Cas clinique
cancer du sein Her2 positif

S.Sami

14 NOVEMBRE 2021

- Madame H.K agée de 49 ans , traitée en 2006 pour une néoplasie du sein droit T2N1M0.
- MC+CA le 18 Décembre 2006.
- AP: CCI, 27m, SBRII, 2N+/11N, RE score 6, RP score 5.
- 6 FAC
- RTH
- Tamoxifene

- En Octobre 2011, se plaint de douleurs dorsales calmées par les antalgiques.
- Scintigraphie osseuse: hyperfixation intense de D11, L2, L4.
- TDM TAP: confirme les métastases osseuses (lésions vertébrales étagées D11, D12, L1 + un nodule hépatique de 10 mm suspect du segment II.

Quelle est votre CAT?

- 1- Hormonothérapie
- 2- Chimiothérapie
- 3- Hormonothérapie + Radiothérapie antalgique
- 4- Autre

Unchanged statement

BIOPSY OF METASTATIC LESION

A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time.

(LoE/GoR: I/B) (98%)

Une biopsie hépatique a été faite.
En cas de discordance entre tumeur primitive et métastase (RH et HER2), traitement:

- 1- En fonction de la tumeur primitive

- 2- En fonction de la métastase.

Discordance entre tumeur primitive et métastase

- Cancers are genetically unstable
- Evidence on this field: retrospective studies

- Methodological issues if such studies (records, pre- and analytical errors, diff pathology labs)
- N9831 trial: local vs centralized HER2 determination: 12% discordance for FISH and 18% for IHC (same tumour!)

Turner NH et al, 2013; Houssami et al, 2011; Perez EA et al, 2006

Unchanged statement

BIOPSY OF METASTATIC LESION

If the results of tumour biology in the metastatic lesion differ from the primary tumour, it is currently unknown which result should be used for treatment-decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of targeted therapy (ET and/or anti-HER-2 therapy) when receptors are positive in at least one biopsy, regardless of timing.

(LoE/GoR: Expert opinion/B) (87%)

- Biopsie hépatique: métastase d’un carcinome d’origine mammaire, RE positif, RP positif, Her2 3+.
- Bilan préthérapeutique (biologique, cardiaque) normal.

Quel traitement proposez vous (+ IRO)?

- Trastuzumab+ Taxane
- Trastuzumab+vinorelbine
- Trastuzumab+ Letrozole
- Trastuzumab+ Pertuzumab+Taxane

Unchanged statement

HER-2 POSITIVE MBC: 1st line

The standard 1st line therapy for patients previously untreated with anti-HER2 therapy is the combination of CT + trastuzumab and pertuzumab, because it has proven to be superior to CT + trastuzumab in terms of OS in this population.

(LoE/GoR: I/A) (86%)

ETUDE HERNATA

Outcome	D+T (n=143)	V+T (n=141)	p value
Median TTP, months	12.4	15.3	0.67
Median OS, months	35.7	38.8	0.98
Median TTF, months	5.6	7.7	< 0.0001
Toxicity Grade 3/4	**D+T (n=139)**	**V+T (n=138)**	**p value**
Febrile neutropenia	37.4	10.8	< 0.001
Leucopenia	40.3	21.0	< 0.001
Infection	23.7	13.0	0.006
Fever	4.3	0	0.03
Neuropathy (sensory)	30.9	3.6	< 0.001
Oedema	5.8	0	0.003
Nail changes	7.9	0.7	0.005

Andersson M, *et al. J Clin Oncol* 2011; **29**:264–271.

HER-2 POSITIVE MBC

Unchanged statement

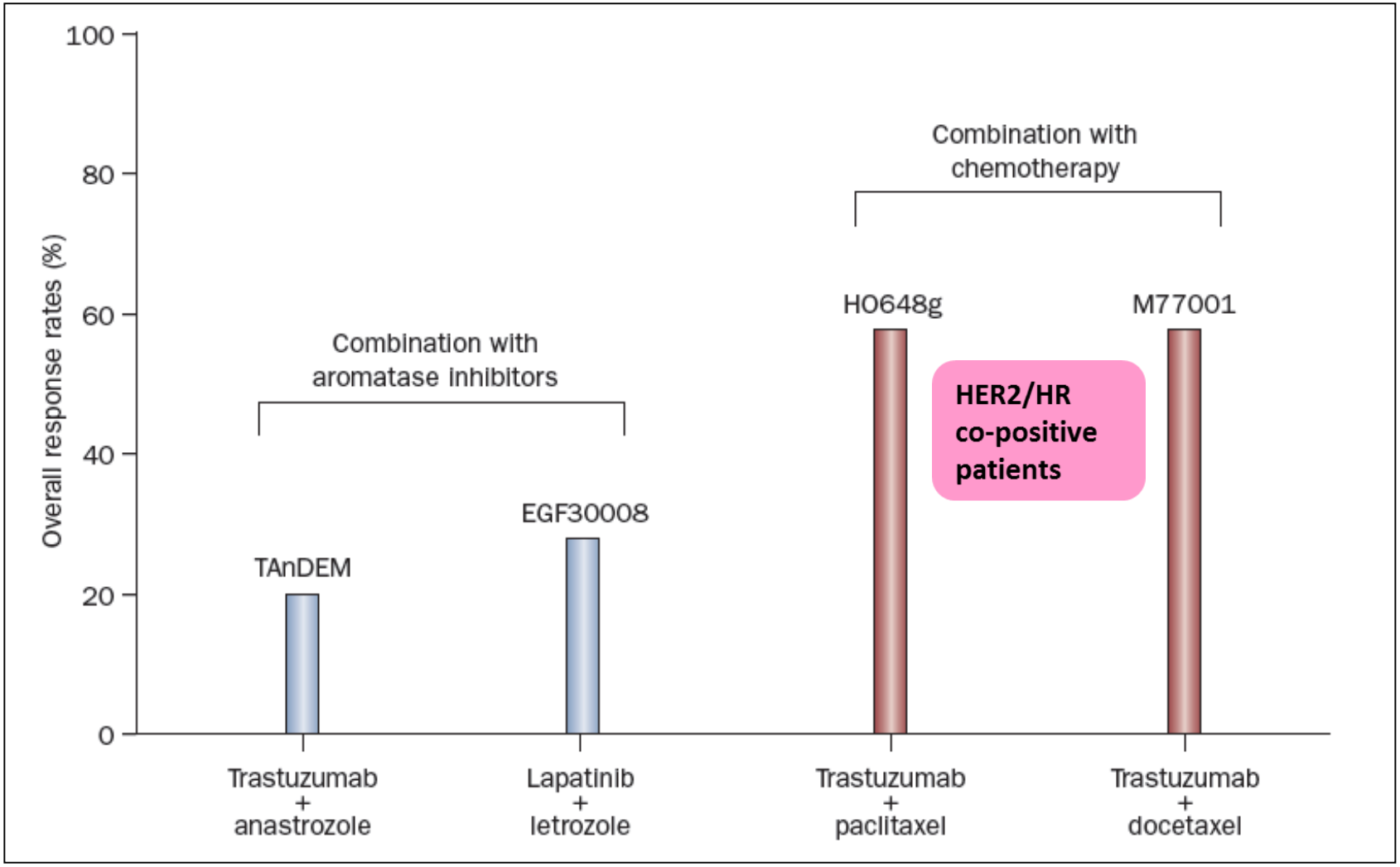
Regarding the CT component of HER2 positive ABC treatment:

When pertuzumab is not given, 1st line regimens for HER2+ ABC can include trastuzumab combined with vinorelbine or a taxane.
(LoE/GoR: I/A) (88%)

Differences in toxicity between these regimens should be considered and discussed with the patient in making a final decision.
Other CT agents can be administered with trastuzumab but are not as well studied and are not preferred.

In manuscript: Single agent vinorelbine in association with anti-HER-2 therapy has shown superior or equal efficacy compared to taxanes and has a better tolerability.

Lower ORR When Endocrine Therapy Was Added to Anti-HER2 Therapy in HER2+/HR+ Patients



Cortés J, et al. Nat Rev Clin Oncol 2011

ABC5

ER + / HER-2+ MBC

Unchanged statement

For the highly selected patients* with ER+/HER-2+ ABC, for whom ET + anti-HER2 therapy was chosen as 1st line therapy, dual anti-HER2 blockade (with either pertuzumab + trastuzumab or lapatinib + trastuzumab) can be used since it provides a benefit in PFS.
This decision must be balanced against the higher side effects, higher costs and lack of OS benefit so far, as compared to ET + anti-HER2 monotherapy.

(LoE/GoR : I/B) (80%)

* Defined in the manuscript

- La patiente a recu 8 cures de Herceptin + docetaxel.

- Evaluation:
- Lésion hépatique: RC
- Lésions osseuses: stabilité

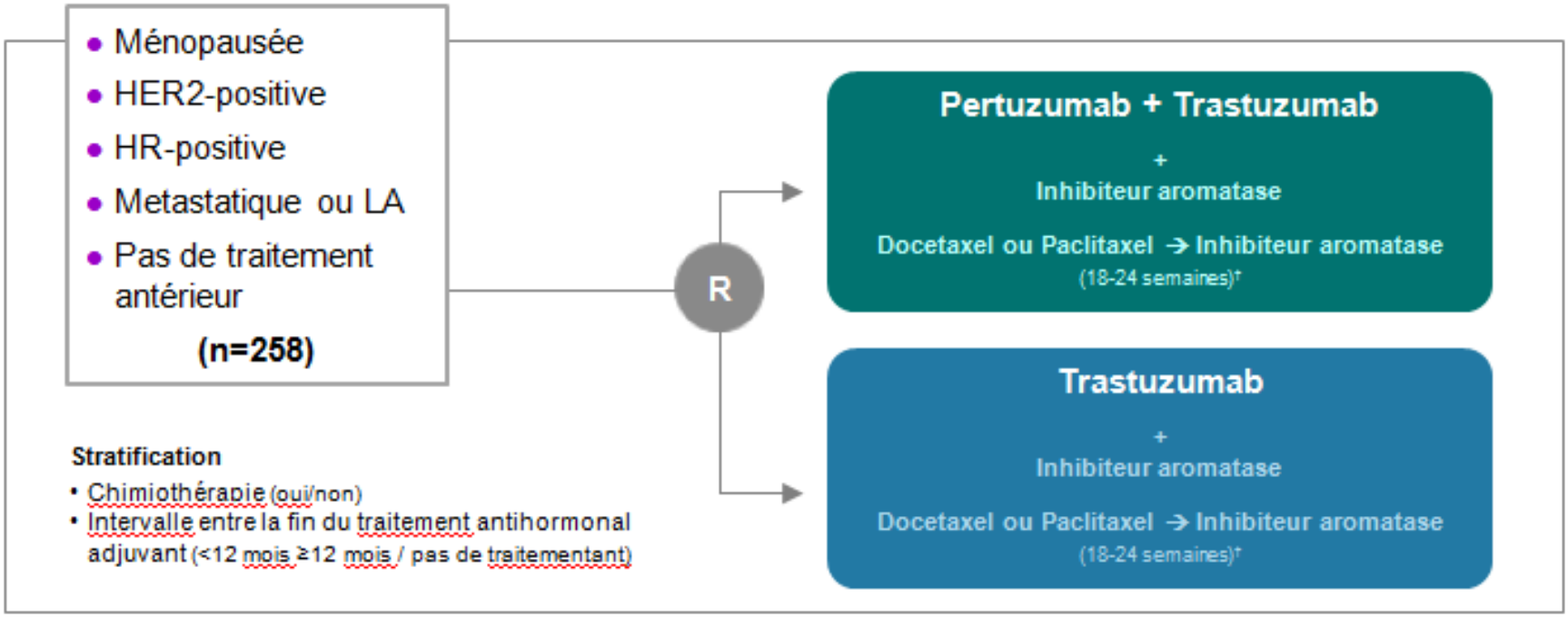
Que proposez vous?

