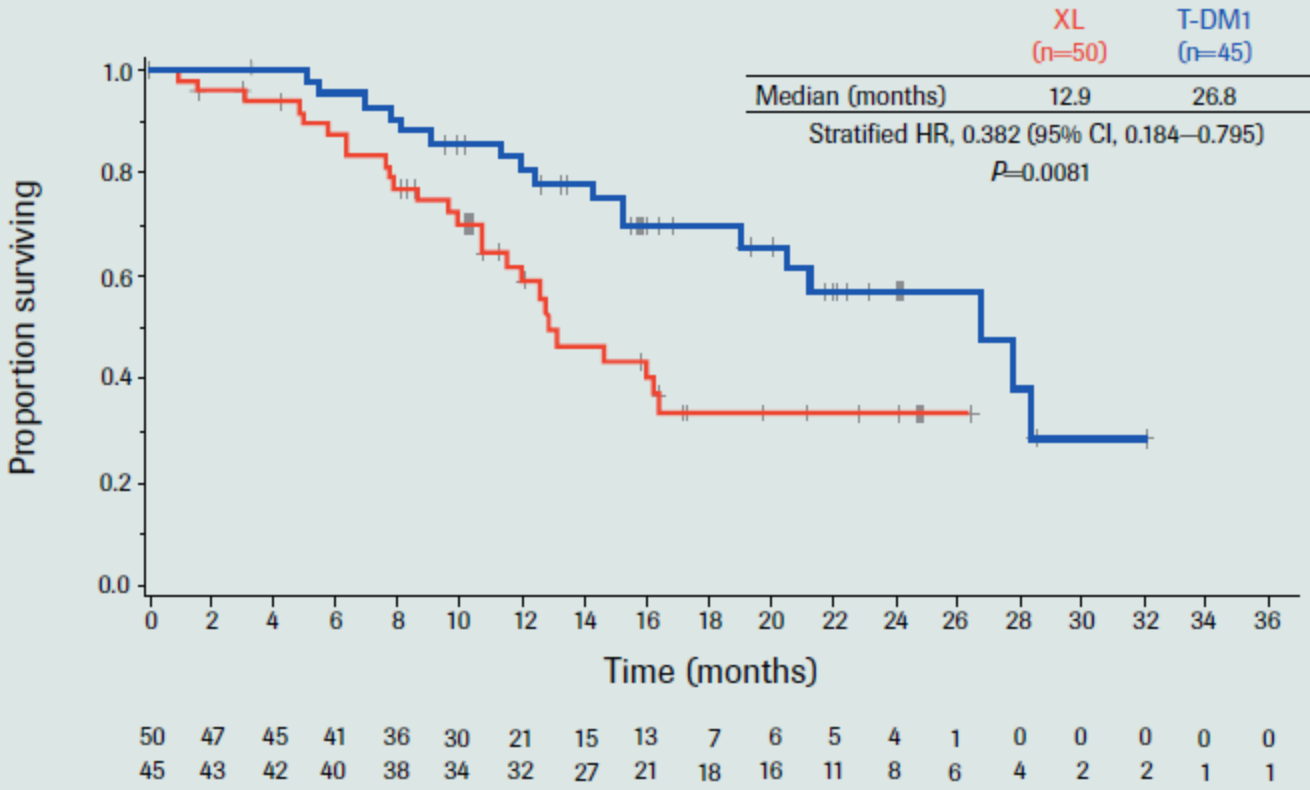
Krop J et al. SABCC 2013

Figure 1A. PFS by IRC for patients with CNS metastases at baseline



CI, confidence interval; CNS, central nervous system; HR, hazard ratio; IRC, independent review committee; PFS, progression-free survival; T-DM1, trastuzumab emtansine; XL, capecitabine + lapatinib.