1- continuer Trastuzumab + docetaxel.

2- continuer trastuzumab.

3- continuer trastuzumab+ hormonothérapie.

Etude PERTAIN



G, Arpino, et al., SABCS® 2020, Abs #PD3-02

Etude PERTAIN

Caractéristiques de la maladie et traitement de CT (ITT)

		Pertuzumab + Trastuzumab +AI (n=129)	Trastuzumab + AI (n=129)
LA/MBC at study entry, n (%)	LABC MBC	8 (6,2) 121 (93,8)	7 (5,4) 122 (94,6)
Disease type at screening, n (%)*	Visceral Non-visceral	94 (72,9) 35 (27,1)	88 (68,2) 41 (31,8)
Number of organ involved, n (%)*	≥3 <3	42 (32,6) 87 (67,4)	44 (34,1) 85 (65,9)
Induction chemotherapy, n (%)	Yes No	75 (58,1) 54 (41,9)	71 (55,0) 58 (45,0)

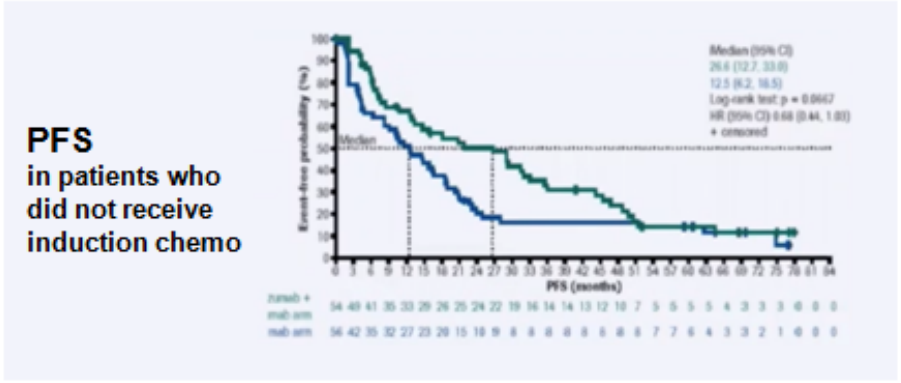
Rimawi & al. SABCS 2016

Etude PERTAIN: Analyse finale

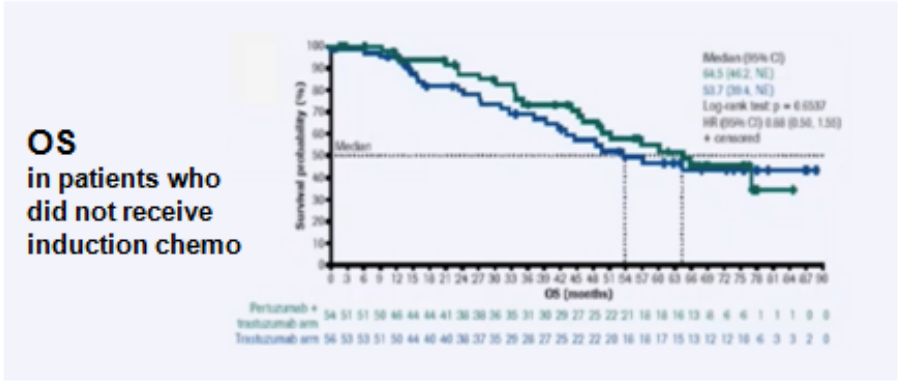
ITT population	
Median follow-up	**6 years**
Median PFS	HP + AI: 20.6 mo H + AI: 15.8 mo HR: 0.67 (0.50-0.89) **P=0.0059**
Median OS	HP + AI: 60.2 mo H + AI: 57.2 mo HR: 1.05 (0.73-1.52) **P=0.7833**

- Enhanced treatment effect in pts who did not receive induction chemotherapy
- No new safety concern; lower incidence of Aes in pts who did not receive inducrion chemo

PFS
in patients who did not receive induction chemo



OS
in patients who did not receive induction chemo



G, Arpino, et al., SABCS® 2020, Abs #PD3-02

- TRT par herceptin + Letrozole
- Après 22 mois de TRT, reprise évolutive au niveau hépatique (2 nodules de 9 mm et 13 mm), Stabilité sur le plan osseux.

Quel traitement proposez vous?