Figure 2. OS for patients with CNS metastases at baseline



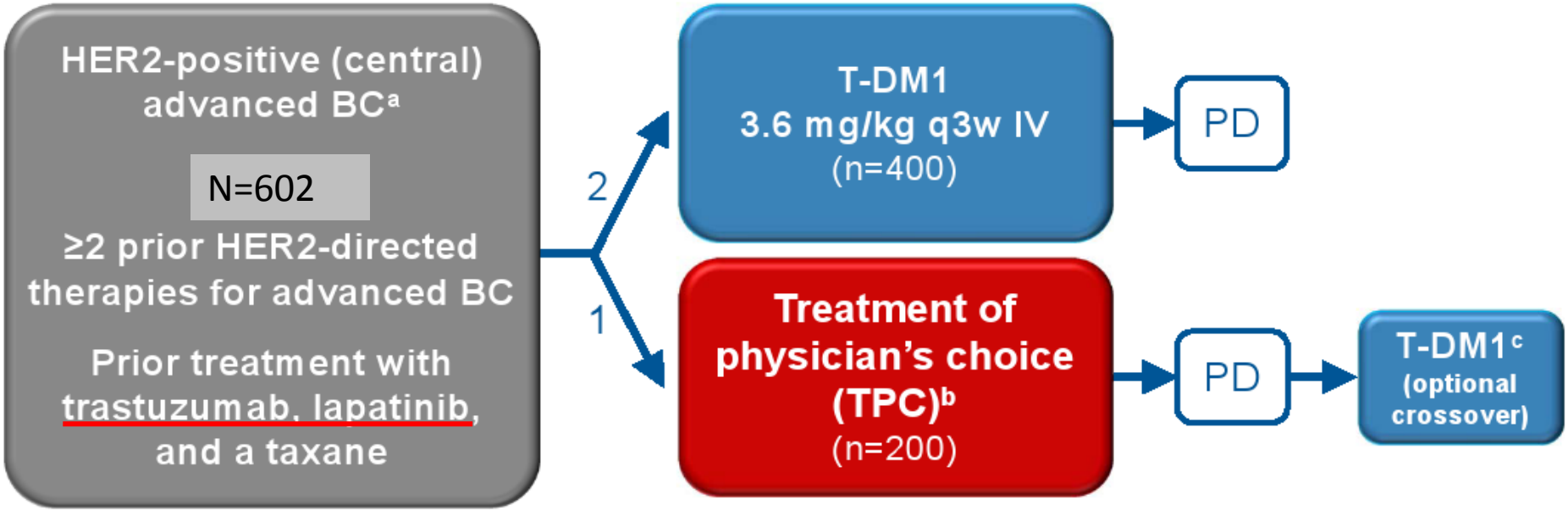
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; XL, capecitabine + lapatinib.

Table 5. Subsequent Anticancer Therapies in Patients With CNS Metastases at Baseline After Study Treatment Discontinuation

Treatment type, n (%)	XL (n=44)	T-DM1 (n=39)
Surgery	2 (4.5)	1 (2.6)
Brain	1 (2.3)	0
Nonbrain	1 (2.3)	1 (2.6)
Radiation	8 (18.2)	13 (33.3)
Brain	6 (13.6)	12 (30.8)
Nonbrain	3 (6.8)	6 (15.4)
Chemotherapy	23 (52.3)	29 (74.4)
Capecitabine	5 (11.4)	23 (59.0)
Taxane	9 (20.5)	5 (12.8)
Vinca alkaloid	15 (34.1)	10 (25.6)
Anthracycline	4 (9.1)	5 (12.8)
Hormonal therapy	4 (9.1)	3 (7.7)
HER2-targeted therapy	21 (47.7)	25 (64.1)
Trastuzumab	18 (40.9)	10 (25.6)
Lapatinib	7 (15.9)	21 (53.8)

CNS, central nervous system; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine; XL, capecitabine + lapatinib.

TH3RESA Study Schema (Phase 3)



- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

[a] Advanced BC includes MBC and unresectable locally advanced/recurrent BC.
[b] TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
[c] First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.
[d] Excluding single-agent hormonal therapy.
BC, breast cancer; IV, intravenous; ORR, objective response rate; PD, progressive disease; q3w, every 3 weeks.

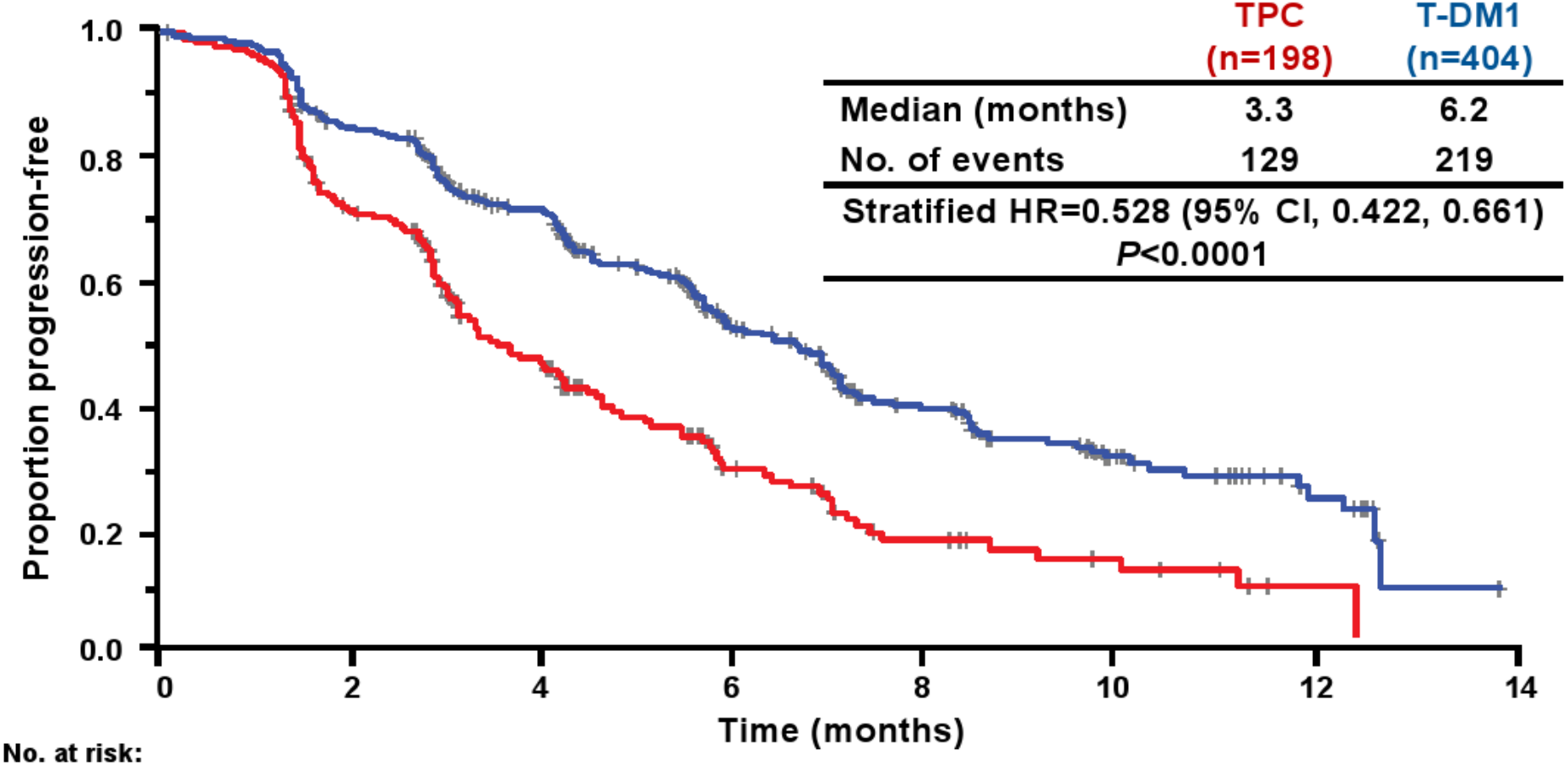
Baseline Characteristics (2)