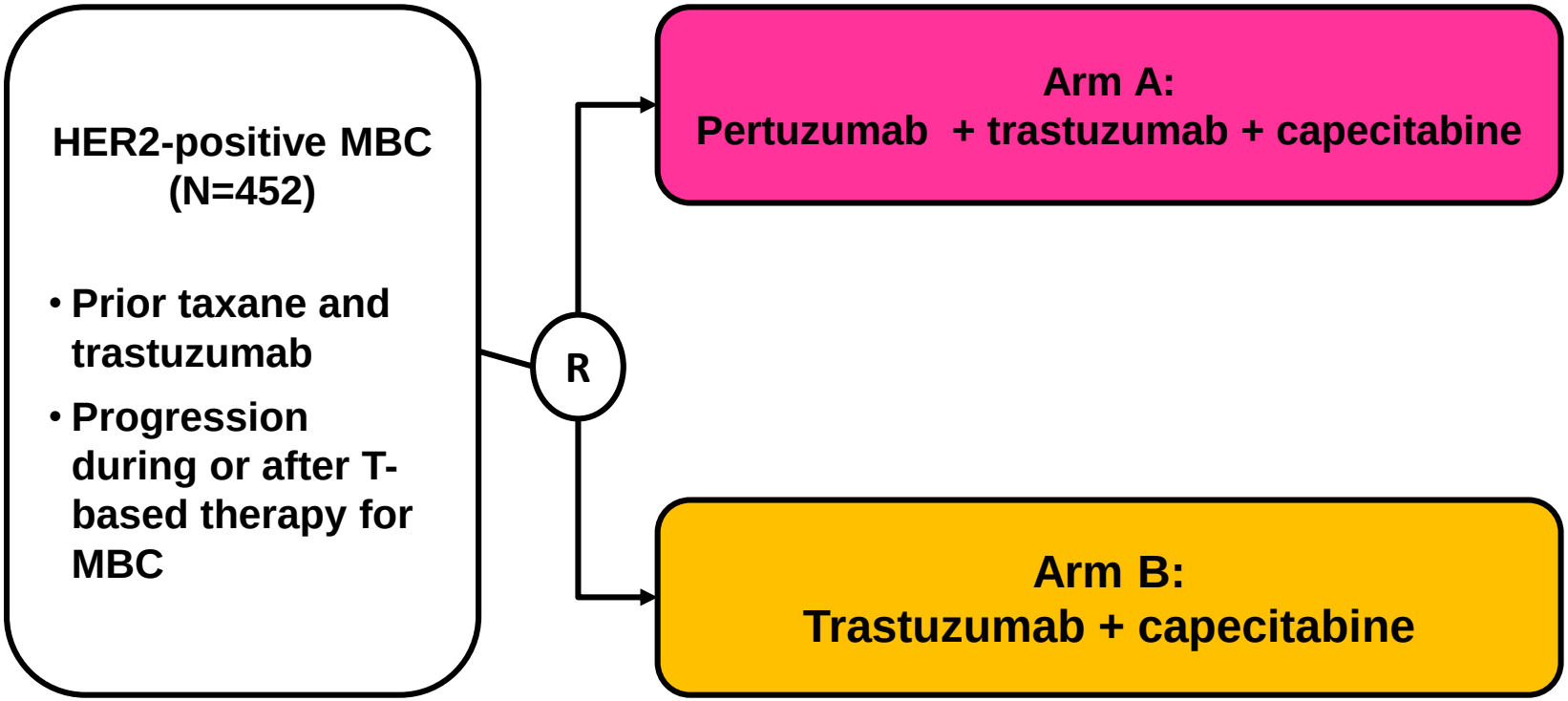
1- trastuzumab+ Capecitabine.

2- Lapatinib+ capecitabine.