Characteristic	TPC (n=198)	T-DM1 (n=404)
ER and/or PR-positive, %	52.0	51.5
Visceral involvement, %	75.8	74.8
Disease extent at study entry, %		
Metastatic	94.4	96.8
Unresectable locally advanced/recurrent BC	5.6	3.2
Number of prior regimens for advanced BC,[a] median (range)	4 (1–19)	4 (1–14)
≤3, %	39.4	32.6
4–5, %	32.8	37.1
>5, %	27.8	30.3
Brain metastasis at baseline, %	13.6	9.9

[a] Two patients in the T[illegible] arm had missing information for prior treatment in the advanced BC setting: TPC, n=198; T-DM1, n=402.
ER, estrogen recept[illegible]egesterone receptor.

TH3RESA trial- ECCO 2013 #LBA15

PFS by Investigator Assessment



	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

No. at risk:

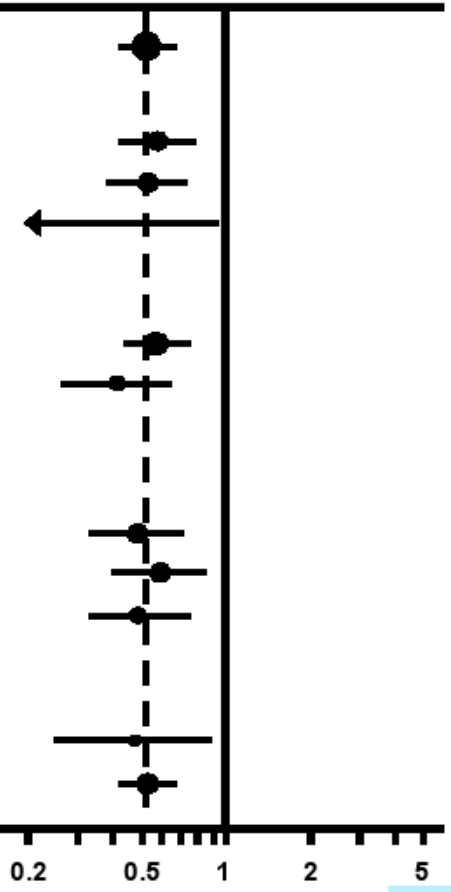
TPC	198	120	62	28	13	6	1	0
T-DM1	404	334	241	114	66	27	12	0

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

TH3RESA trial- ECCO 2013 #LBA15

PFS Subgroup Analyses (2)
By Investigator Assessment

Baseline characteristic	Total n	TPC n	TPC Event	TPC Median (months)	T-DM1 n	T-DM1 Event	T-DM1 Median (months)	HR[a]	(95% CI)
All patients	602	198	129	3.3	404	219	6.2	0.52	(0.42, 0.65)
ER and PR status									
ER+ and/or PR+	311	103	66	3.9	208	109	5.9	0.56	(0.41, 0.76)
ER– and PR–	270	85	58	2.9	185	105	6.0	0.51	(0.37, 0.71)
Unknown	21	10	5	3.9	11	5	8.3	0.17	(0.03, 0.93)
Disease involvement									
Visceral	452	150	95	3.4	302	168	6.2	0.56	(0.44, 0.72)
Nonvisceral	150	48	34	3.1	102	51	6.7	0.41	(0.26, 0.64)
Number of prior regimens for advanced BC									
≤3	209	78	49	3.3	131	60	6.9	0.48	(0.32, 0.70)
4–5	214	65	45	3.7	149	83	6.2	0.58	(0.40, 0.83)
>5	177	55	35	2.9	122	75	5.8	0.48	(0.32, 0.73)
Brain metastasis at baseline									
Yes	67	27	16	2.9	40	24	5.8	0.47	(0.24, 0.89)
No	535	171	113	3.6	364	195	6.2	0.53	(0.42, 0.66)



[a] Unstratified HR.

TH3RESA trial- ECCO 2013 #LBA15

HER2+ BC and brain metastases: QUESTIONS

C- How to integrate surgery, SRS, WBRT, systemic therapy?

D-What is the appropriate sequencing?

Local and systemic therapy in brain metastases from HER2+ BC:

concurrent?

TRASTUZUMAB WITH CONCURRENT WBRT

radiologic ORR (WHO)= 74% at 6 wks

(23/31)*

low trastuzumab-related toxicity

Chargary C, Int J Radiat Oncol Biol Phys 2010

LAPATINIB WITH CONCURRENT WBRT

volumetric ORR=70% at 2 mo
presently, no utilisation in clinical practice

Lin NU, ASCO 2010 #1154

Brain metastases in HER2+ breast cancer

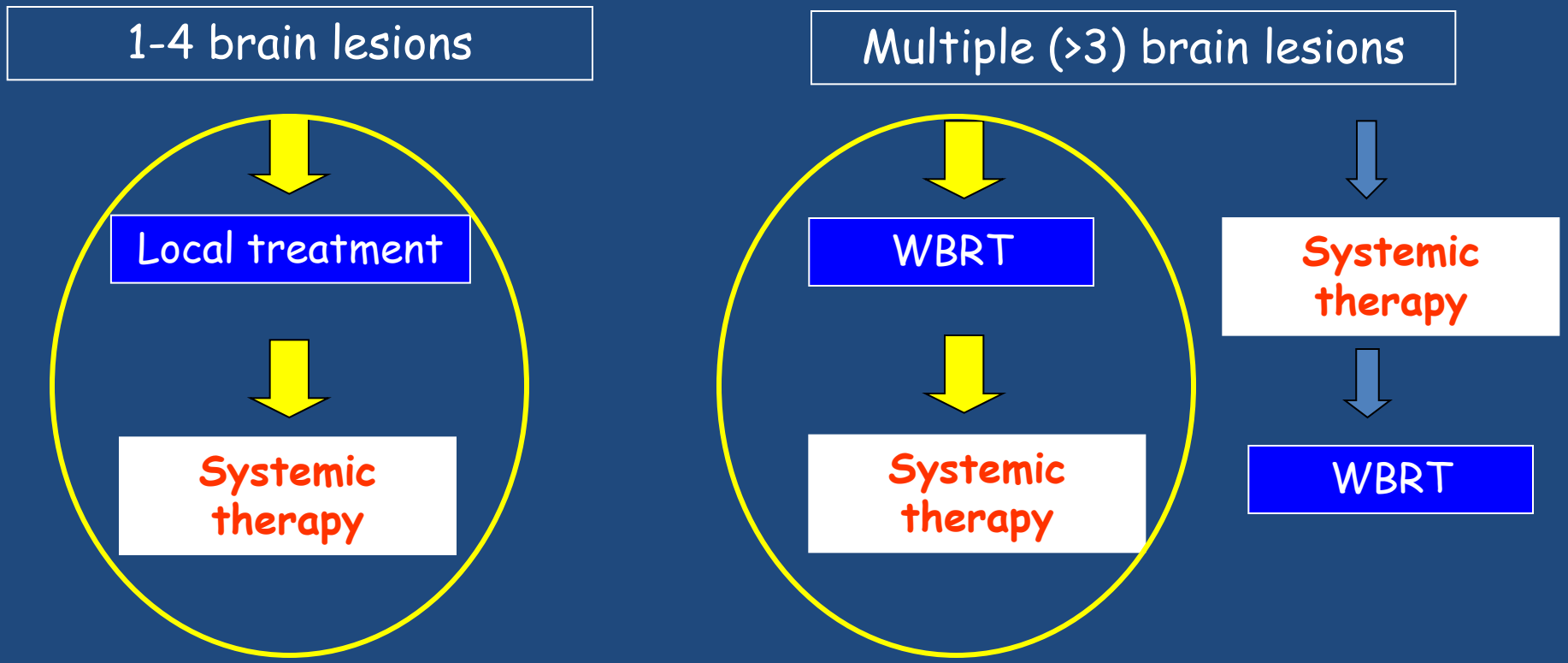
Causes of death

	PRE-Trastuzumab era	POST-Trastuzumab era	p
Park YH, BJC 2009			
Progression in the brain	46%	**60%**	ns
Progression in extra-CNS sites	**37%**	**12%**	**0.014**
Unknown	17%	28%	-
Bendell JC, Cancer 2003			
Progression in the brain	-	**52%**	-
Progression in extra-CNS +/- CNS sites	-	48%	-

Systemic therapy in brain metastases from HER2+ BC:

when?

Extracranial disease and ..



The choice of systemic therapy must be tailored on the following factors: Performance Status and previous agents received

Systemic therapy in brain metastases from HER2+ BC:

what?

Newly diagnosed brain metastases
and
no PD at extracranial sites

→ •NOT switch systemic therapy anti-HER2-based

Newly diagnosed brain metastases
and
PD at extracranial sites

→ •HER2 targeted therapy according to the algoritms for treatment of HER2-MBC

Newly diagnosed, **asymptomatic** and low volume brain metastases, no treated with RT

→ ▪ **Lapatinib + capecitabine**
phase II trial[1]

1.Bachelot T, Lancet Oncol 2013

Systemic therapy in brain metastases from HER2+ BC:

what?

Progression of brain metastases after RT

(not candidate for re-irradiation)

..there are no randomized phase III trials evaluating systemic approaches in pts with progressive CNS metastases in BC