3- trastuzumab +pertuzumab+capecitabine

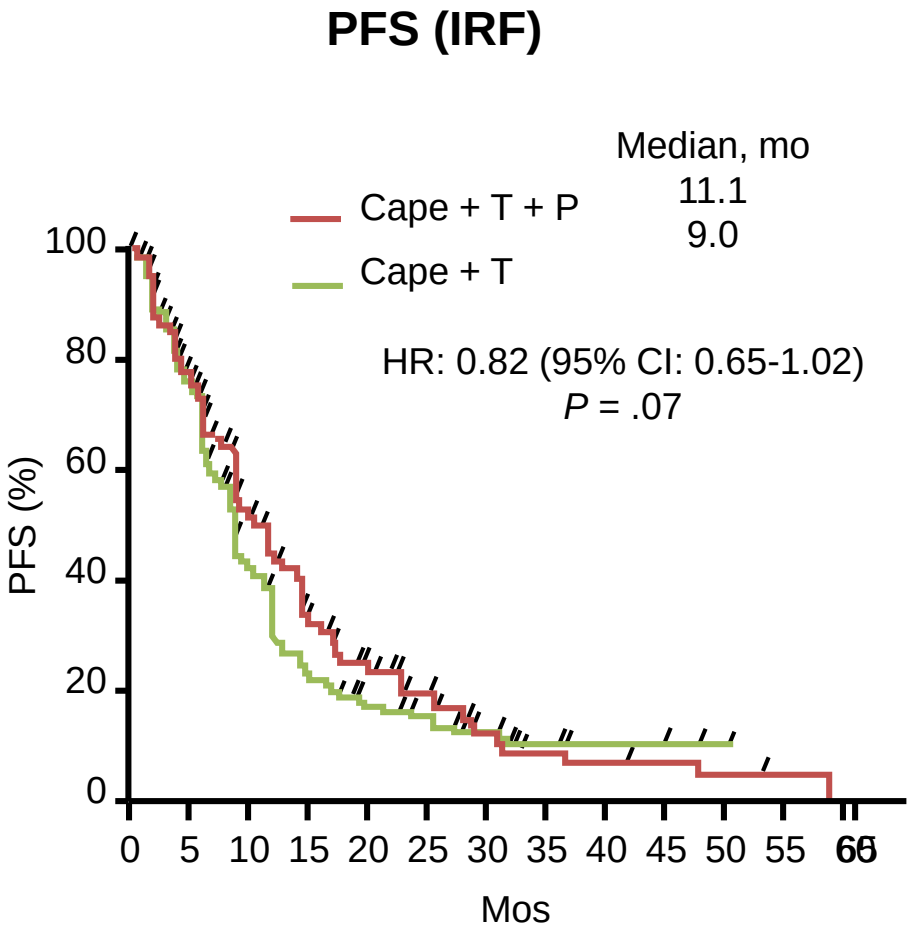
4-TDM1

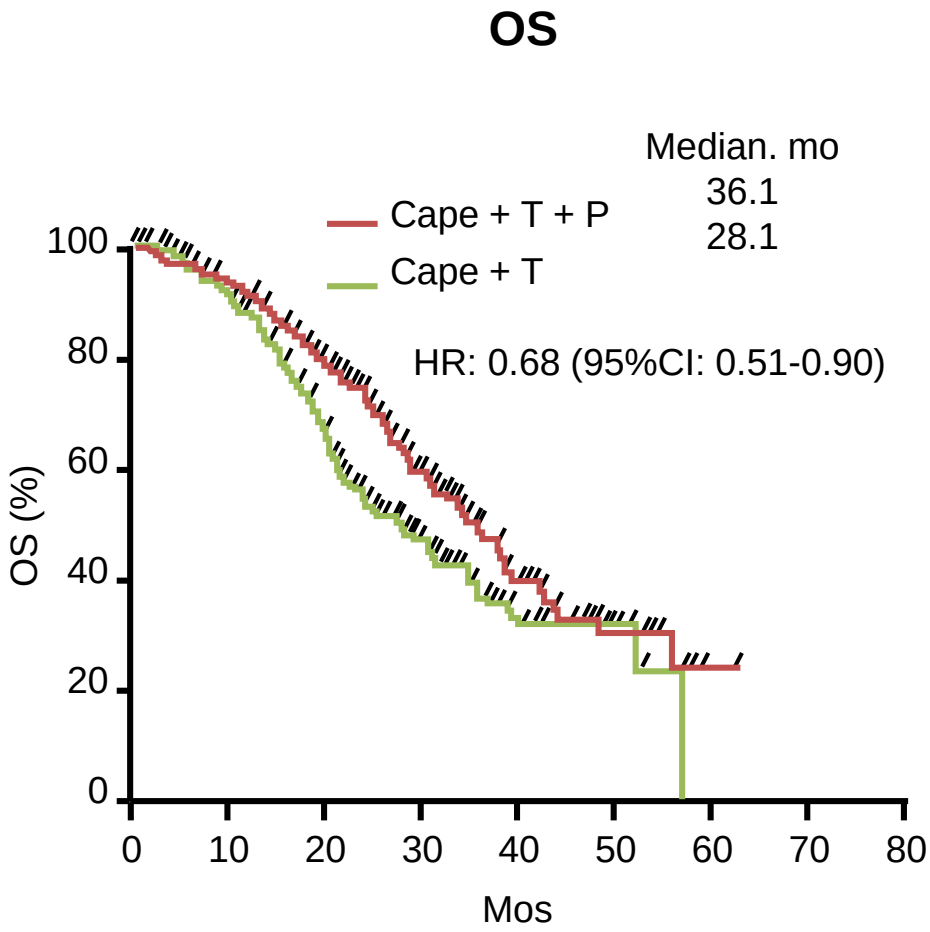
PHEREXA
Capecitabine + Trastuzumab± Pertuzumab



Urruticoechea A, et al. ASCO 2016

PHEREXA: PFS & OS





Urruticoechea A, et al. ASCO 2016

Unchanged statement

HER-2 POSITIVE MBC

In a HER2+ ABC patient, previously untreated with the combination of CT + trastuzumab + pertuzumab, it is acceptable to use this treatment after 1st line.

(LoE/GoR: II/B) (76%)

- La patiente a recu 8 cycles de trastuzumab+ capecitabine.
- Regression des nodules hépatiques.
- Poursuite avec trastuzumab+ fuvestrant.

- Après 6 mois de TRT;la patiente se plaint de céphalées.
- IRM cérébrale: métastases cérébrales multiples.
- Par ailleurs, pas d’évolutivité ailleurs.
- Radiothérapie cérébrale.

METASTASES CEREBRALES

Table 1 Incidence of CNS metastases in series of advanced breast cancer patients administered trastuzumab

Author [ref.]	No. of patients	Median time to CNS metastases (months)	Incidence of CNS metastases
Weitzen et al. [52]	42	12.0	29%
Wardley et al. [53]	33	9.5	33%
Heinrich et al. [54]	51	11.5	43%
Bendell et al. [55]	122	6.0	34%
Clayton et al. [56]	93	10.0	25%
Shmueli et al. [57]	32[b]	4.0	31%
Lower et al. [58]	87	ND	25%
Lai et al. [59]	79	ND	48%
Burstein et al. [60]	289	NR	10%[a]
Arif et al. [61]	47	ND	43%

[a] Only isolated CNS metastases.
[b] Responders to trastuzumab therapy, NR: not reached, ND: not determined.

Duchnowska R, Szczylik C. Cancer Treat Rev 2005

- Dans la maladie HER2, l'IRM cérebrale doit elle etre demandée systématiquement?

1-OUI

2-Non

Unchanged statement

Brain imaging should not be routinely performed in asymptomatic patients.
This approach is applicable to all patients with ABC including those with HER-2+ and/or TNBC ABC.

(LoE/GoR: II/D) (94%)

Unchanged statement

HER-2 POSITIVE ABC & BRAIN METASTASES

Because patients with HER2+ ABC and brain metastases can live for several years, consideration of long term toxicity is important and less toxic local therapy options (e.g. stereotactic radiotherapy) should be preferred to whole brain radiotherapy, when available and appropriate (e.g. in the setting of a limited number of brain metastases).

(LoE/GoR: I/A) (89%)

Quel traitement proposez vous?

1- Trastuzumab+Tucatinb+ Capecitabine.

2- Lapatinib+trastuzumab.

3-TDM1.

4- trastuzumab+Gemcitabine

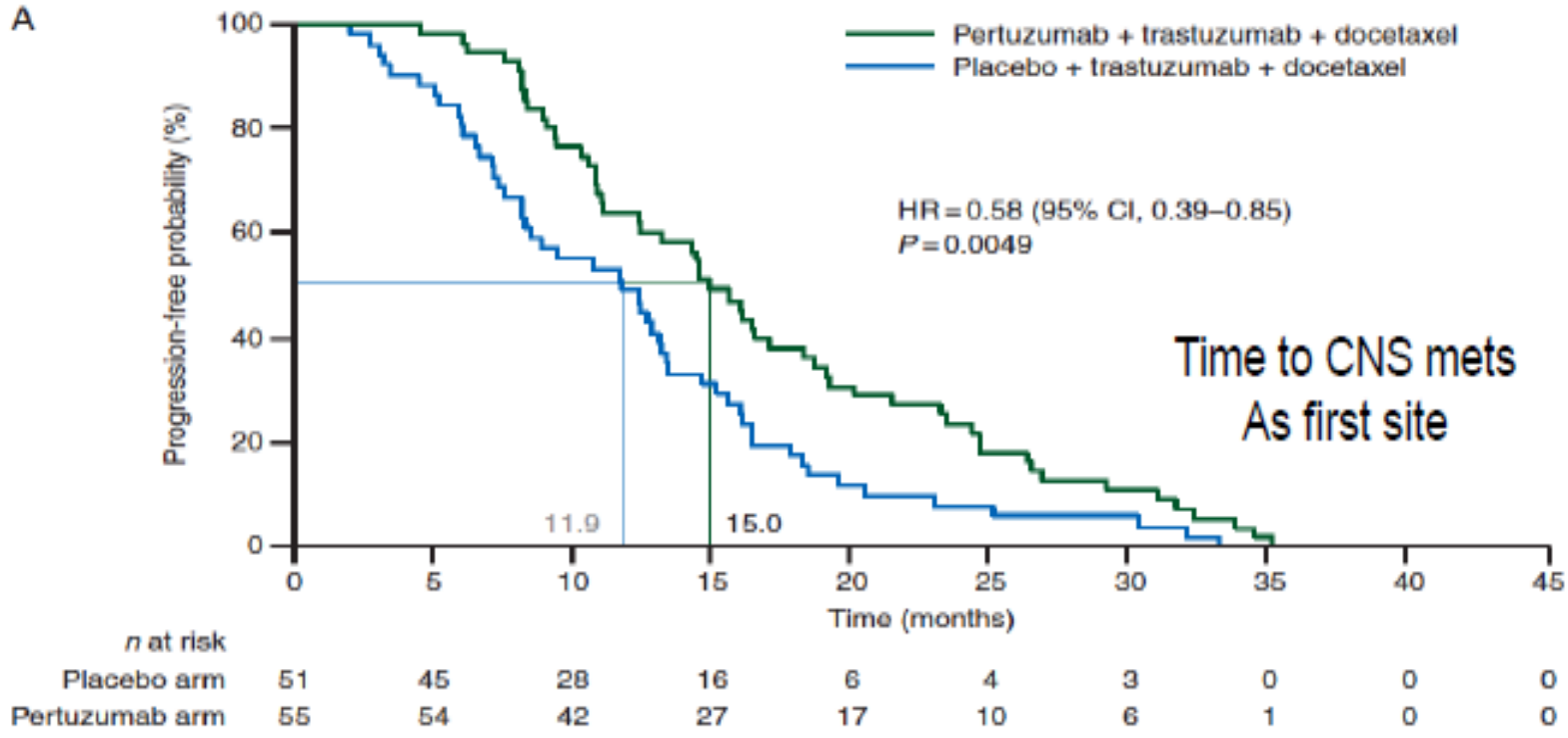
5-Neratinib+ Capecitabine.

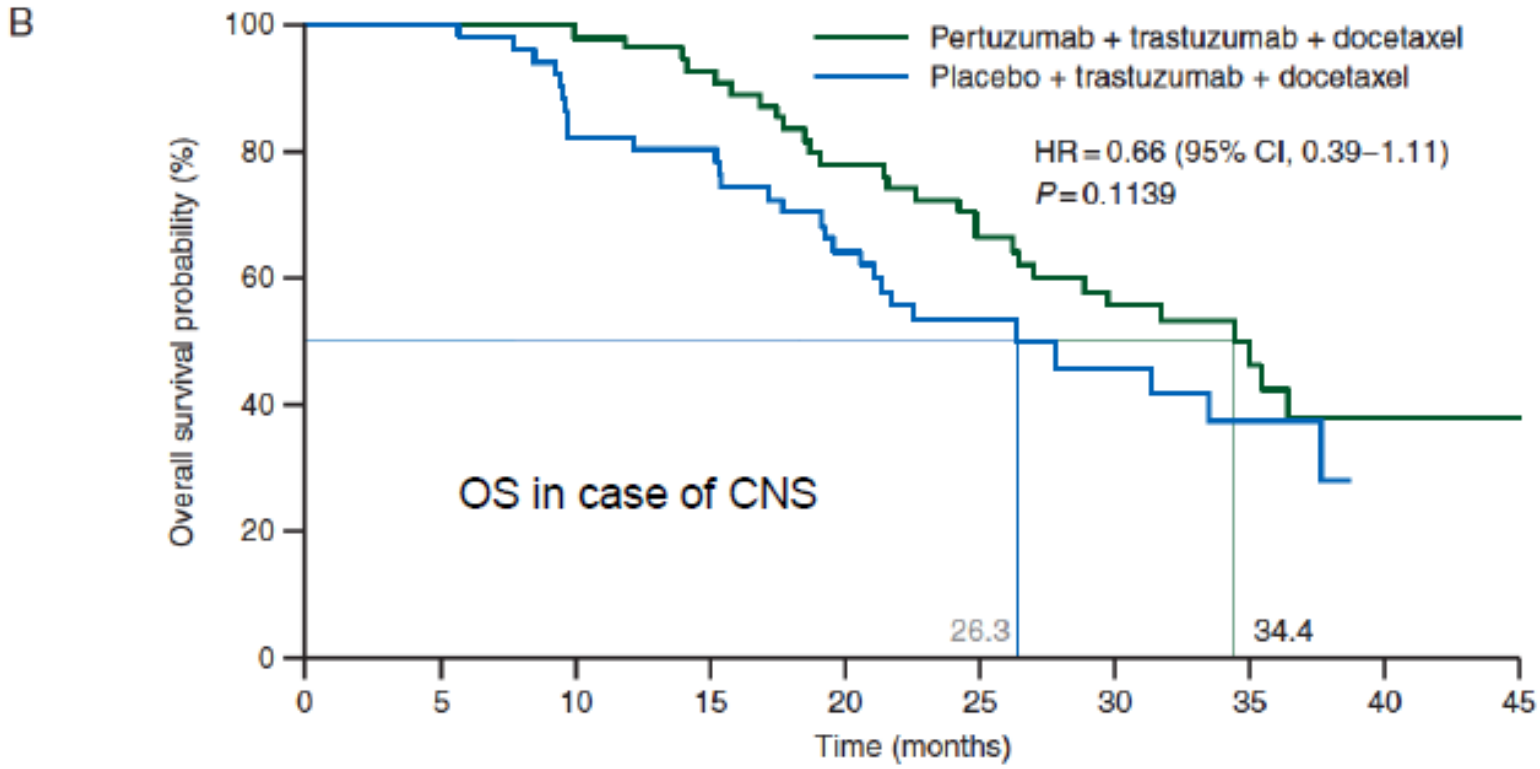
Annals of Oncology 25: 1116–1121, 2014
doi:10.1093/annonc/mdu133
Published online 31 March 2014

Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA

S. M. Swain[1*], J. Baselga[2], D. Miles[3], Y.-H. Im[4], C. Quah[5], L. F. Lee[5] & J. Cortés[6]

[1]*Washington Cancer Institute, MedStar Washington Hospital Center, Washington;* [2]*Memorial Sloan-Kettering Cancer Center, Memorial Hospital, New York, USA;* [3]*Mount Vernon Cancer Centre, Middlesex, UK;* [4]*Division of Hematology and Medical Oncology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea;* [5]*Genentech, Inc., South San Francisco, USA;* [6]*Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

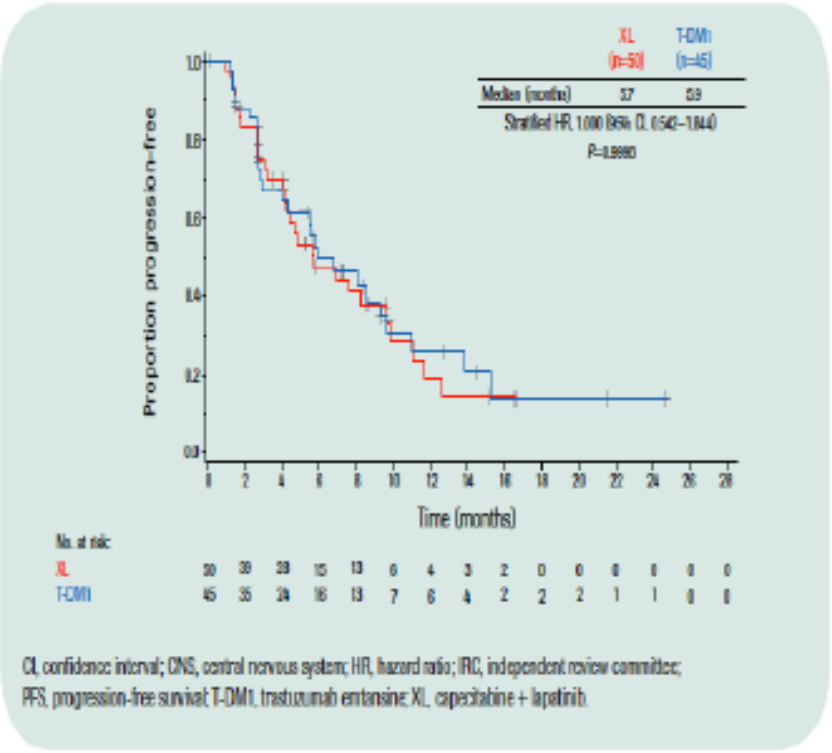



B
Pertuzumab + trastuzumab + docetaxel
Placebo + trastuzumab + docetaxel
HR = 0.66 (95% CI, 0.39–1.11)
P = 0.1139
OS in case of CNS
Overall survival probability (%)
100
80
60
40
20
0
26.3
34.4
0
5
10
15
20
25
30
35
40
45
Time (months)
n at risk
Placebo arm 51 51 42 40 30 16 11 7 0 0
Pertuzumab arm 55 55 54 50 42 33 24 12 8 1

ETUDE EMILIA

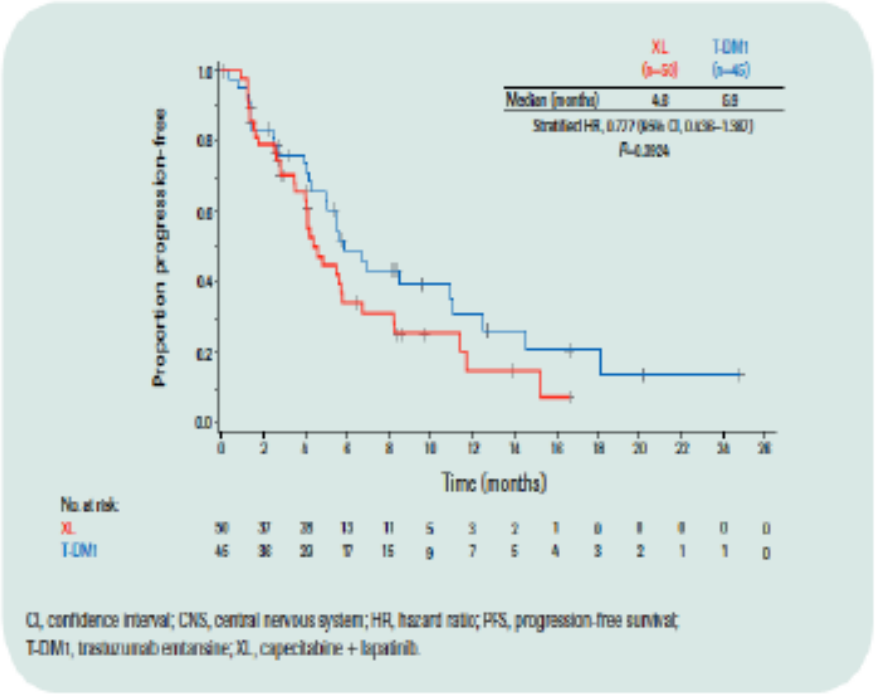
Efficacy and Safety of Trastuzumab Emtansine (T-DM1) vs Lapatinib Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer and Central Nervous System Metastases: Results From a Retrospective Exploratory Analysis of EMILIA

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.