- **Lapatinib+capecitabine**[1-3]
- **Trastuzumab+CT (?)**
- **T-DM1**[4](?)

(In pretreated with T and with L)

- **Chemotherapy**

1.Metro G, Gori S, Ann Oncol 2011 ; 2.Lin NU, Clin Cancer Res 2009; 3.Lin NU, J Neurooncol 2011 ;4. Krop IE, Lancet Oncol 2014 (TH3RESA trial);

HER2+ BC and brain metastases: QUESTIONS

E- Screening of brain metastases

Recommendations on management for HER2+BC and brain metastases : ASCO 2014

Clinical Question D

Should patients with HER2-positive breast cancer be screened for development of brain metastases?

Recommendation VII (screening): VIIA. If a patient does not have a known history or symptoms of brain metastases, clinicians should not perform routine surveillance with brain magnetic resonance imaging. Evidence quality: low.

VIIB. Clinicians should have a low threshold for performing diagnostic brain magnetic resonance imaging testing in the setting of any neurologic symptoms suggestive of brain involvement, such as new-onset headaches, unexplained nausea/vomiting, or change in motor/sensory function. Evidence quality: low. Recommendation strength: strong.

Ramakrishna N et al, JCO 2014;32:2100-08

HER2+ BC and brain metastases: QUESTIONS

G- Prevention of the CNS metastases development?

HER2+ BC and brain metastases

PREVENTION:

- WBRT (?)
- Lapatinib (?)

CEREBEL

CNS as Site of First Relapse on Lapatinib or Trastuzumab Evaluation Trial

EGF111438

HER2+ BC, IV stage, and **negative brain MRI at baseline (n=650)***

STRATIFICATION

prior Trastuzumab (Y/N) ; #line prior treat for MBC (0 vs ≥1)

RANDOMIZATION

LAPATINIB+ Capecitabine

TRASTUZUMAB+ Capecitabine

Primary endpoint:

Incidence of CNS metastases as first site of relapse

5%

3%

*Prior anthra or taxanes

JCO 2014 in press

THANK YOU !

Ospedale Classificato Equiparato

"SACRO CUORE -DON CALABRIA " Negrar-VR

Presidio Ospedaliero Accreditato- Regione Veneto