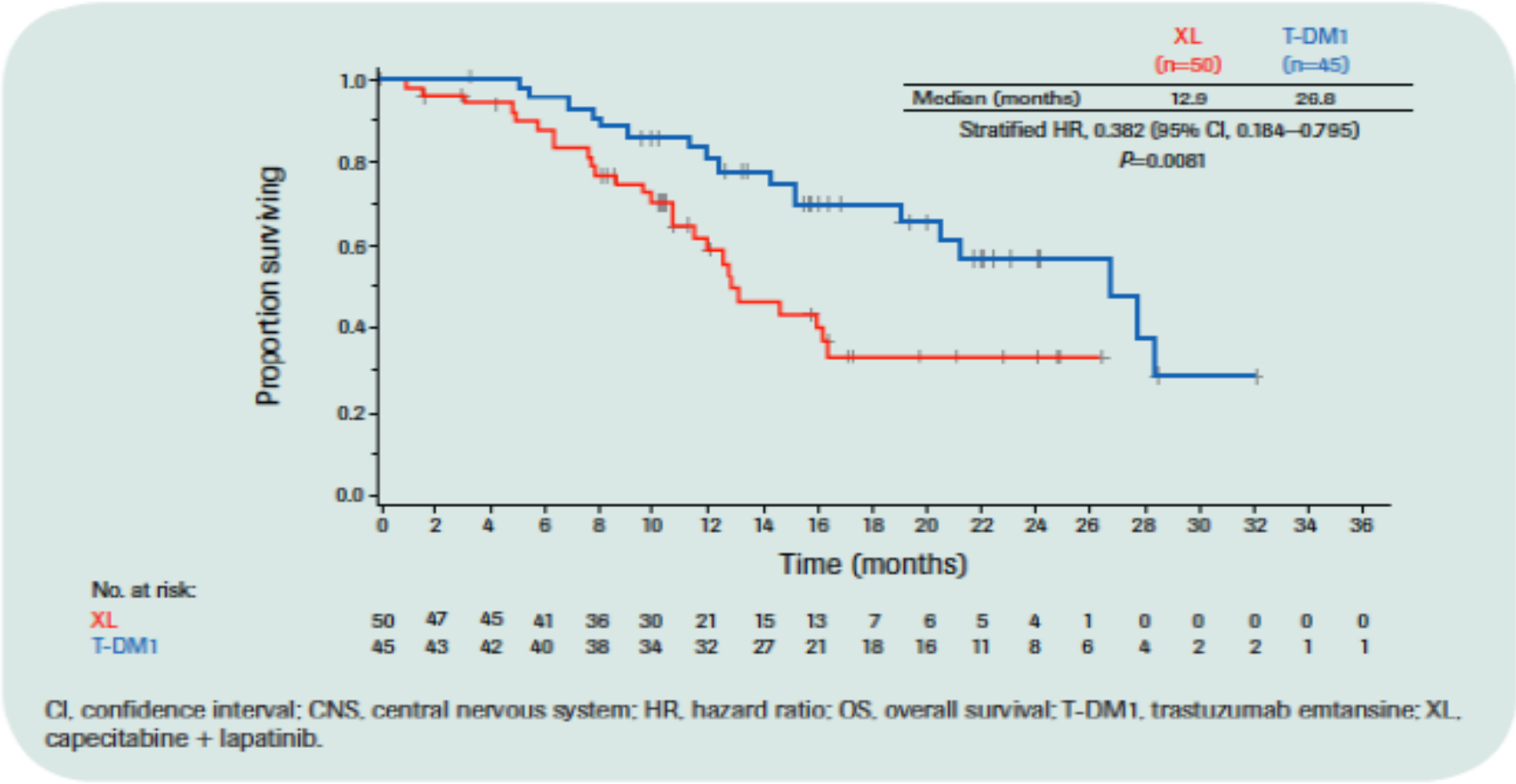
Figure 1B. PFS by investigator for patients with CNS metastases at baseline



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

ETUDE EMILIA

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.

Unchanged statement

HER-2 POSITIVE ABC & BRAIN METASTASES

In patients with HER2 positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed.

(LoE/GoR: I/D) (95%)

Unchanged statement

HER-2 POSITIVE ABC & BRAIN METASTASES

For patients with HER2 positive ABC where brain metastases are the only site of recurrence, the addition of CT to local therapy is not known to alter the course of the disease and is not recommended.
(LoE/GoR: I/D) (83%)

It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped.

(LoE/GoR: I/B) (83%)

- La patiente a eu un TRT locorégional.
- Le traitement par Trastuzumab et fulvestrant a été poursuivi pendant 6 mois, puisque la progression cérebrale etait isolée.

- Progression osseuse et hépatique:nouvelle lésion osseuse de l’aile iliaque gauche + 4 nodules hépatiques de 8, 9, 13 et 17mm.

Quel traitement proposez vous?

1- Lapatinib+tucatinib+ capecitabine

2- trastuzumab+ Lapatinib.

3-trastuzumab+ Chimiothérapie.

4-Trastuzumab deruxtecan

Unchanged statement

HER-2 POSITIVE MBC

For later lines of therapy, trastuzumab can be administered with several CT agents, including but not limited to, vinorelbine (if not given in 1st line), **taxanes** (if not given in 1st line), **capecitabine, eribulin, liposomal anthracyclines, platinum, gemcitabine, or metronomic CM.**
(LoE/GoR: II/A) (91%)

The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.

In manuscript: Data to decide on best sequence are lacking

Unchanged statement

HER-2 POSITIVE MBC

In case of progression on trastuzumab-based therapy, the combination trastuzumab + lapatinib is a reasonable treatment option for some patients.
(LoE/GoR: I/B) (84%)

There are however, no randomized data on the use of this combination after progression on pertuzumab or T-DM1.

- La patiente a été mise sous trastuzumab+ lapatinib.

- Stabilité.